Schedule of Events*  Subject to change

All programs will take place at the Los Angeles Convention Center unless otherwise noted

Friday, March 8, 2013
7:00am – 1:00pm Special Interest Session I: Research Network Symposium, JW Marriott
2:00pm – 6:30pm Satellite Surgical Course, JW Marriott
4:00pm – 6:00pm Special Interest Session II: Allied Health Session, JW Marriott

Saturday, March 9, 2013
6:45am – 7:45am Special Interest Session III: Fellow/Resident/Candidate Sessions
7:45am – 9:30am Opening Scientific Plenary Session I: Clinical Trial Advances
9:35am – 10:15am ACS Lecture: Ed Partridge, MD
10:45am – 12:00pm Education Symposium I: Unraveling the Mystery of TCGA
10:45am – 12:00pm Education Symposium II: Survivorship and Symptom Management
12:15pm – 1:15pm Education Forum I: The Skinny on Obesity in Gynecologic Care
12:15pm – 1:15pm Education Forum II: The Science behind Gynecologic Care: The Best of AACR
12:15pm – 1:15pm Education Forum III: Gynecologic Cancer Genetics: The Practical Implications
1:30pm – 3:00pm Industry Supported Symposium Luncheon
3:15pm – 4:45pm Scientific Plenary Session II: Surgical Advances
3:15pm – 4:45pm Special Interest Session IV: Allied Health Session
4:45pm – 5:30pm Exhibit Reception
6:30pm – 9:00pm Foundation for Gynecologic Oncology Celebration, JW Marriott

Sunday, March 10, 2013
6:30am – 7:30am Featured Poster Session I
6:30am – 7:30am Sunrise Seminar I: TCGA Data Mining: Potential and Pitfalls
6:30am – 7:30am Sunrise Seminar II: Palliative Care in Gynecologic Cancer
6:30am – 7:30am Sunrise Seminar III: To Bleed or Not to Bleed, There is no Question.
6:30am – 7:30am Education Forum IV: Meet the Professor
7:45am – 9:15am Scientific Plenary III: Novel Therapeutics and Trial Design
9:15am – 10:00am Presidential Address, Ronald Alvarez, MD
11:00am – 12:15pm Seminal Abstract Session
12:30pm – 2:00pm Industry Supported Symposium Luncheons
2:15pm – 4:45pm Montz Symposium A: Surgical Mishaps
2:15pm – 3:45pm Education Forum V: Coding Update: ICD-10 and CPT Case Presentations
2:15pm – 3:45pm Education Forum VI: The Future of Clinical Trial Design
2:15pm – 3:45pm Surgical Forum I: Scientific Surgical Films
4:30pm – 5:45pm Scientific Plenary Session IV: Cancer Prevention and Beyond
7:30pm – 10:00pm SGO Social Event

Monday, March 11, 2013
6:30am – 7:30am Featured Poster Session II
6:30am – 7:30am Sunrise Seminar IV: Breast Cancer
6:30am – 7:30am Sunrise Seminar V: It's a Jungle Out There: The Importance of Patient Safety
7:45am – 9:00am Scientific Plenary V: Late Breaking Abstract Session
9:00am – 9:45am SGO Business Meeting/Member Forum
10:45am – 11:30am Presidential Invited Guest Lectureship, Ezekiel Emanuel, MD, PhD
11:30am – 12:30pm Scientific Plenary VI: Health Care Outcomes: Charting the Course
12:45pm – 2:15pm Industry Supported Symposium Luncheon
2:30pm – 5:00pm Montz Symposium B: Surgical Mishaps
2:30pm – 3:30pm Education Forum VII: Are we Hitting the Mark? Targeted Therapies for Gynecologic Cancers
2:30pm – 3:30pm Education Forum VIII: Closer to Zero: An Update on the Progress of Cervical Cancer Screening
3:45pm – 4:45pm Education Forum IX: Contemporary Management of Ovarian Cancer
5:00pm – 6:30pm Special Interest Session V: International Symposium
7:00pm

Tuesday, March 12, 2013
8:00am – 9:25am Scientific Plenary VII: Clinical Practice Management Issues
9:25am – 10:40am Scientific Plenary VIII: Origins of Serous Cancers
10:40am – 11:45am Education Forum X: Tumor Board
Editorial

Foreword
The Society of Gynecologic Oncology (SGO) is proud to host its 44th Annual Meeting on Women's Cancer*—the subspecialty’s premier educational event—March 9-12, 2013, in Los Angeles, CA. On behalf of the Society, I sincerely appreciate those who have generously contributed their time in support of the scientific curriculum presented at this year’s meeting, which attracts more than 1,800 gynecologic oncologists and health professionals from around the world.

This supplement to Gynecologic Oncology contains the selected abstracts scheduled for presentation at the 2013 Annual Meeting. This year 706 abstracts were submitted for consideration. After careful discussion and deliberation, 62 were selected for oral presentation, 38 abstracts were accepted as Featured Poster Presentations and 301 for Poster presentation. For the first time ever, the Program Committee solicited abstracts in six key areas, based on past meeting surveys and priorities in cancer research. These key areas include 1) Development of Clinical Trials and the Evolution of Clinical Studies, 2) Novel surgical techniques, 3) Quality of Life/Survivorship, 4) Health Care Reform and Outcomes, 5) Updates on Fallopian Tube Carcinogenesis, and 6) Palliative Care. Nearly half of the accepted abstracts were in these six key areas. This year, the Annual Meeting is offering a variety of evidence-based educational sessions to expand your knowledge on current topics in gynecologic cancer care. Scientific Plenary Sessions, Education Symposia, Sunrise Seminars and Education Forums have been designed to cover topics in-depth for improved practice. All registrants may attend any educational session for one flat registration fee.

This year’s abstracts were reviewed and selected by the 2013 Annual Meeting Program Committee, chaired by Warner Huh, MD. Members of this year’s committee are:

Paula Anastasia, MN, RN, AOCN
Jubilee Brown, MD
Susanna Campos, MD
Christopher Crum, MD
Michael Gold, MD
Paul Goodfellow, PhD
Jeffrey Hines, MD
Amanda Jackson, MD
Byoung-Gie Kim, MD, PhD
Jae-Hoon Kim, MD, PhD
Jae-Weon Kim, MD, PhD
Tyler Kirby, MD
Jonathan Ledermann, BSc, MD, FRCP
Mario Leitao, Jr., MD
Jaime Lesnock, MD
Dayna McCauley, PharmD, BCOP
Amanda Nickles Fader, MD
Dennis Scribner, Jr., MD
Chirag Shah, MD
Pamela Soliman, MD
Gillian Thomas, MD
Edward Trimble, MD, MPH
Christine Walsh, MD

In addition to the Program Committee, these members served on the new Annual Meeting Program Steering Committee to help guide synthesized education delivered to attendees:

Angeles Alvarez Secord, MD
John Chan, MD
David Cohn, MD
Anil Sood, MD

I hope that, while reviewing the following abstracts included within this supplement, you are both educated and inspired. This body of scientific research embodies what the Society truly represents: an organization that embraces the highest quality of new research findings, innovative patient care models and advanced surgical techniques that continue to contribute toward SGO's vision of one day eradicating women's cancers.

Again, on behalf of the SGO, I thank the member volunteers whose dedicated time assisted in the Annual Meeting's overall success.

Ronald D. Alvarez, MD
2012-2013 SGO President
CONTENTS

Abstracts Presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

SGO – 2013 Annual Meeting Schedule ....................................................... S2
Foreword ................................................................................ S3

ABSTRACTS

Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology ........... S5
Author Index ........................................................................... S157
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

Opening Plenary Session I: Clinical Trial Advances
Saturday, March 9, 2013, 7:45a.m.-9:35a.m.
Concourse Hall (Los Angeles Convention Center)

Moderators, Abstracts: 1-6: Al Covens, MD, Sunnybrook Health Sciences Center, Toronto, ON, Canada; Jonathan Ledermann, BSc, MD, FRCP, UCL Cancer Institute & UCL Hospitals, London, United Kingdom

1 Phase III randomized trial of cisplatin plus paclitaxel vs the non-platinum chemotherapy doublet of topotecan plus paclitaxel in women with recurrent, persistent, or advanced cervical carcinoma: A Gynecologic Oncology Group study


1UC Irvine Medical Center, Orange, CA, 2Roswell Park Cancer Institute, Buffalo, NY, 3St. Joseph’s Hospital and Medical Center, Phoenix, AZ, 4Mayo Clinic, Rochester, MN, 5The University of Texas, MD Anderson Cancer Center, Houston, TX, 6University of Oklahoma, Oklahoma City, OK, 7Hospital Vall d’Hebron, Barcelona, Spain, 8University of Cincinnati College of Medicine/ Women’s Cancer Center at Kettering, Kettering, OH, 9Memorial Sloan-Kettering Cancer Center, New York, NY, 10Clarian North Medical Center, Carmel, IN

Objective: With increasing use of radiosensitizing cisplatin-based chemoradiation for locally advanced cervical cancer, many patients with recurrent disease may be platinum-resistant. This is suggested by decreasing response rates (RR) to platinum-based therapy in the recurrent setting noted in the preceding randomized Gynecologic Oncology Group (GOG) trials in this population (GOG 169, 179, 204). We sought to determine whether the non-platinum chemotherapy doublet, topotecan plus paclitaxel (TP), improves overall survival (OS) when compared to cisplatin plus paclitaxel (CP) in recurrent, persistent, or advanced cervical carcinoma. (A 2x2 factorial design was used to also assess the independent question concerning the impact of antiangiogenesis therapy, but these data are not yet mature.)

Methods: Patients were randomly assigned to C 50 mg/m² plus P 135-175 mg/m² or T 0.75 mg/m² d1-3 plus P 175 mg/m² d1. Cycles were repeated every 3 weeks until progression, unacceptable toxicity, and/or complete response. OS was the primary endpoint, with a reduction in the hazard of death by 30% with substitution of T for C considered important (90% power, alpha=2.5%).

Results: Four hundred fifty-two patients were accrued from 4/6/09 to 1/3/12. A planned interim analysis was conducted after 174 patients died. A total of 229 patients received the CP backbone and 223 received the TP backbone. Seventy-five percent of the entire study group had previously received platinum (75.5% CP arm, 74% TP arm). Patients were well-matched for age, histology, race/ethnicity, grade, and recurrent, persistent, or advanced disease. The experimental-to-CP HR of death was 1.20 (98.74% CI 0.82-1.76; 1-sided P=0.08). Median survival was 15 months (CP) and 12.5 months (TP). The HR for progression-free survival (PFS) was 1.39 (95% CI 1.09-1.77; 2-sided P=0.0008). The RR at the time of analysis were 38.4% CP and 28.7% TP (P=not significant). TP was associated with significantly less grade 3-4 neutropenia and infection with grade 3-4 neutropenia was not significantly increased with TP.

Conclusions: This is the largest phase III randomized clinical trial in this population to complete accrual. The substitution of T for C does not result in improved OS. Consistent with previous experience, the RR for CP remains high. Treatment of recurrent/persistent/advanced cervical cancer with CP or TP should be predicated on toxicity screening.

2 Prognostic factors for stage IVB persistent or recurrent cervical cancer (from the results of the JCOG0505 Trial)

S. Nishio1, R. Kitagawa2, T. Shibata3, K. Ushijima4, H. Yoshikawa1, T. Kamura1

1Keisei University School of Medicine, Kusako, Japan, 2NTT Medical Center Tokyo, Tokyo, Japan, 3National Cancer Center, Tokyo, Japan, 4University of Tsukuba, Ibaraki, Japan

Objective: JCOG0505 demonstrated the statistically significant non-inferiority of paclitaxel plus carboplatin (TC) to paclitaxel plus cisplatin (TP) in terms of overall survival (OS) in stage IVB or recurrent cervical cancer. In the present trial, patients with incurable disease (with previous therapy with up to 1 regimen of platinum-based chemotherapy permissible) were randomized with the minimization method, adjusting for institution and known prognostic factors such as performance status (PS), histologic type, and the history of radiation therapy (RT). The objective of this study was to investigate the appropriateness of the adjusting factors used in the random allocation of treatments and to investigate new prognostic factors from the results of the trial, thereby contributing to future studies of similar patients.

Methods: Of 244 eligible patients of the JCOG0505 trial who were assigned to receive either TP or TC, one patient was excluded from analysis because of missing covariate data. The effects on OS of pretreatment hemoglobin levels (median, 11.8 g/dL: higher than or equal vs. lower than the median value) and pretreatment platelet counts (median, 271.5 x 10³/mm³: higher than or equal vs. lower than the median value) and the adjustment factors used for randomization in the JCOG0505 trial, PS, histologic type, and history of RT were investigated using a multivariate Cox regression model with adjusting factors and other background factors, i.e., age, lesion site, platinum-free interval (PFI).

Results: The median follow-up was 17.6 months. Median OS was 18.3 months in the TP group, 17.5 months in the TC group, and 18.0 months in both groups combined. The HR was 0.69 in patients with pretreatment hemoglobin levels higher than or equal to the median value (P=0.016; 95% CI, 0.51-0.93), 2.23 in patients with a PFI <6 months (P=0.0001; 95% CI, 1.38-3.60), 1.60 in patients with a PFI >6 to <12 months (P=0.045; 95% CI, 1.01-2.53), and 1.83 in patients with a PS of 1 or higher (P<0.001; 95% CI, 1.31-2.55). On the other hand, significant differences were not obtained for pretreatment platelet count or other factors.

Conclusions: In addition to the known prognostic factors of PS, which was used as one of the adjusting factors, lower hemoglobin level and a PFI of <12 months were newly found to be associated with poor outcomes in patients with cervical cancer. These variables should, therefore, be considered as new adjusting factors in future clinical trials of similar patients.

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥60 years (vs.&lt;60 years)</td>
<td>0.81</td>
<td>0.61-1.08</td>
<td>0.156</td>
</tr>
<tr>
<td>PS 0 or higher (vs. PS 0)</td>
<td>1.83</td>
<td>1.33-2.56</td>
<td>0.001</td>
</tr>
<tr>
<td>Squamous cell carcinoma (vs. non-squamous cell carcinoma)</td>
<td>1.04</td>
<td>0.71-1.51</td>
<td>0.839</td>
</tr>
<tr>
<td>History of RT: prior RT for all recurrent lesions</td>
<td>0.77</td>
<td>0.50-1.19</td>
<td>0.246</td>
</tr>
<tr>
<td>(vs. no RT/ at least 1 lesion without RT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease status: recurrent (vs. stage IVB)</td>
<td>0.97</td>
<td>0.62-1.50</td>
<td>0.876</td>
</tr>
<tr>
<td>Disease status: re-recurrent (vs. stage IVB)</td>
<td>0.88</td>
<td>0.51-1.53</td>
<td>0.657</td>
</tr>
<tr>
<td>Lesion size: B (vs. A)</td>
<td>0.74</td>
<td>0.42-1.35</td>
<td>0.279</td>
</tr>
<tr>
<td>Lesion size: C (vs. A)</td>
<td>1.36</td>
<td>0.83-2.24</td>
<td>0.226</td>
</tr>
<tr>
<td>Platinum-free interval &gt;6 months (vs. no history of treatment)</td>
<td>2.23</td>
<td>1.38-3.60</td>
<td>0.001</td>
</tr>
<tr>
<td>Platinum-free interval &gt;12 months (vs. no history of treatment)</td>
<td>1.60</td>
<td>1.01-2.53</td>
<td>0.045</td>
</tr>
<tr>
<td>Complications before treatment: yes (vs. no)</td>
<td>1.03</td>
<td>0.69-1.55</td>
<td>0.881</td>
</tr>
<tr>
<td>Hemoglobin levels ≥11.8 g/dL (vs. &lt;11.8 g/dL)</td>
<td>0.69</td>
<td>0.45-0.93</td>
<td>0.019</td>
</tr>
<tr>
<td>Pretreatment platelet counts &gt;27.15 x 10³/mm³ (vs. ≤27.15 x 10³/mm³)</td>
<td>1.31</td>
<td>0.98-1.76</td>
<td>0.071</td>
</tr>
<tr>
<td>A. At least 1 metastatic lesion outside the pelvic cavity except in the para-aortic lymph node (LN) and inguinal LN</td>
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</tr>
<tr>
<td>B. No metastasis outside pelvic cavity except in the para-aortic lymph node (LN) and inguinal LN and at least 1 of the these lesions has been irradiated</td>
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<tr>
<td>C. All lesions are localized inside the pelvic cavity and at least 1 of them has been irradiated</td>
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</table>
A phase II evaluation of carboplatin/paclitaxel/bevacizumab in the treatment of advanced stage endometrial carcinoma

The Ohio State University, Columbus, OH

Objective: To report the treatment efficacy of carboplatin, paclitaxel, and bevacizumab (C/T/Bev) in stage III/IV endometrial cancer patients who have undergone primary surgical treatment.

Methods: On day 1, carboplatin (AUC 5), paclitaxel (175 mg/m²), and bevacizumab (15 mg/kg) was given every 21 days in single-arm open-label phase II for a maximum of 6 cycles in patients with or without measurable disease. Toxicity was reported using CTCAE v3 as maximum grade per pt. Thirty-eight pts were enrolled to assess whether the 24-month failure-free rate (FFR) (events defined as disease progression, death without progression, or discontinuation due to progression, death, or unacceptable toxicity) is at least 50% against the alternative that the 24-month FFR is at least 70% (alpha of 0.1, beta of 0.1, power of 90%). Patients without a defined event were censored at the last tumor assessment date.

Results: Thirty-eight pts were evaluable (6 stage IIIA; 24 stage IIIC; 8 stage IVB). 31/38 (82%) completed the 6 cycles. Four pts were removed due to a significant adverse effect (fascia dehiscence, vaginal dehiscence, pulmonary embolism, neutropenic sepsis), and 21/38 (55%) experienced grade 3/4 neutropenia. Four of 38 (11%) pts experienced febrile neutropenia. There were no bowel perforations or fistulas. Median PFS was 26 months (mo) (range, 2-57 mo). Two pts are failure-free with less than 24 m of follow-up. 20/36 (55%) were failure-free at 24 mo. Two pts are failure-free with less than 24 m of follow-up. 20/36 (55%) were failure-free at 24 mo.

Conclusions: This is the first phase II trial to report efficacy with C/T/Bev in first-line advanced uterine cancer treatment. The regimen is relatively well-tolerated, with manageable acute toxicities. Evisceration (1 fascia, 1 vaginal) was seen in 2 pts, suggesting that consideration should be given to omitting Bev until cycle 2 in adjuvant uterine cancer trials. C/T/Bev had more than a 50% grade 3/4 neutropenia and 11% febrile neutropenia occurrence. C/T/Bev x 6 cycles failed to meet the primary objective of 70% FFR, although it is important to note that the 24-mo FFR in GOG 209 was approximately 40%. Future trials should consider including Bev maintenance following C/T/Bev in this high-risk population in an attempt to improve the FFR.

Symptoms and adverse effects with chemotherapy ± bevacizumab for platinum-resistant recurrent ovarian cancer: analysis of the phase III AURELIA trial

1AGO and University of Schleswig-Holstein Campus Kiel, Kiel, Germany, 2GINECO and CRLC Val d’Aurelle, Montpellier, France, 3GEICO and Hospital Universitario Reina Sofia de Córdoba, Córdoba, Spain, 4AGO and Universitat Marburg, Marburg, Germany, 5NSGO and Linköping University Hospital, Linköping, Sweden, 6MITO and University of Rome “Sapienza”, Rome, Italy, 7BGOG and CMSE Namur, Namur, Belgium, 8DGOG and University Medical Center Utrecht, Utrecht, Netherlands, 9HECOG and General Peripheral Hospital of Athens “Alexandra”, Athens, Greece, 10GINECO and Universitat París Descartes, Paris, France

Objective: The phase III AURELIA trial met its primary objective of improving progression-free survival (PFS) with the addition of bevacizumab (BEV) to chemotherapy (CT) for platinum-resistant ovarian cancer (OC) [Pujade-Lauraine, ASCO 2012]. The PFS hazard ratio was 0.48 (95% CI: 0.38-0.60; P<0.001). Median PFS was 6.7 months with BEV-CT vs 3.4 months with CT. Overall response rates (REGIST and/or CA-125 criteria) were 30.9% and 12.6%, respectively (P<0.001). We analyzed data for symptoms and adverse effects to describe clinical benefit-risk in AURELIA.

Methods: Patients with platinum-resistant (progression <6 months after platinum-based therapy) measurable/assessable OC who had received 1-2 previous anticancer regimens were randomized to receive single-agent CT (investigator’s choice of paclitaxel, topotecan, or pegylated liposomal doxorubicin) alone or with BEV until disease progression or unacceptable toxicity. The primary endpoint was PFS; secondary endpoints included response, safety, and tolerability.

Results: The median number of CT cycles was 6 in the BEV-CT arm vs 3 in the CT arm. Grade ≥3 adverse events (AEs) occurred in 58% vs 54% of patients. Hypertension, proteinuria (both typical of BEV), hand-foot syndrome, and peripheral sensory neuropathy were more common with BEV-CT than CT. However, grade ≥3 AEs associated with high tumor burden (abdominal pain, fatigue, dyspnea, vomiting) were consistently less frequent with BEV-CT than CT in each cycle.

Conclusions: The significant improvement in PFS and response rate with the addition of BEV to CT is accompanied by a modest increase in treatment-related toxicities and improvement in AEs related to tumour burden. Additional exploratory analyses of symptoms over time will be presented.

Hyperthermic intraperitoneal chemotherapy following extensive cytoreductive surgery in patients with primary advanced epithelial ovarian cancer: Result of a prospective phase II study

M. Lim, M. Im, H. Yoo, S. Seo, S. Kang, S. Park
National Cancer Center, Goyang-si, Republic of Korea

Objective: To investigate the pattern of failure and survival outcome associated with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with primary advanced epithelial ovarian cancer.

Methods: Intraoperative HIPEC (cisplatin [75 mg/m²], 41.5°C, 90 minutes) was performed in 30 patients with residual tumor < 1 cm after cytoreductive surgery between January 2007 and February 2008. All the patients received adjuvant chemotherapy with combination platinum and taxane.

Results: The stages of ovarian carcinoma were III (n=25) and IV (n=5). The histology of ovarian carcinoma was: serous carcinoma (n=24), mucinous carcinoma (n=2), endometrioid carcinoma (n=2), clear cell carcinoma (n=1), and transitional cell carcinoma (n=1). No mortality or grade IV morbidities were identified. Twenty-one grade III morbidities requiring intervention were identified. The most common morbidity was pleural effusion (19%) and pneumothorax (14%) at diaphragmatic stripping/resection site. Median progression-free survival was 17.3 months (systematic error [SE], 5.83; 95% CI 5.83-28.73). Median overall survival was 53 months (SE, 5.43; 95% CI 42.35-63.65).

Conclusions: This is the first phase II study of HIPEC showing satisfactory survival outcomes in ovarian cancer. Results from an ongoing randomized trial (NCT01091636, www.ClinicalTrials.gov) of HIPEC for ovarian cancer are awaited.

Long-term survival advantage of intraperitoneal chemotherapy treatment in advanced ovarian cancer: An analysis of a Gynecologic Oncology Group ancillary data study

D. Tewari, J. Java, R. Salani, D. Armstrong, M. Markman, T. Herzog, B. Monk, J. Chan
1Southern California Permanente Medical Group, Los Angeles, CA, 2Gynecologic Oncology Group, Buffalo, NY, 3The Ohio State University, Columbus, OH, 4Johns Hopkins Kimmel Cancer Center, Baltimore, MD, 5Cancer Treatment Centers of America, Philadelphia, PA, 6New York Presbyterian Medical Center, New York, NY, 7Creighton University School of Medicine, Phoenix, AR, 8UCSF Comprehensive Cancer Center, San Francisco, CA
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

S7

Objective: To determine the long-term survival of advanced ovarian cancer patients after intraperitoneal (IP) chemotherapy.

Methods: Data from Gynecologic Oncology Group clinical trials 114 and 172 were collected. Cox proportional hazards regression models were used for statistical analyses.

Results: Among 876 patients, the median survival of IP vs. intravenous (IV) therapy was 61.8 and 51.4 months after extended follow-up (P=0.048). IP therapy was associated with a 17% decrease risk of death (adjusted hazard ratio [AHR]=0.83, 95% CI: 0.71–0.97; P=0.02). Prognostic factors associated with improved survival after IP therapy included: younger age (AHR=1.01, 95% CI: 1.01–1.02; P=0.001), better performance status (AHR=0.75, 95% CI: 0.56–0.99; P=0.049), non-clear cell/mucinous histology (AHR=0.36; 95% CI: 0.26–0.49; P<0.001), low-grade histology (AHR=0.75, 95% CI: 0.56–0.99; P=0.049), and microscopic residual disease (AHR=0.53, 95% CI: 0.45–0.63; P<0.001). Further, the survival advantage of IP therapy was evident in those with macroscopic disease (IP vs. IV: 65% vs. 58%) and gross residual disease (IP vs. IV: 44% vs. 35%). Those who completed 5 or 6 cycles of IP therapy had a 5-year overall survival of 59% compared to 18% vs. 33% with 1 or 2 vs. 3 or 4 cycles, respectively (P<0.001). Younger patients and those with microscopic residual disease were more likely to complete 6 cycles.

Conclusions: The advantage of IP over IV therapy extends beyond 10 years. Younger age, better performance status, microscopic residual disease, non-clear cell histology were important prognostic factors associated with long-term survival after IP therapy. IP therapy was beneficial in those with gross residual disease.

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Education Symposium I: Unraveling the Mysteries of TCGA
Saturday, March, 9, 2013, 10:45 a.m.-12:00 p.m.
Concourse Hall (Los Angeles Convention Center)
Moderators, Abstracts: 7-11: Douglas Levine, MD, Memorial Sloan-Kettering Cancer Center, New York, NY. Christopher Crum, MD, Harvard Medical School Brigham and Women’s Hospital, Boston, MA

7

A novel strategy to identify ovarian cancer molecular signaling pathways and drug repurposing candidates
E. Al Sawah, D. Marchion, X. Xiong, I. Ramirez-Diaz, F. Abbasi, N. Bou Zghieb, X. Stickles, P. Judson Lancaster, R. Wenham, J. Lancaster
H. Lee Moffitt Cancer Center, Tampa, FL

Objective: Ovarian cancer (OVCA) has the highest mortality of all gynecologic cancers, in part due to an incomplete understanding of the molecular basis of disease development and a paucity of highly effective therapeutic options. We present a novel strategy to identify new and existing drugs that selectively target pathways associated with the development and survival from OVCA.

Methods: We compared genomewide expression data from normal ovarian surface epithelium (NOSE) and OVCA from a total of 814 samples within 4 Affymetrix gene expression datasets: 1) Moffitt (MCC) (U133Plus: 28 NOSE, 78 OVCA); 2) Total Cancer Care (TCC) (HuRSTA: 12 NOSE, 57 OVCA); 3) the Cancer Genome Atlas (TCGA) (U133A: 8 NOSE, 568 OVCA); and 4) MD Anderson (MDA) (U133Plus: 10 NOSE, 53 OVCA). Datasets were analyzed for differentially expressed genes using SAM t-test and pathway representation via Metacore software. Common differentially expressed pathways (>3 datasets) were evaluated for associations with survival in 5 OVCA datasets: 1) MCC, n=142; 2) TCC, n=55; 3) TCGA, n=497; 4) MDA, n=53; and 5) AUS, n=220, based on principal component analysis (PCA) modeling. In vitro expression of identified pathways was correlated with sensitivity of 59 cancer cell lines to 48,000 agents. Activity of identified agents on OVCA proliferation was evaluated in vitro.

Results: Four pathways were differentially expressed between NOSE and OVCA in all 4 datasets and 32 pathways common to >3 datasets: 1) Cytoskeleton remodeling/TGF-WNT,2) Immune response/Alternative complement pathway, 3) Immune response/MIF, and 4) Integins. Expression of 3 of these pathways was associated with OVCA survival in >2 datasets. Pearson’s correlation of pathway expression and cancer cell sensitivity identified agents associated with expression of the integrin (n=25; P<0.001), WNT2 (n=14; P<0.001), and TGF/ WNT (n=81; P<0.0001) pathways. In vitro evaluation of a selection of agents (including mequitazine, dasatinib, and artesunate) predicted to target pathways showed antiproliferative activity against OVCA.

Conclusions: Our integrated in silico and in vitro analysis of NOSE and OVCA datasets has identified pathways associated with carcinogenesis and overall survival as well as agents predicted to target them. This strategy has the potential to identify new therapeutic candidates or established drugs that may be successfully repurposed for use in OVCA.

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8

Identification of master regulators of cisplatin resistance in ovarian cancer
H. Dinkelspiel, A. Iyer, C. Lefebvre, J. Wright, S. Lewin, T. Herzog, J. Kitajewski, A. Califano
Columbia University College of Physicians and Surgeons, New York, NY

Objective: To identify and validate transcription factors that regulate cisplatin resistance in high-grade serous ovarian cancer.

Methods: We assembled a genomewide, regulatory network from The Cancer Genome Atlas (TCGA) ovarian cancer dataset. We further interrogated this dataset by comparing patients who were resistant to cisplatin treatment with those who were sensitive to treatment. Using Master Regulator Interference algorithm (MARINa), we identified master regulators, transcription factors that are differentially active between the 2 groups of patients. MARINA is an algorithm for the unbiased inference of transcription factors that implement a specific cellular phenotype to produce experimentally validated, cell context-specific maps of molecular interactions. Candidate master regulators were assessed for expression and siRNA-mediated silencing, followed by assessment of cisplatin sensitivity in intrapatient, paired tumor cell lines. The cell lines were derived from high-grade serous ovarian cancer patients with initial platinum sensitivity and subsequent platinum resistance, PEO1/PEO4. Western blot analysis was used to assess putative master regulator expression, and cell viability was measured after cisplatin treatment.

Results: The Ovarian Cancer Interactome from TCGA identified 30 potential master regulators of cisplatin resistance and sensitivity. Among other genes, MARINA inferred that PAX2 expression was downregulated in cisplatin resistance. Western blots showed that PAX2 was undetected in PEO4, the cisplatin-resistant cell line, and expressed in PEO1, the cisplatin-sensitive cell line. PAX2 siRNA silencing was confirmed by western blot, and reduction of PAX2 decreased the sensitivity of PEO1, as shown using a cisplatin cell viability assay (Figure).

Conclusions: Computational analysis has identified 30 potential regulators or biomarkers of cisplatin sensitivity. Among these, PAX2 is differentially expressed in cisplatin-resistant and -sensitive cell lines, and PAX2 silencing results in acquisition of the resistant phenotype in the PEO1 cell line. We conclude that PAX2 is a potential target for in vivo study of cisplatin resistance in mouse xenografts, and if validated, for study in targeted pharmacologic therapy in humans.
9 Molecular determinants for lymph node metastasis in early-stage endometrial cancer
N. Bou Zghohei1, D. Marchioni2, I. Ramirez2, P. Teefey, P. Judson Lancaster3, R. Wenham3, S. Apte3, J. Lancaster3, J. Gonzalez Bouquet1
1University of South Florida College of Medicine, Tampa, FL, 2H. Lee Moffitt Cancer Center, Tampa, FL

Objective: While the majority of patients with endometrioid type endometrial cancer (EC) present with early-stage disease, a significant subset have occult nodal metastasis and are prone to develop recurrence with worse outcomes. Identified clinicopathologic risk factors for nodal metastasis have low predictive value and are not uniformly applied. Our objective is to add molecular parameters (gene and protein expression) to the existing clinicopathologic criteria to improve lymph node (LN) metastasis prediction.

Methods: Using publicly available data on patients with EC collected by The Cancer Genome Atlas, we performed a univariate analysis of differentially expressed genes (n=262), proteins, and clinicopathologic parameters (n=200), including myometrial invasion and tumor grade), comparing EC patients with and without LN metastasis. Only those molecular and pathologic parameters found to be significant in the univariate analysis were introduced in the multivariate model. All independently significant molecular factors were evaluated in a pathway enrichment analysis with MetaCore 6.0 (www.genego.com) to identify biologic processes that may participate in LN invasion in EC.

Results: LN metastasis was associated with the expression of 268 unique genes (P=0.001), 19 unique proteins (P<0.05), tumor grade, and myometrial invasion in univariate analysis. The multivariate analysis demonstrated 10 genes independently associated with LN metastasis in EC (RSL, RNFI83, DNER, DUSP19, TEX19, RP66KA6, FBN3, MUC6, GABBRQ, FLJ16779), and 4 independently associated proteins (EF2K, EGFRI, PDK1, YB). Myometrial invasion was the only independent clinicopathologic parameter associated with LN status in EC. The enrichment pathway analysis demonstrated that the expression of EGFGR, Rcl2 antagonist of cell death, and PTEN pathways (P ≤10-4) to be significantly involved in LN metastasis. A gene expression signature to predict LN status in EC was created for future reference and validation.

Conclusions: Few studies have focused on the association between molecular characteristics of EC and the presence of nodal metastasis. Defining molecular risk factors for EC LN metastasis may help to individualize surgical and overall EC treatment and improve outcomes of patients.

10 Separating the good, the bad, and the ugly: New directions in genomic prediction of outcome in ovarian cancer
B. Zand, C. Ivan, C. Pecot, R. Rupaimoole, H. Dalton, J. Bottsford-Miller, W. Hu, A. Nick, A. Sood
The University of Texas, MD Anderson Cancer Center, Houston, TX

Objective: To identify genomic predictors of overall survival in women with high-grade serous ovarian cancer.

Methods: Massive data analysis of The Cancer Genome Atlas dataset of high-grade serous epithelial ovarian cancer was carried out with “training” (n=375) and “validation” (n=188) datasets. A software program code was written specifically to identify genes with high expression that gave the greatest predictive potential for patient survival. The top 10 lowest sums of the validation set were chosen to be included with Kaplan-Meier survival curves for analysis.

Results: The 10 genes with high expression that had the smallest P values in their respective order were: SLC6A1, LIPK, EHPB1, SUSD5, PEX3, SLC22A3, RABGFI1, PPM2C, KIAA1219, and GALNT10. The range of P value sum ranged from 2.4E-4 to 9.9E-4. The lowest P value was for SLC6A1, which encodes for GABA transporter-1 (GAT1) that removes GABA from extracellular to intracellular space. Interestingly, 4 of the 10 genes predictive for poor outcome are directly involved in cell metabolism: LIPK, PPM2C, PEX3, and GALNT10. The median overall survival (OS) of the high gene expression group ranged from 28.3 to 41.5 months. The median OS of the low gene expression group ranged from 44.4 to 64.8 months. The median OS difference of high gene vs. low gene expression groups ranged from 12.3 to 26.5 months. EHPB1 gene, involved in endocytic trafficking of transferrin into endosomes and GLUT4 into adipocytes, had the biggest difference in median OS between high and low expressions at 26.5 months. Finally, low expression of PPM2C compared to its high expression was significantly associated with >5 year survival and no recurrence in both training and validation sets (10.1% vs. 1.1%; P=0.001; 12.5% vs. 2.2%, P=0.04, respectively). PPM2C encodes for pyruvate dehydrogenase-phosphatase 1 that catalyzes the dephosphorylation and reactivation of the alpha subunit of the EI component of the pyruvate dehydrogenase complex. Pyruvate dehydrogenase complex in the active form transforms pyruvate from glycolysis to acetyl-CoA in the mitochondria to be used in TCA cycle for energy production when converted to citrate.

Conclusions: Genes involved in cell metabolism, neurotransmitter functioning, and endocytic trafficking are highly predictive of outcome in women with high-grade serous ovarian cancer. These pathways likely reflect novel and important therapeutic targets.

11 The Eph Family: Not playing nice in uterine cancer
H. Dalton, C. Ivan, C. Pecot, R. Rupaimoole, B. Zand, J. Bottsford-Miller, W. Hu, A. Nick, R. Coleman, A. Sood
The University of Texas, MD Anderson Cancer Center, Houston, TX

Objective: The Eph family of receptor tyrosine kinases is known to play seminal roles in cancer growth and metastasis in many solid tumors. We sought to analyze its role in endometrial cancer.

Methods: Level 3 data from The Cancer Genome Atlas was used to assess the clinical significance of all 14 Eph receptors available in the database (EphA1 through 8, EphA10, EphB1 through 4, and EphB6). We also examined gene methylation status and copy number changes in these tumors. Clinical information extracted included age, body mass index (BMI), tumor histology, tumor grade, clinical stage, estrogen (ER)/progesterone (PR) receptor status, and overall survival.

Results: A total of 320 samples were available for analysis. Increased EphA2, EphA4, EphB1, and EphB2 expression was significantly correlated with poorer overall survival (P=0.03, P=0.04, P=0.01, and P=0.008, respectively) and lack of ER and PR expression (r=-0.34, P=2.25E-6; r=0.24, P=0.0007; r=-0.22, P=0.002; r=-0.46, P=2.38E-11, respectively). Compared to endometrioid histology, serous histology was associated with increased expression of EphA2 (P=0.0001), EphA4 (P=0.0002), EphB1 (P=0.0001), and EphB2 (P=0.0001). Similarly, grade 3 tumors demonstrated increased expression of EphA2 (P=0.03), EphA4 (P=0.006), EphB1 (P=0.001), and EphB2 (P=0.0001) compared to lower-grade samples. EphA2, EphB1, and EphB2 expression was higher in samples from patients with advanced stage (FIGO Stage IIIA-IVB) when compared to those with early-stage disease (P=0.008, P=0.0183, and P<0.001, respectively). Patients age >63 years had greater tumoral expression of EphA4 (P=0.0001) and EphB2 (P=0.001). Increased copy number correlated with EphB2 expression (r=0.41, P=0.001). Gene methylation inversely correlated with EphA2, EphA4, EphB1, and EphB2 receptor expression (r<-0.22, P<0.0001; r<-0.26, P=0.0002; r<-0.23, P<0.0006; r<-0.21, P<0.003, respectively). No significant relationship between Eph receptor expression and BMI was observed. In a multivariate analysis, stage and Eph expression were the strongest independent predictors of poor survival, and EphA4 was the most significant predictor (P=0.0024).

Conclusions: Concordant with emerging roles of the Eph receptor in driving malignant biology, increased EphA2, EphA4, EphB1, and EphB2 expression are predictive of poor patient outcome and constitute attractive targets for biologic therapies.
Education Symposium II: Survivorship and Symptom Management
Saturday, March, 9, 2013, 10:45 a.m.-12:00 p.m.
Petree Hall C (Los Angeles Convention Center)
Moderators, Abstracts: 12-17: Paula Anastasia, MN, RN, AOCN, Cedars Sinai Medical Center, Los Angeles, CA, Cecelia Boardman, MD, Medical College of Virginia, Richmond, VA

12 Cognitive function during chemotherapy for front-line treatment of ovarian, primary peritoneal or fallopian tube cancer: A Gynecologic Oncology Group study
L. Hess1, H. Huang1, W. Robinson1, R. Johnson1, D. Alberts1
1Indiana University School of Medicine, Indianapolis, IN, 2Gynecologic Oncology Group, Buffalo, NY, 3Tulane Medical School, New Orleans, LA, 4Kansas University Medical Center, Westwood, KS, 5The University of Arizona Cancer Center, Tucson, AZ

Objective: Changes in cognitive function that occur during and following chemotherapy treatment have been identified in and reported by many cancer survivors. These changes have the potential to affect patient quality of life and functional ability. Little research has been conducted on this issue in ovarian cancer. Therefore, this prospective longitudinal study was designed to quantify the incidence of change in cognitive function in newly diagnosed ovarian cancer patients throughout and following primary therapy.

Methods: Patients were eligible if they had a new diagnosis of ovarian cancer and no prior chemotherapy or radiation therapy but were planning to receive 6 cycles of platinum/paclitaxel-based chemotherapy. Web-based and patient-reported cognitive and patient quality-of-life assessments were conducted before chemotherapy, before cycle 4, after cycle 6, and 6 months after completion of primary therapy. Each patient served as her own control to measure changes from baseline, with a decline of 1.5 standard error of measurement per cognitive domain defined as a cognitive impairment.

Results: A total of 1,018 of 1,924 (53%) survivors completed surveys. Of the 557 survivors (55%) who reported of SD, 64% had SD during/after cancer treatment. There were no differences in body mass index, ethnicity, alcohol use, or household income between respondents with or without SD. Compared to patients without SD, those with SD were younger at time of diagnosis (54 vs 47 years, P<0.01) and at time of survey (60 vs 56 years, P<0.01). Disease site was associated with SD (P=0.005), with highest prevalence in ovarian cancer survivors (42.5%). Univariate analysis showed significant associations between SD and hot flashes (P<0.001), bowel (P<0.001) and bladder (P<0.003) symptoms, prior treatment with chemotherapy and/or radiation therapy compared to surgery alone (P<0.001), and anxiolytic/antidepressant medication use (P<0.003). In multivariate analysis, hot flashes, bowel complaints, urinary urgency, and treatment history were associated with SD (P<0.05). Patients who received chemoradiation were more likely to experience SD (odds ratio=4.5; 95% CI [2.0, 10.0]) compared to all other patients. Survivors with SD also reported bowel and urinary problems as among the most significant health concerns affecting quality of life.

Conclusions: SD in gynecologic cancer survivors is a common problem that may persist for years after treatment completion. Previous studies found untreated SD to affect antitumor immune response and overall survival. SD is closely associated with fatigue, productivity, and quality of life. Efforts should focus on screening and treating these health issues because they not only affect SD but may ultimately impact survival.

13 Sleep disturbances: A critical issue among gynecologic cancer survivors
C. Tung1, S. Westin1, C. Sun1, R. Lacour1, L. Meyer1, M. Schlumbrech1, D. Bodurka1
1Baylor College of Medicine, Houston, TX, 2The University of Texas, MD Anderson Cancer Center, Houston, TX, 3Louisiana State University Health Science Center, Shreveport, LA, 4University of Texas Medical School at Houston, Houston, TX, 5Banner Health, MD Anderson Cancer Center, Houston, TX

Objective: Cancer survivors often report sleep disturbances (SD) that affect quality of life, productivity, and overall health. The purpose of this study was to evaluate the prevalence of SD and identify risk factors of SD among gynecologic cancer survivors.

Methods: A detailed survey of 18 health issues was mailed to gynecologic cancer survivors seen at a comprehensive cancer center from 1997-2007. Respondents were asked to disclose demographics, treatment history, and current health concerns. This abstract focuses on patients whose SD during cancer treatment and persisted after treatment was completed. SD was defined as “unable to fall asleep/stay asleep through the night.” Differences between groups were examined by Chi-square and Mann-Whitney and Kruskal-Wallis tests. Multivariable regression was used to determine associations between SD and risk factors.

Results: A total of 1,018 of 1,924 (53%) survivors completed surveys. Of the 557 survivors (55%) who reported of SD, 64% had SD during/after cancer treatment. There were no differences in body mass index, ethnicity, alcohol use, or household income between respondents with or without SD. Compared to patients without SD, those with SD were younger at time of diagnosis (54 vs 47 years, P<0.01) and at time of survey (60 vs 56 years, P<0.01). Disease site was associated with SD (P=0.005), with highest prevalence in ovarian cancer survivors (42.5%). Univariate analysis showed significant associations between SD and hot flashes (P<0.001), bowel (P<0.001) and bladder (P<0.003) symptoms, prior treatment with chemotherapy and/or radiation therapy compared to surgery alone (P<0.001), and anxiolytic/antidepressant medication use (P<0.003). In multivariate analysis, hot flashes, bowel complaints, urinary urgency, and treatment history were associated with SD (P<0.05). Patients who received chemoradiation were more likely to experience SD (odds ratio=4.5; 95% CI [2.0, 10.0]) compared to all other patients. Survivors with SD also reported bowel and urinary problems as among the most significant health concerns affecting quality of life.

Conclusions: SD in gynecologic cancer survivors is a common problem that may persist for years after treatment completion. Previous studies found untreated SD to affect antitumor immune response and overall survival. SD is closely associated with fatigue, productivity, and quality of life. Efforts should focus on screening and treating these health issues because they not only affect SD but may ultimately impact survival.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

2) more information for patients about self-management of treatment-related for: 1) better awareness by primary care physicians about presenting symptoms, 2) more information about managing adverse effects, 26% would require an extra 4-6 months of life, and 21% were willing to try a drug that gave them 1-2 months extra life irrespective of adverse effects, 26% would require an extra 4-6 months of life, and 21% required >11 months extra. However, the majority (87%) were willing to try a drug that improved their quality of life, but might not extend their life.

Conclusions: These results indicate relationships between patient self-reports of spirituality presurgery and an important proinflammatory and proangiogenic cytokine (IL-6) as well as important psychosocial correlates of spirituality. These findings may have implications for clinical care of ovarian cancer patients.

Objective: Ovarian cancer (OC) management is often palliative and aims to reduce the symptoms of disease without creating too many extra burdens and iatrogenic harms. We wished to examine United Kingdom (UK) patients’ experience of and preferences for treatment and care and identify the most bothersome symptoms and adverse effects, how well these are monitored, the types and amounts of information patients require about the disease, treatment options, and preference for follow-up.

Methods: Women with stage II-IV ovarian cancer from 16 centers across the UK were invited to join an interview study (face-to-face or by telephone) about their treatment and care preferences. Preference for quality versus length of life was examined in a hypothetical scenario together with current quality of life and information needs.

Results: One hundred seventy-five women have been interviewed to date, with a mean age of 63 years (range, 31 - 81 years). Their main presenting symptom was abdominal swelling (91/175 [52%]). Many had other symptoms and repeated visits to primary care physicians before referral and diagnosis for OC. Carboplatin plus paclitaxel was the most usual first-line treatment and 82/161 (51%) had chemotherapy presurgery. During chemotherapy, the most difficult adverse effects with which to cope were fatigue/lethargy (89/166 [54%]), hair loss (86/166 [52%]), constipation (63/166 [38%]), and numbness of fingers/toes (51/166 [31%]). Follow-up care was extremely variable after chemotherapy; some had none, others had 3 monthly appointments. Not all included CA125 blood tests and scans. Supportive care was also patchy, with some cancer centers providing access to dieticians, psychologists, and complementary and alternative medicine therapists and others offered no access. 25% of women were willing to try a drug that gave them 1-2 months extra life irrespective of adverse effects, 26% would require an extra 4-6 months of life, and 21% required >11 months extra. However, the majority (87%) were willing to try any drug that improved their quality of life, but might not extend their life.

Conclusions: These preliminary results reveal an alarming variability in management policies and care in the UK of OC patients, highlighting the need for: 1) better awareness by primary care physicians about presenting symptoms, 2) more information for patients about self-management of treatment-related adverse effects, 3) an update to health-care practitioner guidelines about follow-up policies. Most of the patients in this survey wanted management programs that enhanced quality of life, not just quantity of life.

16 Results of timely palliative medicine consultation on end-of-life care outcomes for women with gynecologic malignancies

N. Nevadunsky, S. Gordon, L. Spozsak, K. Harris, E. Riveria, A. Van Arsdale, B. Rapkin, P. Selwyn, G. Goldberg

Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

Objective: Quality of end-of-life care has recently been measured using distinct outcome variables that have been used to improve care. Many of these variables are related to aggressive care interventions in patients at the end of life (ACE). Our objective was to compare the ACE scores of patients with and without a timely palliative medicine consultation at the end of life. Our hypothesis was that an early palliative medicine consultation would result in lower ACE scores at the end of life.

Methods: A retrospective study of the medical records of the past 100 consecutively cared for patients who died from their primary gynecologic malignancies at a single institution was performed. ACE scores were computed for each patient using the following metrics: admission to intensive care unit within 30 days of death, hospital admission more than 14 days in the last 30 days of life, more than 1 hospital admission during the past 30 days of life, more than 1 emergency department visit during the last 30 days of life, death in an acute care setting, initiation of a new chemotherapy during the last 30 days of life, last chemotherapy within 14 days of death, and hospice admission less than 3 days before death. Using the Mann-Whitney U Test, we compared median ACE scores of patients receiving a palliative medicine consultation more than 30 days before death to the group of women who either received no palliative medicine consultation or received consultation fewer than 30 days before death.

Results: Forty-nine percent of patients had a palliative medicine consultation, and the median number of days from consultation to death was 16 days (range, 0-159 days). 18% of patients had palliative medicine consultation more than 30 days before death, with the median number of days from consultation until death being 63 days (range, 33-159) in this group. The median ACE score for patients with palliative medicine consultation more than 30 days before death was 0 (range, 0-3) versus 2 for those receiving no palliative medicine consultation or consultation fewer than 30 days before death (range, 0-6) (P=0.025) (Table).

Conclusions: At our institution palliative medicine consultation resulted in lower ACE scores when compared to patients without a timely palliative medicine consultation. It would be important to validate improved patient quality of life following palliative medicine consultation with prospective testing of quality of life assessments in patients with gynecologic malignancies at the end of life.

Table. Indicators of Aggressive Care at the End of Life

<table>
<thead>
<tr>
<th>Events Occurring within the Last 30 Days of Life</th>
<th>Total (n=100)</th>
<th>Palliative Care* (n=18)</th>
<th>No Palliative Care** (n=82)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median ACE score (range)</td>
<td>1 (0-6)</td>
<td>0 (0-3)</td>
<td>2 (0-6)</td>
<td>0.025</td>
</tr>
<tr>
<td>Chemotherapy within the last 14 days of life</td>
<td>9</td>
<td>0</td>
<td>9 (11%)</td>
<td>0.14</td>
</tr>
<tr>
<td>New chemotherapy</td>
<td>9</td>
<td>0</td>
<td>9 (11%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Hospice ≥3 days</td>
<td>11</td>
<td>1 (5.5%)</td>
<td>10 (12%)</td>
<td>0.4</td>
</tr>
<tr>
<td>≥1 emergency department visit</td>
<td>9</td>
<td>1 (5.5%)</td>
<td>2 (2.4%)</td>
<td>0.48</td>
</tr>
<tr>
<td>≥1 hospital admission</td>
<td>13</td>
<td>1 (5.5%)</td>
<td>12 (15%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Death in acute care setting</td>
<td>42</td>
<td>5 (28%)</td>
<td>37 (43%)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*Patients with ≥30 days of palliative care
**Patients with <30 days of palliative care
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

17 Palliative medicine consultation at the end of life decreases inpatient hospital costs in women with gynecologic malignancies
N. Nevadunsky, S. Gordon, L. Spouzak, E. Rivera, K. Harris, A. Van Arsdale, P. Selwyn, B. Rapkin, G. Goldberg
Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

Objective: Evidence suggests that palliative care consultations in patients at the end of life decreases costs while improving quality of life. However, there is a paucity of data on the impact of a palliative medicine consultation on these costs for women with gynecologic malignancies. Our objective was to compare the direct inpatient hospital costs in the last month of life in women with and without a timely palliative medicine consultation.

Methods: Data were abstracted from the medical records of the past 100 patients who died from their gynecologic malignancies. Inpatient direct costs were calculated for the last 30 days of life. These included hospital stay, radiologic studies, blood bank, medications, and procedures. Using the Mann-Whitney U test, we compared median direct hospital costs in patients receiving a palliative medicine consultation >14 days (timely) before death and those receiving either no palliative medicine consultation or receiving consultation in <14 days before death (not timely).

Results: Data were evaluable for 98 patients, 28 of whom had a timely palliative medicine consultation. Median costs for those who had a timely palliative care consultation in the last 30 days of life was $3,246 (range, 0-$52,720) compared with $8,098 (range, 0-$36,749) (P=0.007) for those who did not receive timely consultation. There was a significant difference in median cost per day during the last 30 days of life: $613 (range, 0-$1,757) for patients who had a timely palliative medicine consultation vs $702 (range, 0-$63,545) for patients who did not (P=0.002). There was a difference in the total cost for the last 14 days of life for patients with timely (median, $0 [range, $0-$18,184]) compared to those without timely consultation (median, $5,106 [range, $0-$26,795]) (P<0.01). Additionally, there was less cost per day in patients who had a timely consultation versus those who did not (median of $0 [range, $0-$679] vs median of $676 [range, $0-$3,545]) (P=0.007). There was a significant difference in the percentage of patients with timely palliative consultation admitted to the hospital within the last 14 days of life compared with those who did not have a consultation (35.7% vs 71.4%, Pearson's Chi-squared: P=0.001).

Conclusions: At our institution, a palliative medicine consultation resulted in lower inpatient overall and daily costs when compared to a lack of timely consultation. It would be important to validate cost savings following palliative medicine consultation with prospective testing in patients with gynecologic malignancies.

Scientific Plenary II - Surgical Advances
Saturday, March 9, 2013, 3:15 p.m.–4:45 p.m.
Concourse Hall (Los Angeles Convention Center)

Moderators, Abstracts: 18-23: Amanda Nickles Fader, MD, Greater Baltimore Medical Center/Johns Hopkins Medical Institutions, Baltimore, MD. Michael Frumovitz, MD, The University of Texas, MD Anderson Cancer Center, Houston, TX

19 What is the role of retroperitoneal exploration in optimally debulked stage IIC epithelial ovarian cancer? A Gynecologic Oncology Group ancillary data study
B. Rungnagul1, A. Miller2, T. Krivak3, N. Horowitz4, N. Rodriguez5, C. Hamilton6, M. Bookman7, G. Maxwell8, S. Richard9
1Georgia Health Sciences University, Augusta, GA, 2Gynecologic Oncology Group Statistic Data Center, Buffalo, NY, 3Mage-Womens Hospital of UPMC, Pittsburgh, PA, 4Brigham & Women’s Hospital, Boston, MA, 5Loma Linda University Medical Center, Loma Linda, CA, 6Walter Reed Army Medical Center, Washington, DC, 7University of Arizona, Tucson, AZ, 8Inova Fairfax Hospital Women’s Center, Fairfax, VA, 9Hahnemann University Hospital, Philadelphia, PA

Objective: To determine the effect of retroperitoneal (RP) exploration on progression-free (PFS) and overall survival (OS) in epithelial ovarian cancer (EOC) patients with intraperitoneal (IP) stage IIC disease who underwent optimal debulking surgery in a large, multi-institutional trial.

Methods: Demographic, pathologic, surgical, and outcome data were collected from GOG 182 records of stage IIC EOC patients cytoreduced to no gross residual disease (NGRD) or minimal (<1 cm) gross residual disease (MGRD) at primary debulking surgery. Those patients with stage IIC disease by IP tumor were included and divided into 3 groups: 1) those with >2 cm IP tumor without lymph node involvement (IP/RP- group), 2) those with >2 cm IP tumor with lymph node involvement (IP/RP+ group), and (3) those with >2 cm IP tumor with no RP exploration (IP/RP0). The effects of disease distribution and RP exploration on PFS and OS were assessed using Kaplan-Meier and Proportional Hazards methods.

Results: Of 4,312 women with stage III or IV EOC who were enrolled on GOG 182, 1,876 patients had stage IIC disease with >2 cm IP tumor, underwent primary debulking surgery to optimal residual disease (<1 cm), and were included in this analysis. Of these, 699 (37.3%) underwent RP exploration with removal of at least 1 lymph node and 1,177 (62.7%) did not. There were 293 (15.6%) in the IP/RP- group, 406 (21.7%) in the IP/RP+ group, and 1,177

18 Predictive role of biology in the feasibility of optimal versus suboptimal cytoreduction in advanced serous ovarian cancer
H. Lee Moffitt Cancer Center, Tampa, FL

Objective: Cytoreductive surgery is the cornerstone of advanced ovarian cancer (OVAR) treatment. Detractors of initial maximal surgical effort argue that the initial extent of disease correlates with aggressive tumor biology, which will dictate survival, not the surgical effort. We aim to investigate the role of biology in achieving optimal cytoreduction in serous OVAR using microarray gene expression analysis.
(62.7%) in the IP/RP group. Overall, RP exploration was associated with improved PFS (18.5 vs. 15.9 months [mo], P<0.0001) and OS (53.3 vs. 42.7 mo, P<0.0001) vs. no exploration (Figure). This trend was noted in both the NGRD and MGRD patients, but only reached statistical significance in the latter group with better PFS (16.7 vs. 15.1 mo, P=0.0028) and OS (45.2 vs. 40.4 mo, P=0.0017) vs. no exploration. The IP/RP group had better PFS (21.7 vs. 15.9 mo, P<0.0001) and OS (63.1 vs. 42.7 mo, P<0.0001) vs. the IP/RP group. Among those with RP exploration, the IP/RP group had better PFS (21.7 vs. 17.1 mo, P=0.0055) and OS (63.1 vs. 46.1 mo, P=0.0014) vs. IP/RP+.

Conclusions: Evidence in this large multi-institutional trial suggests that RP exploration at the time of primary debulking surgery of patients with IP stage IIIC EOC may provide survival benefit.

Figure 1. Progression-free (A) and Overall Survival (B) for Stage IIIC epithelial ovarian cancer patients with intraperitoneal tumor >2cm who did and did not undergo retroperitoneal exploration with removal of at least one lymph node at the time of primary debulking surgery.

20
Phase II trial of robotic cyberknife radiation therapy in patients with recurrent gynecological malignancies

C. Kunos, J. Brindle, S. Singh, G. Pettigrew, R. DeBernardo
Case Western Reserve - MacDonald Women’s Hospital, Cleveland, OH

Objective: Robotic cyberknife radiation therapy has been shown to provide a significant benefit in progression-free survival in 2 limited case series targeting patients with recurrent gynecologic malignancies. The therapeutic impact of cyberknife treatment on progression of disease (PD) in the setting of disease recurrence was evaluated in this phase II trial.

Methods: Between July 2009 and September 2011, 50 patients with measurable recurrent disease to undergo cyberknife therapy. The cohort included patients with recurrent ovarian (n=25), endometrial (n=14), cervical (n=9), and vulvar (n=1) cancers. Each patient had received at least one chemotherapy or radiation regimen and had a Gynecologic Oncology Group performance status of 0, 1, or 2. Patients underwent image guided cyberknife therapy and received a total of 2400 cGy delivered in 3 daily doses of 800 cGy. Using noncontrast CT and 18F-FDG PET/CT overlays, both the radiation and gynecologic oncologists determined treatment planning and target volumes. The primary endpoints were 6-month clinical benefit rates (complete response + partial response + stable disease)/50] and less than 30-day toxicities.

Results: The median posttherapy follow-up period was 9 months. At 3 months, 50% (n=25) had a complete response, 46% (n=23) had a partial response, and 4% (n=2) had stable disease in targeted lesions. Overall, 52% (n=26) eventually had PD of nontarget lesions and 36% (n=18) died from PD. Thirty-three patients had a PD-free interval of at least 6 months, resulting in a clinical benefit rate of 66%. Less than 30-day toxicities included grade 2 fatigue (n=9, 18%), grade 2 nausea (n=3, 6%), grade 3 nephropathy (n=2, 4%), and grade 4 hyperbilirubinemia (n=1, 2%).

Conclusions: This is the first phase II trial of robotic cyberknife radiation therapy to demonstrate a clinically relevant benefit in the setting of recurrent gynecologic malignancy. Despite excellent control of targeted lesions with minimal toxicity, the rates of PD outside of targets remain high. We are currently evaluating cyberknife radiation therapy with concurrent chemotherapy to control nontargeted lesions in a phase I clinical trial.

21
Lymphoscintigraphic detection in sentinel node biopsy for early cervical cancer: Results of the SENTICOL study

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Objective: To evaluate the feasibility and detection ability of lymphoscintigraphy (LS) as well as anatomic location of preoperative sentinel nodes (SNs) in the SN technique applied to early cervical cancer.

Methods: In this multicenter prospective study (January 2005-June 2007), patients with early cervical cancer (FIGO stage IA with emboli to IB1) received intracervical injection of 60 or 120 MBq of radioactive tracer the day before (long protocol) or the morning (short protocol) of surgery, followed by preoperative lymphoscintigraphy. Intraoperative SN detection used a combined technetium/Patient Blue labeling technique. SNs were electively sampled and a systematic bilateral pelvic lymphadenectomy was performed by laparoscopy. Following centralized review of LSs, we assessed feasibility, detection, and anatomic location of preoperative SNs.

Results: One hundred forty-five patients were enrolled and 139 included in a modified intention-to-disease analysis. Isotopic injection was performed in 133 patients and preoperative LS in 131 of 133 (98.5%) patients, including, respectively, 31 and 98 short and long protocol. Lymphoscintigraphic detection rate was 87.8%, with a median number of SNs per patient of 2 (range, 1-4). In multivariate analysis, age (odds ratio [OR]=0.41 [0.23-0.66] P<0.001) and protocol (short vs. long) (OR=8.23 [2.01-41.9] P=0.005) were independent factors significantly influencing preoperative detection. The preoperative bilateral detection rate was 67%, independently influenced by age (OR=1.06 [1.02-1.09] P<0.001) and time between isotopic injection and lymphoscintigraphy (OR=5.42 [2.21-13.27] P<0.001). Although 60.5% of preoperative SNs were located in the external iliac territory, unusual drainage was identified in common iliac (19.6%), para-aortic (10.8%), and parametrical (6%) areas in a significant number of cases.

Conclusions: Our study demonstrates the feasibility and good detection rate of preoperative lymphoscintigraphy. Our high rate of SNs in unexpected territories appears interesting to guide intraoperative detection. Further studies are still needed to better evaluate preoperative detection and to assess the contribution of lymphoscintigraphy to intraoperative detection.

22
Sentinel lymph node mapping: A valuable tool for assessing nodal metastasis in low grade endometrial cancer with superficial myoinvasion

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Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

**Objective:** To report the incidence of nodal metastasis in patients who present with low-grade endometrioid cancer (G1, G2) and with <50% myoinvasion on final pathology using a sentinel lymph node (SLN) mapping protocol that includes pathologic ultrastaging.

**Methods:** All patients who underwent endometrial cancer staging surgery with attempted SLN mapping for preoperative G1/G2 tumors and had <50% invasion on final pathologic assessment of the uterus were included. In all cases, a cervical injection of blue dye was performed. SLNs were examined by routine hematoxylin and eosin (H&E) stain, and if negative, by a standardized institutional ultrastaging protocol that involved additional sectioning and immunohistochemistry staining to detect low-volume micrometastasis and isolated tumor cells.

**Results:** Between 9/2005 and 12/2011, 426 patients met the inclusion criteria. Preoperative endometrial sampling included 321 (75.4%) G1 and 105 (24.6%) G2 endometrioid tumors. On final pathology, the histologic types were: 416 (97.7%) endometrioid, 5 (1.2%) serous, 1 (0.2%) clear cell, 1 (0.2%) carcinosarcoma, and 3 (0.7%) undifferentiated. Fourteen (3.3%) patients who had preoperative G1 or G2 tumors were upgraded to G3 disease on final pathology. Two hundred forty-one (56.6%) patients had no myoinvasion and 185 (43.4%) had <50% invasion. At least one SLN was detected in 347 (81.5%) cases. Lymph node metastasis was found in 27 (6.3%) patients with endometrioid histology on final pathology. This included 11 (2.6%) patients on routine SLN H&E, 3 (0.7%) patients with micrometastasis in SLN on ultrastaging, 10 (2.3%) patients with isolated tumor cells in SLN on ultrastaging, and 3 (0.7%) patients on assessment of non-SLNs. No nodal metastasis was found in the 14 patients who had G3 disease on final pathology.

**Conclusions:** The use of a SLN mapping algorithm with pathologic ultrastaging allows detection of nodal disease in a presumably low-risk group of patients who, in some practices, may not undergo any nodal evaluation. Approximately half of the node-positive patients had low-volume disease discovered upon ultrastaging. These data emphasize the value of adding a SLN mapping protocol to the surgical staging strategy of apparent early endometrial cancer. The clinical significance of low-volume nodal disease detected only by ultrastaging requires further investigation.

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**Detection of sentinel lymph nodes using indocyanine green and near-infrared fluorescence imaging for gynecological malignancies**


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**Objective:** To assess the detection rate of sentinel lymph nodes (SLNs) for gynecologic malignancies using indocyanine green (ICG) and near-infrared (NIR) fluorescence imaging.

**Methods:** NIR fluorescence imaging for the robotic platform was obtained at our institution in December 2011. We identified all cases planned for SLN mapping using fluorescence imaging from 12/2011 to 7/2012. ICG was the fluorophore used in all cases. The ultimate concentration believed to be optimal was 1.25 mg/mL. ICG 4 mL was injected into the cervix alone divided into the 3- and 9-o’clock positions, with 1 mL deep into the stroma and 1 mL submucosally before initiating laparoscopically. Lymphazurin was concurrently injected in some cases and in the same way as described for ICG. Appropriate statistical tests were used.

**Results:** Seventy-seven cases were performed. The median age was 60 years (range, 28-87 years). The median body mass index was 29.9 (range, 17.9-49). The final histology was a gynecologic malignancy in 74 cases (96.1%): uterine (n=63), cervix (n=10), and ovary (n=1). In 3 cases, the final pathology was complex atypical hyperplasia of the uterus. ICG alone was used in 47 (61%) cases and both ICG and Lymphazurin were used in the others. The median time to perform the SLN mapping was 29 minutes (range, 3-84 minutes). The median SLN count was 4 (range, 1-13). A SLN was identified in 75 (97.4%) cases, with bilateral pelvic mapping possible in 62 (80.5%) cases. An aortic SLN was identified in 5 (7%) of the 75 mapped cases. All patients were mapped in cases where ICG alone was used compared to a mapping rate of 93% (28/30) in cases where both dyes were used (P=0.1). Bilateral mapping was seen in 39/47 (83%) ICG cases and 23/30 (76.7%) ICG and Lymphazurin cases (P=0.2). Metastatic disease was identified in the SLN in 7 cases (9.1%). In patients with no cancer identified in the SLN, 22 patients (31%) also had a complete lymph node dissection (LND), with 1 case of cancer identified in the additional LND for a false-negative rate of 4.5%.

**Conclusions:** NIR fluorescence imaging with ICG using the robotic platform has a very high bilateral SLN detection rate and appears to be favorable compared to other reports using blue dye alone and/or other modalities. Combined use of both ICG and Lymphazurin appears unnecessary.

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**24 Phase I/II study of the PARP inhibitor (PARPi) olaparib (O/AZD2281) in combination with carboplatin (C) in ovarian cancer (OvCa) patients with BRCA1/2 mutations (OvCaMUT+) and high grade serous OvCa (HGSOCS) with low genetic risk (NCT00647062)**

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**Objective:** Olaparib (O) is a PARPi with single-agent activity against OvCa in BRCA1/2MUT+ carriers. Approximately 50% of HGSOCS are deficient in homologous recombination due to germline BRCA1/2MUT+ or acquired deficits in DNA double-strand break repair. We hypothesized that the addition of C to O to stress the DNA repair machinery would improve the clinical benefit of O in OvCaMUT+ and HGSOCS.

**Methods:** A 3x3 dose escalation design incorporated continuous daily O capsule at 100 and 200 mg q 12 hour (dose level [DL] 1/2) with C AUC3 on day 8 and then every 21 days; DL6-9 gave O q 12 hours days 1-7 at 200 then 400 mg, with C on days 1 and 2. O was escalated to a maximum OUC 5 expansion cohorts administered the maximum tolerated dose (MTD). No more than 8 O/C cycles were administered, after which O was given daily. Response Evaluation Criteria in Solid Tumors (RECIST) response was assessed every 2 cycles. Peripheral blood mononuclear cells were collected before cycle 1, day 3 or day 7, and before cycle 2.

**Results:** Fifty-four pts (37 OvCaMUT+ + BRCAMut+1/2both: 27/81; BRCApro score 68%; 17 HGSOCS) were treated. All pts were previously exposed to platinum (6-82 months (mo) from last platinum; median 15), with 21 platinum-resistant and 16 refractory. Dose-limiting toxicity was marrow suppression in both cohorts. MTD was O 400 mg q 12 hours days 1-7, with C AUC3 in OvCaMUT+ and AUC4 in HGSOCS. Grade 3/4 events included neutropenia (38%), thrombocytopenia (25%), anemia (13%), and fatigue (6%). 9 pts prematurely discontinued C due to either allergic reaction (4) or myelosuppression (5). 14/21 pts with C AUC5 required PEG-filgrastim on at least 1 cycle. Of 45 evaluable pts, partial response (PR) was seen in 14/33 (42%) OvCaMUT+ (4-35+ cycles; median 15.5) and 4/13 (31%) HGSOCS (4-11 cycles; median 8). Stabilization occurred in 14/33 (42%) OvCaMUT+ (4-35+ cycles; median 15.5) and 4/13 (31%) HGSOCS (4-11 cycles; median 8). Stabilization occurred in 14/33 (42%) OvCaMUT+ (4-30+ cycles; median 11.5) and 8/13 (62%) HGSOCS (4-14 cycles; median 7.5). This yielded a clinical benefit rate of 85% in OvCaMUT+ and 92% in HGSOCS. Of 26 evaluable platinum-resistant/refractory pts, 4 PR (22%; 6-22 cycles; median 6.5) and 10 stable disease (SD) (56%; 4-30 cycles; median 11) were seen in 18 OvCaMUT+, 2 PR (18%; 4 cycles, 11) and 5 SD (45%; 4-14 cycles; median 5) were seen in 11 HGSOCS. O/C yielded clinical benefit in platinum-resistant/refractory OvCa (78% OvCaMUT+ and 88% HGSOCS).

**Conclusions:** O 400 mg bid days 1-7 with C AUC3/5 q 21 days is active and tolerable in OvCaMUT+ and HGSOC pts. Interactive marrow suppression was observed, although early discontinuation of carboplatin did not appear to prejudice outcome. Resistance to platinum did not significantly decrease the activity of the O/C combination in OvCa.
25
A phase-I trial of a novel autologous oxidized whole-tumor antigen vaccine therapy for recurrent ovarian cancer
University of Pennsylvania Medical Center, Philadelphia, PA

Objective: To examine the use of an enhanced, more rapid, and more immunogenic dendritic cell vaccine platform developed for clinical testing. Application of this novel immunotherapy platform composed of dendritic cell (DC)-based autologous whole tumor antigen vaccination is evaluated in a pilot study of patients with recurrent ovarian cancer.

Methods: To determine the optimal tumor lysate preparation for loading DCs, we compared three different lysate treatments: freeze-thaw cycles only, ultraviolet B-irradiation, and hypochlorous (HOCl) oxidation. We evaluated the ability of DCs to engulf tumor lysate, produce cytokines and chemokines, induce allogeneic T-cell proliferation, and finally control tumor growth. In our phase I study, 15 patients (age 58.6±7.03 years) with recurrent stage IIIB-IV epithelial ovarian cancer with available tumor lysate from surgery underwent intranodal vaccination with OC-DC, an autologous DC preparation pulsed with HOCl oxidized autologous tumor cells (5-10x10^6 DC per dose, planned 5 doses every 2 weeks) alone or in combination with bevacizumab. Feasibility, safety, and biological and clinical efficacy were evaluated.

Results: DCs loaded with HOCl-oxidized lysate produced the highest levels of Th1-priming cytokines and chemokines and controlled tumor growth in vitro with the highest progression-free survival. Therefore, our patients received a mean 6.5 (range, 2-25) intranodal vaccinations with OC-DC, which produced limited grade 1 toxicities. The vaccination elicited tumor-specific T-cell responses against various ovarian tumor antigens, including HER-2/new, MUC1, NYESO-1, mesothelin, and WT1. The percent of peripheral T regulatory cells and sera IL-10 was reduced in four of five patients analyzed postvaccination. Eight (53%) patients exhibiting antitumor immune response showed clinical benefit (6/15 [40%] stable disease and 2/15 [13.3%] no evidence of disease), which correlated with high interleukin-12 production. Furthermore, patients experienced prolonged progression-free survival, with two patients experiencing remission inversion (24 and 25 months) on vaccine maintenance. (ClinicalTrials.gov, NCT01132014).

Conclusions: We developed a DC-HOCl-oxidized whole-tumor lysate vaccine that was safe and well-tolerated alone or in combination with bevacizumab. This is the first comprehensive study to define the optimal tumor lysate preparation for DC-based therapy and the first study demonstrating the long-lasting efficacy of DC-HOCl-oxidized tumor lysate therapy.

26
Combination of irinotecan and bevacizumab for heavily pretreated recurrent ovarian cancer: A phase II trial
New York University School of Medicine, New York, NY

Objective: Irinotecan and bevacizumab have single-agent activity in both platinum-sensitive and -resistant recurrent ovarian cancer. We sought to evaluate the efficacy and safety of irinotecan in combination with bevacizumab in these patients. The primary end point of the study was to estimate the progression-free survival (PFS) rate at 6 months. Secondary objectives included overall survival, observed response rate, duration of response, and toxicity.

Methods: Patients with recurrent ovarian cancer who had received any number of prior regimens were eligible. Irinotecan 250 mg/m^2 (amended to 175 mg/m^2 after treatment-related toxicities in the first 6 patients) and bevacizumab 15 mg/kg every 3 weeks were administered until disease progression or toxicity. Response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) every 2 cycles and by CA-125 criteria for those patients without measurable disease.

Results: Thus far, 25 of the planned 35 patients have been enrolled in the study. The median age was 61 years (range, 45-78 years). Seven patients were platinum-sensitive and 18 patients were platinum-resistant. The median number of prior regimens was 5 (range, 1-12), with 10 patients having received prior bevacizumab-containing therapies and 9 patients prior topotecan-containing therapies. The median number of study treatments received was 6 cycles (range, 1-25 cycles); 4 patients withdrew after only 1 cycle (3 due to toxicity and 1 due to physician discretion). Of the 19 patients assessable for response at this time, 5 patients experienced partial response (PR), 11 patients maintained stable disease (SD), and 3 patients had progressive disease. Eleven of the patients with PR/SD were platinum-resistant. The observed clinical benefit rate (PR+SD) was 68% (95% CI: 50%, 86%) for the 25 enrolled patients (intention to treat). Durable responses were observed, with 9 patients having longer than 24 weeks of sustained response. The median PFS was 8.1 months, and the median overall survival was 15.9 months. The PFS rate at 6 months was 56% (95% CI: 36%, 74%). Grade 3/4 neutropenia was observed in 2 patients (1 prior to protocol amendment) and grade 3 diarrhea in 5 patients (2 prior to protocol amendment).

Conclusions: Results of this trial to date showed encouraging activity of the combination of irinotecan and bevacizumab in heavily pretreated recurrent ovarian cancer. The median PFS of 8.1 months exceeds that of bevacizumab alone in a similar population from GOG-170D. The main dose-limiting toxicities were diarrhea and neutropenia.

27
A phase II evaluation of AZD6244, a selective MEK-1/2 inhibitor in the treatment of recurrent or persistent endometrial cancer: A Gynecologic Oncology Group study
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Objective: Activation of the mitogen-activated protein kinase pathway (MAPK) plays a pivotal role in cell proliferation and is a frequent event in endometrial cancer. We sought to evaluate the efficacy and safety of AZD6244, a selective MEK-1/2 inhibitor, in women with recurrent endometrial cancer.

Methods: This was a phase II, single-arm, open-label, two-stage trial, utilizing response and 6-month progression-free survival (PFS) as the primary endpoints. The study looked for 15% to 20% increases at the 10% level of significance with 90% power. Eligible patients were required to have measurable disease, at least 1 but no more than 2 prior cytotoxic chemotherapy regimens, and a performance status of 0-2. AZD6244 dosing was 75 mg bid orally every day until progression or intolerance. One cycle was 28 days.

Results: Fifty-four patients were enrolled; 4 were excluded due to wrong histology (1), improper prestudy treatment (1), inadequate pathology (1), and never treated (1), currently leaving 50 evaluable for efficacy and toxicity. Three patients are pending pathology review. Median age was 62 years; histology was endometrioid (62%), serous (16%), and mixed (20%). Grade 1/2 endometrioid tumors were seen in 36%. Fifteen patients (30%) had 2 prior cytotoxic regimens. The median number of courses administered was 2 (range, 1-29). Overall 3 (6%) patients had objective response (1 complete response, 2 partial responses); 13 had stable disease as the best response. The proportion of patients with 6-month PFS was 22%. Median PFS and overall survival were 2.4 months and 8.4 months, respectively. Drug-attributed grade 3 and 4 toxicities observed (25%) were fatigue (14%), anemia (10%), pain (10%), extremity edema (8%), and dyspnea (6%). There was one grade 4 infection (renal) and one death due to progression and liver dysfunction.

Conclusions: AZD6244 was tolerable in this population but will not meet pretrial specifications for clinical efficacy regardless of final eligibility. Translational endpoints, including fibroblast growth factor/MAPK pathway aberrations, are pending.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

28 Phase 0 study: Prospective evaluation of the molecular effects of metformin on the endometrium in women with newly diagnosed endometrial cancer
The University of Texas, MD Anderson Cancer Center, Houston, TX

Objective: Metformin reduces cancer incidence and improves overall survival in diabetic patients. Preclinical studies have shown that metformin decreases endometrial cancer cell growth by activation of AMPK and mTOR inhibition. The purpose of this study was to determine the molecular effects of metformin on endometrial cancer cells in women diagnosed with endometrial cancer.

Methods: In this institutional review board-approved, prospective trial, women with newly diagnosed endometrial cancer underwent pretreatment endometrial biopsy, were administered oral metformin 850 mg daily for a minimum of 7 days, and then underwent definitive surgery. Immunohistochemical analyses of tumor tissue from the pre- and posttreatment samples were compared to evaluate molecular changes in the PI3K/AKT pathway (PTEN, phosphoAKT, phosphoS6 ribosomal protein), apoptosis (caspase 3), proliferation (Ki67), and AMPK activity (Ras-MAPK and phosphoACC).

Results: Fifteen patients completed the study. Median age and body mass index were 56.9 years (range, 27-68 years) and 37.4 (range, 21.9-50.0). Median waist circumference was 113 cm (range, 80-156 cm). Median duration of metformin treatment was 10 days (range, 7-24 days). A majority of women had endometrioid adenocarcinomas (86.7%) with the following grades: 1 (5/13 [38.5%]), 2 (7/13 [53.8%]), and 3 (1/13 [7.7%]). Most were stage IA (13/15 [86.7%]); the remaining were stage IB (1/15 [6.7%]) and IIIC (1/15 [6.7%]). After treatment with metformin, there was decreased expression in phosphoACC (5/13 [38.5%]), phosphoAKT (66.7% [8/12]), and Ras-MAPK (6.7% [1/15]). In the posttreatment samples, there was increased expression in phosphoACC (3/13 [23.1%]), phosphoAKT (86.7% [11/13]), and Ras-MAPK (76.9% [10/13]). There was no difference in Ki67, phosphoACC, or caspase 3 expression in pre- and posttreatment samples. Both low- and high-grade tumors demonstrated decreases in pS6, phosphoAKT, and Ras-MAPK.

Conclusions: In this prospective phase 0 study, we demonstrated that relevant molecular changes occur in endometrial cancer cells, even with a short course of low-dose metformin. Downregulation of the AKT pathway may be associated with mTOR inhibition and a decrease in cell growth. This is the first study to assess the direct effect of metformin on the endometrium in women with newly diagnosed endometrial cancer.

29 Endpoints in clinical trials: What do our patients consider important? A survey of the Ovarian Cancer National Alliance (OCNA)
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*The University of Texas, MD Anderson Cancer Center, Houston, TX; †University of Alabama at Birmingham, Birmingham, AL; ‡Columbia University College of Physicians and Surgeons, New York, NY

Objective: Recent editorials in response to the magnitude of risk: benefit from published phase III clinical trials have claimed that incremental benefits seen in intermediate endpoints such as progression-free survival (PFS) are insufficient to warrant drug approval, particularly in the absence of overall survival (OS) gains. We sought to characterize measures of efficacy and toxicity frequently collected in these trials among patient survivors with ovarian cancer to provide the patient's perspective to the debate.

Methods: A 28-question anonymous online survey was constructed and distributed to the OCNA membership requesting opinions on clinical trial endpoints, drug-related toxicities, type and magnitude of treatment effects they deemed important, and impact of therapy on their quality of life. Hypothetical clinical scenarios were also presented to assess treatment effects: toxicity, which resonated with respondents as “minimally acceptable” for use.

Results: Over a 3-week period, 2,218 visits were made to the questionnaire website from which 1,063 full and 366 partially completed surveys were recorded (64% response rate). The general demographic of respondents were age 51-60 years (38%), Caucasian (94%), history of ovarian cancer (94%), and have suffered recurrence (62%). Of those who have had recurrences, 52% have been treated with 4 or more chemotherapeutic regimens. 22% have participated in a clinical trial. When asked what minimum benefit in PFS and OS a new drug would have to achieve to be meaningful to them, 77% and 84% chose 5 or more months, respectively. When asked to choose between a PFS gain of 3-4 months without toxicity or a OS gain of 5-6 months with triple the rate of neurotoxicity, 44% chose the latter; notably, 37% found neither acceptable. However, 55% felt a treatment that produced stable disease without an OS gain would be acceptable. This was significantly more acceptable among those with recurrent disease (P < 0.001). When presented the option treatment “cure,” 34% reported that infection would be an unacceptable adverse effect. However, rates of unacceptable toxicity doubled in every category when cure was presented as “unlikely.”

Conclusions: Surveyed patients with a personal history of ovarian cancer have high expectations for treatment with regard to efficacy and toxicity. Tradeoffs are strongly influenced by expectations of outcome and personal history of current treatments.

Surgical Forum I: Scientific Surgical Films
Sunday, March 10, 2013, 2:15 p.m.-3:45 p.m.
Concourse Hall (Los Angeles Convention Center)
Moderators, Surgical Films: 30-38: Jubilee Brown, The University of Texas, MD Anderson Cancer Center, Houston, TX; Kenneth Kim, MD, University of North Carolina Medical School, Chapel Hill, NC

30 Radical resection of intravascular & intracardiac tumor
P. Ramirez*, I. Gregoric*, A. Vaporiyan*, S. Lucchini*
*The University of Texas, MD Anderson Cancer Center, Houston, TX; †Hospital Nacional de Clinicas, Cordoba, Argentina

Objective: To demonstrate surgical removal of intravascular and intracardiac tumor and to provide a detailed technique of vascular exposure and control of bleeding.

31 Laparoendoscopic single-site surgery ("LESS"): Class III radical hysterectomy and pelvic lymphadenectomy
A. Tergas, A. Nickles Fader
Johns Hopkins Hospital, Baltimore, MD

Objective: To demonstrate the indication and technique for laparoendoscopic single-site ("LESS") class III radical hysterectomy and pelvic lymphadenectomy. LESS represents one of the latest innovations in minimally invasive surgery and has several potential applications in gynecologic oncology surgery.

32 Robotic assisted modified posterior exenteration with total intracorporeal primary sigmoid rectal anastomosis
P. Lim
Center of Hope at Renown Regional Medical Center, Reno, NV

Objective: To demonstrate a robotic surgical technique in performing an en bloc resection of uterus, fallopian tubes, ovaries, and pelvic and cul de sac peritoneum along with sigmoid resection for stage II ovarian cancer.
33 Robotic splenectomy for ovarian cancer
R. Holloway, J. James
Florida Hospital Cancer Institute, Orlando, FL

Objective: To describe a novel and safe technique for robotic-assisted laparoscopic splenectomy in a patient with recurrent ovarian cancer.

34 How to approach suspicious lymph nodes on the upper abdomen
L. Chiva, A. Gonzalez-Martin, S. Alonso, F. Lapuente
MD Anderson International Spain, Madrid, Spain

Objective: To show some recommendations when dissection of lymph nodes above the renal vessels is indicated. The video contains surgical cases of patients with tumor-infiltrated lymph nodes in the following anatomic areas: suprarenal vessels, porta hepatitis, celiac trunk, cisterna chyli, splenic hilum and pleuropericardial recess. It demonstrates the anatomic boundaries of these surgical locations as well as practical tips to improve skills when performing these procedures.

35 Laparoendoscopic single-site radical hysterectomy for treatment of early cervical cancer
D. Boruta, L. Bradford
Massachusetts General Hospital/Brigham and Women's Hospital, Boston, MA

Objective: Performance of radical hysterectomy via laparoendoscopic single-site surgery (LESS) demonstrates the potential of LESS to be safely used for completion of even the most technically challenging of gynecologic surgical procedures. We hope to spur further interest in the development of this exciting approach within minimally invasive surgery.

36 Robotic total intracorporeal pelvic exenteration: Maximally invasive pelvic surgery performed in a minimally invasive fashion
K. Levinson1, L. Weinberg2, M. Moslemi-Kebrab2
1Cleveland Clinic, Cleveland, OH, 2The Cleveland Clinic Foundation, Cleveland, OH

Objective: This surgical film demonstrates techniques to perform a robotic total intracorporeal pelvic exenteration with construction of an ileal conduit, end colostomy, and small bowel reanastomosis. Critical lessons learned are demonstrated.

37 Identification of sacral plexus at robot-assisted nerve-sparing radical hysterectomy with extended lymphadenectomy
Y. Lee, O. Chong, G. Hong
Kyungpook National University, Daegu, Republic of Korea

Objective: A robotic system has technical advantages over laparoscopic surgery because it increases the precision and accuracy of anatomic dissection, especially deep pelvic tissue. We used the da Vinci system to demonstrate the surgical technique of identifying the sacral plexus as part of robot-assisted nerve-sparing radical hysterectomy with extended lymphadenectomy for early cervical cancer. Understanding the anatomy of the deep sacral plexus is necessary to prevent nerve injury in cases of extensive lymphadenectomy for high-risk cervical cancer.

38 Laparoscopic radical hysterectomy for bulky early-stage cervical cancer
J. Nung, I. Park, D. Kim, J. Kim, Y. Kim, Y. Kim
University of Ulsan College of Medicine, Asan Medical Center, Seoul, Republic of Korea

Objective: To present the surgical technique of laparoscopic radical hysterectomy in patients with bulky (> 4 cm) early-stage cervical cancer (FIGO stage IB2 or IIA2).

39 Rural-urban disparity in declining ovarian cancer mortality rates: Analysis of US death records data from 1999 to 2009
A. Melamed1, J. Rauh-Hain1, R. Clark2, L. Bradford2, A. Goodman2, M. Del Carmen1, W. Growdon3, D. Boruta3, J. Schorge4
1Massachusetts General Hospital/Brighton and Women's Hospital, Boston, MA, 2Massachusetts General Hospital/Harvard University, Boston, MA

Objective: In the United States (US), ovarian cancer mortality rates have decreased among women of most racial and ethnic groups. Since access to centers specializing in ovarian cancer treatment is greater in urban centers, we hypothesized that the recent decline in ovarian cancer mortality has been more pronounced in highly urban areas than in more rural ones.

Methods: The Multiple-Cause-of-Death database, which contains all US deaths from 1999-2009, was quarried using the Centers for Disease Control and Prevention's internet-based WONDER interface. Ovarian cancer deaths were identified using ICD-10 codes. Age-adjusted rates were calculated using National Center for Health Statistics (NCHS) population estimates and Prevention's internet-based WONDER interface. Ovarian cancer deaths were identified using ICD-10 codes. Age-adjusted rates were calculated using National Center for Health Statistics (NCHS) population estimates.

Results: We identified 163,725 ovarian cancer-related deaths in the US during the study period. Overall age-adjusted mortality rates declined by 13% during the study period (relative risk [RR] 0.87, CI 0.85-0.89). Of these deaths, 89% occurred among non-Hispanic white women, whose age-adjusted mortality rate declined by 12% (RR 0.88, CI 0.86-0.90) from 1999 to 2009. Among whites, ovarian cancer mortality rates were higher in urban centers (5.8 deaths per 100,000 person-years, CI 5.7-5.8) than in rural counties (5.1 deaths per 100,000 person-years, CI 5.0-5.2). Between 1999 and 2009, there was a statistically significant difference in the decrease of the ovarian cancer rates between whites residing in the most and least urban counties in the US (P<0.04). The rate of ovarian cancer-associated mortality declined by 17% (RR 0.83, CI 0.79-0.87) in urban centers, this rate declined by 6% (RR 0.94, CI 0.88-0.99) in rural counties. Secular trends in annual ovarian cancer-related mortality rates for highly urban and rural counties are illustrated in the Figure.
Conclusions: Over the last decade, ovarian cancer-related mortality has declined. Improvements in mortality rates between 1999 and 2009 were significantly greater in urban areas than in rural ones. Although absolute differences between urban and rural mortality rates may result from reporting variation, differing trends are likely to represent true phenomena. Our findings are consistent with a disparity of access to those centers that have made progress in ovarian cancer treatment during this study period.

40 Black and white women in Maryland receive different treatment for cervical cancer
S. Temkin, S. Fleming, N. Schluterman, J. Tracy
University of Maryland, Baltimore, MD

Objective: Despite an overall decrease in incidence, the death rate from cervical cancer (CC) in the United States and the state of Maryland remains higher in black (B) women than their white (W) counterparts. When W and B women receive equivalent treatment, they have similar outcomes. Prior studies suggest that stage at diagnosis, socioeconomic, or insurance factors may account for treatment differences more than race. We examined the Maryland Cancer Registry (MCR) to determine factors in initial treatment that may explain differences in CC outcomes between W and B women in the state of Maryland.

Methods: The MCR is a population-based registry of incident solid tumors in the state. This study analyzed MCR data from the years 1999-2008 and included 2,034 incident CC cases.

Results: During the study period, B women had an annual CC incidence of 12.1 per 100,000 women, compared to 9.7 per 100,000 women for W women. B women were more likely to have locally advanced or metastatic disease at diagnosis (53.5% versus 45.7%; P<0.01). Both races were increasingly likely to receive chemotherapy as the study period progressed, but B women were more likely to receive chemotherapy than W women (P<0.01). When adjusted for stage (S) and insurance status (I), the odds of receiving chemotherapy for B women was 1.43 (CI 1.11-1.82). Overall, B women were more likely to receive any radiation or chemotherapy combined with radiation (P<0.01). The odds ratio for receipt of radiation, comparing B to W women, was 1.50 (CI 1.20 – 1.87) when adjusted for S and I. The odds ratio for receipt of external beam radiation without brachytherapy for B women was 1.58 (CI 1.27 - 1.97). W women were more likely to receive surgery than B women (69.6% versus 54.3%; P<0.01). This difference in receipt of surgery remained significant, even when adjusted for S and I, with an odds ratio of 0.51 (CI 0.41-0.65) comparing B to W women.

Conclusions: Surgical treatment for newly diagnosed CC in the state of Maryland was significantly less common among B than W women during our study period. B women were also more likely to complete radiation without brachytherapy, a treatment that requires a surgical intervention. Limited access to a gynecologic oncologist for surgical care is likely to contribute to racial disparities in outcomes for women with CC.

41 Efficacy of the human papillomavirus vaccination in women aged 20–45 years with high-grade cervical intraepithelial neoplasia treated by loop electrosurgical excision procedure
S. Kim, W. Kang, H. Choi
Chonnam National University Medical School, Gwangju, Republic of Korea

Objective: This study was conducted to determine whether vaccination with the human papillomavirus (HPV) quadrivalent vaccine after a loop electrosurgical excision procedure (LEEP) for high-grade cervical intraepithelial neoplasia (CIN2-3) is effective in preventing recurrent CIN2-3.

Methods: Between August 2007 and July 2010, 737 patients aged 20-45 years with CIN2-3 were treated by LEEP and followed with cytology, the hybrid capture II assay (HC2), and high-dose chemotherapy. There were 360 patients with HPV quadrivalent vaccination and 377 patients without HPV quadrivalent vaccination after LEEP for CIN2-3. The vaccination group received the first vaccination at 1 week after LEEP and 3 doses of quadrivalent HPV vaccine at day 1, month 2, and month 6. Post-conization follow-up was performed at 3, 6, 12, 18, and 24 months during the first 2 years and yearly thereafter.

Results: Irrespective of HPV type, among the 737 patients, 36 (4.9%) developed a recurrence (Table). Nine of 360 patients (2.5%) in the vaccination group developed a recurrent CIN2-3 compared with 27 of 377 patients (7.2%) without vaccination (P <0.01). Five of 198 patients (2.5%) with vaccination and 18 of 211 patients (8.5%) without vaccination developed recurrent disease related to vaccine HPV types (HPV 16 or 18 types) after LEEP (P <0.01). On multivariate analysis, no vaccination with HPV quadrivalent vaccine after LEEP was an independent risk factor for a recurrent CIN2-3 (hazard ratio = 2.840; 95% CI, 1.335–6.042; P <0.01).

Conclusions: Vaccination with quadrivalent HPV vaccine among women aged 20-45 years who had surgical treatment for CIN2-3 is effective protection against recurrent CIN2-3.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

Objective: While endometrial cancer (EC) has an excellent prognosis, survivors are at risk from comorbidities, including secondary primaries. The purpose of this study was to determine the association between positive family cancer history (PCH) and secondary primary cancers in EC survivors.

Methods: Between 11/15/1997 and 7/20/2007, 205 ECs and 199 controls (no cancer history or cancer-free for 5 years) were prospectively enrolled into an observational study. Subjects completed baseline questionnaires regarding PCH, with results confirmed by chart review. PCH was verified by pathology or when unavailable, using the state's tumor registry. The median follow-up (range) for ECs and controls was 77.7 (1.5-82.5) months, respectively; the last date of data entry was 8/23/2012. Statistical methods included ANOVA, χ², and Fisher's Exact tests for measures of association and univariate and multivariate logistical regression to determine effect size.

Results: Controls (Table) were older, menopausal, more likely to use estrogen replacement therapy (ERT)/oral contraceptives (OC), and had lower body mass indexes (BMIs). No differences were observed in menarche, parity, or tobacco/ alcohol use. More ECs had a PFCH (115 [62.8%] vs 90 [45.4%], P=0.002), and ≥2 family members (34.2% vs. 23.7%, P=0.036). These differences were significant for non-Hispanic whites only (P=0.004). As expected, ECs more often reported PFCH consistent with Lynch syndrome (18.0% vs. 6.0%, P<0.001), but not BRCAl-2 (10.1% vs. 7.0%, P=0.29); controlling for Lynch/BRCAl-2, PFCH was still more common in ECs (P<0.004). In multivariate models, adjusting for age, race/ethnicity, BMI, ERT, diabetes, smoking, alcohol, and PFCH, ECs were still significantly more likely to report PFCHs; the number of cancers also increased (test for linear trend 0.015 [odds ratio 1.60, 95% CI 1.10-2.33]). A PCH was also higher among ECs (62 [30.4%] vs. 17 [8.5%], P<0.001). The most common cancers reported in cases were gastrointestinal/colon (17 [21.8%]), breast (14 [17.9%]), ovary (7 [9.0%]), and skin (8 [10.3%]). In controls, the most common cancers were gastrointestinal/colon (3 [17.6%]), breast (6 [35.3%]), and skin (4 [23.5%]).

Conclusions: Both personal family cancer history (PFCH) and secondary primaries (PFCHs) were higher than expected in ECs, a result only partially explained by Lynch/ BRCAl-2 mutation history. The PCH risk will be tested further using appropriate longitudinal modeling/time to event methods. Nonetheless, these results underscore the importance of cancer screening in EC survivors.

Table. Case/Control Demographics and Cancer Risk

<table>
<thead>
<tr>
<th>Variables</th>
<th>EC Cases (205)</th>
<th>Controls (199)</th>
<th>OR (95% CI), P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race/ethnicity</td>
<td>Wald P=0.055</td>
<td>Wald P=0.013</td>
<td></td>
</tr>
<tr>
<td>NHW</td>
<td>192 (49.9%)</td>
<td>118 (59.3%)</td>
<td>0.86 (0.66-1.13), P=0.28</td>
</tr>
<tr>
<td>Hispanic</td>
<td>73 (33.6%)</td>
<td>61 (30.7%)</td>
<td>0.98 (0.64-1.52), P=0.85</td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td>35 (16.8%)</td>
<td>12 (6.0%)</td>
<td>1.08 (0.69-1.71), P=0.71</td>
</tr>
<tr>
<td>Age (± SD)</td>
<td>58.1 ± 0.9</td>
<td>65.1 ± 0.6</td>
<td>0.93 (0.91-0.95), P&lt;0.001</td>
</tr>
<tr>
<td>Menopausal (Y es)</td>
<td>141 (64.8%)</td>
<td>193 (97.0%)</td>
<td>0.07 (0.03-0.16), P&lt;0.001</td>
</tr>
<tr>
<td>Parity (± SD)</td>
<td>2.3 ± 0.18</td>
<td>2.7 ± 0.12</td>
<td>0.54 (0.39-0.76), P=0.006</td>
</tr>
<tr>
<td>Smoking (yes)</td>
<td>78 (39.4%)</td>
<td>95 (47.7%)</td>
<td>0.78 (0.52-1.20), P=0.22</td>
</tr>
<tr>
<td>Alcohol use (yes)</td>
<td>70 (35.0%)</td>
<td>57 (29.7%)</td>
<td>0.97 (0.63-1.50), P=0.90</td>
</tr>
<tr>
<td>PCH</td>
<td>62 (30.2%)</td>
<td>17 (8.5%)</td>
<td>4.64 (2.68-8.29), P&lt;0.001</td>
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<tr>
<td>Race/ethnicity</td>
<td>Wald P=0.002</td>
<td>Wald P=0.004</td>
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</tr>
<tr>
<td>0 family members</td>
<td>74 (37.2%)</td>
<td>108 (54.6%)</td>
<td>0.69 (0.51-0.92), P=0.01</td>
</tr>
<tr>
<td>1 family member</td>
<td>83 (40.9%)</td>
<td>94 (49.0%)</td>
<td>1.07 (0.83-1.38), P=0.56</td>
</tr>
<tr>
<td>≥2 family members</td>
<td>48 (23.9%)</td>
<td>6 (3.0%)</td>
<td>1.06 (0.83-1.38), P=0.56</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>Wald P=0.004</td>
<td>Wald P=0.002</td>
<td></td>
</tr>
<tr>
<td>NHW</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.81 (95% CI 0.43-1.51)</td>
<td>0.81 (95% CI 0.43-1.51)</td>
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<tr>
<td>Non-Hispanic</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>Age (± SD)</td>
<td>0.94 (95% CI 0.91-0.97), P&lt;0.001</td>
<td>0.94 (95% CI 0.91-0.97), P&lt;0.001</td>
<td></td>
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<td>BMIs</td>
<td>1.00 (95% CI 1.04-1.12), P=0.001</td>
<td>1.00 (95% CI 1.04-1.12), P=0.001</td>
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<td>ERT use (yes)</td>
<td>0.14 (95% CI 0.08-0.27), P&lt;0.001</td>
<td>0.14 (95% CI 0.08-0.27), P&lt;0.001</td>
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</tr>
<tr>
<td>Diabetes (yes)</td>
<td>2.15 (95% CI 1.06-4.36), P=0.03</td>
<td>2.15 (95% CI 1.06-4.36), P=0.03</td>
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</tr>
<tr>
<td>Alcohol use (yes)</td>
<td>0.55 (95% CI 0.29-0.96), P=0.04</td>
<td>0.55 (95% CI 0.29-0.96), P=0.04</td>
<td></td>
</tr>
<tr>
<td>PCH</td>
<td>4.64 (2.68-8.29), P&lt;0.001</td>
<td>4.64 (2.68-8.29), P&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>Wald P=0.018</td>
<td>Wald P=0.018</td>
<td></td>
</tr>
<tr>
<td>0 family members</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
<td></td>
</tr>
<tr>
<td>1 family member</td>
<td>2.48 (95% CI 1.25-4.91)</td>
<td>2.48 (95% CI 1.25-4.91)</td>
<td></td>
</tr>
<tr>
<td>≥2 family members</td>
<td>2.26 (95% CI 1.04-4.52)</td>
<td>2.26 (95% CI 1.04-4.52)</td>
<td></td>
</tr>
</tbody>
</table>
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

43 Diet-induced obesity increases tumor aggressiveness in a genetically engineered mouse model of serous ovarian cancer

Y. Rae-Jump1, Y. Zong1, X. Du1, L. Makowskii, W. Jia1, C. Zhou1
1University of North Carolina at Chapel Hill, Chapel Hill, NC, 2University of North Carolina at Charlotte, Charlotte, NC, 3University of North Carolina at Greensboro, Greensboro, NC

Objective: Obesity is associated with increased risk and worse outcomes for ovarian cancer (OC). We theorize that the metabolic effects of obesity may play a contributing role in the pathogenesis of OC and may lead to biologically and phenotypically different cancers than those that arise in normal-weight women. Thus, we sought to examine the effects of obesity on OC development and progression in a genetically engineered mouse model of serous OC.

Methods: We have previously described a unique serous OC mouse model that specifically and somatically deletes the tumor suppressor genes, Brca1 and p53, and inactivates the retinoblastoma (Rb) proteins in adult ovarian surface epithelial cells via injection of an adeno viral vector-expressing Cre (AdCre) into the ovarian bursa cavity of adult female mice (KpB mouse model). At 6 months, tumors develop in the affected ovary, while the uninjected ovary remains normal. KpB mice were subjected to a 60% calories derived from fat high-fat diet (HFD) versus a 10% calories from fat low-fat diet (LFD) to mimic diet-induced obesity (DIO). Untargeted metabolomic profiling was performed using gas chromatography (GC)- and liquid chromatography (LC)-mass spectrometry (MS). The resulting MS data were analyzed using uni- and multivariate statistical methods to determine if there were significant metabolic differences between the tumors from the HFD and LFD mice.

Results: The KpB mice on a HFD demonstrated a >10% increase in body weight in just 1 week (n=14 mice per group). At 6 months of exposure to the HFD or LFD, obese mice were twice the weight of nonobese mice (51 g vs 31 g, P=0.0003). Ovarian tumors were significantly larger in the obese (mean size, 3.7 cm²) vs. nonobese (mean size, 1.2 cm²) mice (P=0.0065). Data from GC-MS metabolomics profiling of tissues indicated statistically significant differences between the 2 groups, and about a dozen metabolites have been identified that contributed to these differences.

Conclusions: This work suggests that the obese state can promote tumor progression in the KpB mouse model of OC, similar to epidemiologic findings in humans. Further work will focus on the investigation of the identified obesity-dependent metabolic biomarkers as well as potential novel targets of treatment that may be specific to obesity-driven ovarian cancers.

44 Self-efficacy, quality of life, and weight loss in overweight/obese endometrial cancer survivors (SUCCEED): A randomized controlled trial

M. McCarron1, H. Frasure5, K. Gill1, M. Kavanagh6, S. Waggoner3, V. Von Gruenigen1
1Summa Health System, Akron, OH, 2University Hospitals Case Medical Center, Cleveland, OH, 3Northeastern Ohio Universities College of Medicine, Akron, OH, 4Case Western Reserve University, Cleveland, OH

Objective: Early-stage endometrial cancer (EC) survivors who are overweight or obese are at increased risk of dying from obesity related comorbidities. The purpose of this study was to improve self-efficacy for the treatment of obesity in EC survivors during a lifestyle intervention program.

Methods: Survivors of early-stage EC who were overweight or obese (n=75) were randomized to: 1) Survivors of Uterine Cancer Empowered by Exercise and Healthy Diet (SUCCEED) (LI), a 6-month lifestyle intervention consisting of nutrition, exercise, and behavioral modification counseling; or 2) a usual care group (UC). Participants completed the Weight Efficacy Lifestyle Questionnaire (WEL) measuring self-efficacy, the FACT-G survey measuring quality of life (QOL), and weight loss outcomes at baseline, 3, 6, and 12 months. Student’s t-test, repeated measures analysis of variance, and Pearson’s correlation coefficient were completed using SPSS 20.0.

Results: Self-efficacy measured by total WEL scores differed significantly between LI (135.3±24.1) and UC (121.3±42.4) at 3 months (P=0.006) as well as LI (136.3±28.2) and UC (125.6±37.2) at 6 months (P=0.003). QOL measured by FACT-G differed significantly between LI (44.6±5.0) and UC (43.6±6.4) at 3 months (P=0.008) in the fatigue domain as well as LI (25.8±2.7) and UC (25.3±2.6) at 6 months, (P=0.048) in the physical domain. Weight loss (kg) was significantly different between LI (91.8±19.35) and UC (94.6±23.80) at 6 months (P<0.001) as well as LI (92.7±20.11) and UC (95.4±25.42) at 12 months (P<0.001). Negative correlations were noted at 6 months in the LI group between body mass index (BMI) and the WEL domains of negative emotions (r=−0.5, P=0.003), physical discomfort (r=0.4, P=0.02), and availability (r=−0.4, P=0.02). Participants who lost at least 1.0 of the calculated BMI had significantly different scores in the UC domains of negative emotions (P=0.003), availability (P=0.03), and positive activities (P=0.04) at 6 months compared with participants who did not lose weight.

Conclusions: The SUCCEED intervention program improved weight loss and overall self-efficacy relative to UC. Interventions using strategies that improve self-efficacy for the self-regulation of eating behavior like SUCCEED can be an effective option for EC survivors. Further robust studies with longer interventions are warranted to improve EC survivorship.

Scientific Plenary VI - Healthcare Outcomes: Charting the Course

Monday, March, 11, 2013, 11:30 a.m.-12:30 p.m.
Concourse Hall (Los Angeles Convention Center)

Moderators, Abstracts: 45-48: Heidi Gray, MD, University of Washington Medical Center, Seattle, WA. Chirag Shah, MD, Pacific Gynecology Specialists, Seattle, WA

45 NCCN treatment guidelines for ovarian cancer: A population-based validation study of structural and process quality measures

R. Bristow, J. Chang, A. Ziaogas, H. Anton-Culver
University of California Irvine - Medical Center, Orange, CA

Objective: To identify structural healthcare characteristics predictive of adherence to National Comprehensive Cancer Network (NCCN) guideline care for ovarian cancer and to validate guideline adherence as a quality process measure associated with improved survival.

Methods: Consecutive patients diagnosed with epithelial ovarian cancer between 1/1/99 and 12/31/06 undergoing a minimum surgical procedure of oophorectomy were extracted from the California Cancer Registry. Adherence to NCCN guideline care was defined by stage-appropriate surgical procedures and recommended chemotherapy. Multivariate logistic regression models were used to identify patient, disease-related, and treatment characteristics independently predictive of NCCN guideline adherence and overall survival.

Results: A total of 13,321 patients were identified. Overall, 37.2% received NCCN guideline-adherent care. High-volume hospitals (≥20 cases/year) accounted for 18.8% of cases, and 16.4% of surgeries were performed by high-volume surgeons (≥10 cases/year). The structural healthcare characteristic most predictive of NCCN guideline adherence was annual ovarian cancer case volume. High-volume hospitals were significantly more likely to deliver guideline-adherent care (50.8%) compared to low-volume hospitals (34.1%, P<0.001). High-volume surgeons were significantly more likely to deliver guideline-adherent care (47.6%) compared to low-volume surgeons (34.5%,
Objective: Concurrent chemosensitizing radiation with brachytherapy has become the standard of care in the treatment of locally advanced cervical cancer. The purpose of this study was to evaluate the likelihood of receiving standard-of-care therapy and treatment outcome based on facility volume using a large national cancer database.

Methods: We identified all patients included in the National Cancer Data Base (NCDB) diagnosed with stage IIB – IIIB cervical cancer from 1/1998 through 12/2010. Patients treated with hysterectomy or pelvic exenteration were excluded from analysis. Demographic, clinicopathologic, treatment, and outcome data were collected. Facility volume was quartiled (with divisions at 28, 62, and 113 patients seen over this time period). Overall survival was determined using the Kaplan-Meier method. Univariate and multivariate analyses were performed to determine variables that affect survival. Factors that were associated with receiving chemotherapy or brachytherapy were identified using chi-square test and binary logistic regression for categorical variables and Mann-Whitney U or Kruskal-Wallis H and multiple linear regression for nonparametric continuous variables.

Results: A total of 27,660 patients were identified, with a median age of 53 years. Stage distribution included 45.5% IIB, 4.9% IIIA, and 49.6% IIIB. Most of the patients were Caucasian (73.0%), were treated in a metropolitan area, had squamous cell histology (83.7%). For the entire cohort, the median survival was 45.7 months (95% CI 44.1-47.3). The percentages of patients receiving concurrent chemotheraphy based on facility volume quartiles were 76.3%, 79.7%, 81.2%, and 82.3% (P<0.001), and brachytherapy were 20.5%, 25.7%, 26.9%, and 26.1% (P<0.005), respectively. Median overall survival by facility volume quartile (Figure) was 42.3 months (range, 39.8-44.8), 48.4 months (range, 45.4-51.4), 51.5 months (range, 48.5-54.5), and 53.8 months (range, 50.1-57.5) (P<0.001) on univariate analysis. When age, stage, and facility volume were entered into a Cox proportional hazards model, all 3 variables significantly predicted overall survival (P<0.005 for all).

Conclusions: Patients with stage IIB-IIIB cervical cancer treated at high-volume centers were more likely to receive concurrent chemoradiation and brachytherapy and experienced better overall survival.

Objective: To report the surgicopathologic findings, postoperative complications, and outcomes in a subset of 715 pts ≥70 years old (yo) who participated in the GOG Lap2 trial, a randomized comparison of laparoscopic versus open surgical staging in clinically early-stage endometrial cancer (EC).

Methods: An ancillary data analysis of the Lap2 trial was performed. Pts were classified into age groups, and descriptive statistics were used to describe demographic, clinical characteristics, and surgicopathologic data. Wilcoxon, Pearson, and Kruskal-Wallis tests were used for univariate and multivariate analysis. Log-rank tests were used to compare progression-free survival (PFS) and overall survival (OS).

Results: There were 715 pts ≥70 yo and 160 patients ≥80 yo. Pts ≥70 yo had a lower body mass index (P<0.001) and higher performance status (P<0.001) compared to pts <70 yo. Pts ≥70 yo more frequently had serous carcinoma (21 vs 8%; P<0.001), higher-stage disease, (stage IB disease 19% vs 10%; P<0.001; lymph vascular space invasion 25% vs 18%; P<0.001) and more lymph node metastasis (12% vs 9%; P=0.009) compared to women <70 yo. There was a higher rate of conversion to laparotomy in pts ≥70 yo (29% vs 24%; P=0.039). There were no differences in intraoperative complications by age. In the laparotomy group, any grade ≥2 postoperative complication occurred more commonly with increasing decade of age (P=0.002). Pts ≥70 yo had higher recurrence rates (15% vs 8%; P<0.001) and poorer OS (73% vs 91% at 60 months; P<0.001) than pts <70 yo, with cause of death significantly more associated with disease and treatment. When pts were assigned to GOG 99/ PORTEC 1 and 2 high-intermediate risk (HIR) criteria, >90% of pts ≥70 yo met HIR criteria. Despite this, fewer pts ≥70 yo who met HIR criteria were given adjuvant therapy compared to younger age groups (42% vs. 77% in 70-80 yo vs ≤50 yo; P<0.001). In multivariate analysis, factors associated with OS included age (P<0.001; hazard ratio [HR] 1.06), stage IVB disease (P<0.001; HR 4.41), poor tumor grade (P<0.005; HR 2.06), and lymph vascular space invasion (P=0.002; HR 1.52). Lymph node status was not significant.

Conclusions: This is the largest study of prospectively evaluated elderly pts with EC. In this group of pts, surgery was well tolerated, with some increase in postoperative complications for laparotomy pts. Pts ≥70 yo have higher risk features, with nearly all meeting GOG 99/PORTEC HIR criteria. Despite this, only 42% of pts between 70 and 80 yo were given adjuvant therapy. Evaluation of specific risks of recurrence and indications for adjuvant therapy are warranted in this population.
48 The Affordable Care Act and its impact on the care of gynecologic oncology patients in the absence of Medicaid expansion in central Virginia
M. Courtney-Brooks1, C. Engelhard2, E. Pelkoński2, L. Duskal1
1University of Kentucky Health System, Charlottesville, VA, 2University of Virginia, Charlottesville, VA

Objective: Many new gynecologic oncology (GO) patients in the central Virginia referral area are uninsured and their care is supplemented through Disproportionate Share Hospital (DSH) funds. With the implementation of the Affordable Care Act (ACA), DSH funding will decrease sharply beginning in 2014. Our objective was to estimate how many of the new referrals to the GO service per year will lose access to care in the event the state forgoes Medicaid expansion.

Methods: All women with a new patient visit to the GO service of a single institution between July 1, 2010 and July 1, 2012 were identified. Data were collected regarding age, race, referral diagnosis, payor, and state pay-scale assignment. Of note, pay-scale 1 (PS1) matches the federal poverty level (FPL). Assumptions in our study model include: 1) the pay-scale, calculated using formulas that include income, dependents, and assets, is a surrogate for income; (2) in Virginia, women who are not on Medicaid with an income <100% of the FPL will be ineligible for discounted insurance through health exchanges and thus will not purchase health insurance; and (3) the reduction of DSH funds will result in a reduction of the current free-care pool.

Results: There were 1,623 referrals to the GO service over the study time period. The majority were white (83%), with smaller percentages of black (11%) and Hispanic (0.8%) patients. Among the study population, 44% had commercial insurance, 5.6% had Medicaid, 31% had Medicare, and 10.4% were uninsured. 361 (22%) women were classified as PS1. In this subgroup, 32% were uninsured, 24% had Medicaid, 26% had Medicare, and 10% had commercial insurance. Thirty percent of PS1 patients were minorities and 47% of black women were PS1. Greater than half of PS1 patients (52.5%) had a malignancy, with the most common being endometrial, cervical, and ovarian cancers. Of note, 52% of new patients with cervical cancer were PS1.

Conclusions: A substantial proportion of GO patients in central Virginia have an income <100% of the FPL. Uninsured women in this category are likely to have difficulty affording care once DSH funds are no longer available. This phenomenon will be particularly prevalent in states with lean Medicaid and who opt out of the Medicaid expansion, such as Virginia. 8% of our patient population is PS1, is uninsured, and contains a disproportionately high number of minorities and women with cervical cancer, suggesting that the burden of lack of access to care will be shouldered by an unfortunate few.

Education Symposium III - The Future of Screening: Biomarker and Radiologic Advances
Monday, March, 11, 2013, 3:45 p.m.-4:45 p.m.
Concourse Hall (Los Angeles Convention Center)
Moderators: Abstracts: 49-52: Elise Kohn, MD, National Cancer Institute, Bethesda, MD. Anil Sood, MD, The University of Texas, MD Anderson Cancer Center, Houston, TX

49

Serial use of tumor morphology index during ultrasound-based screening may reduce false-positive results
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Objective: Transvaginal sonography (TVS) with a tumor morphology index (MI) has been used to predict the risk of ovarian malignancy. Our objective was to evaluate the significance of MI scores over time for both malignant and nonmalignant ovarian tumors in a TVS screening population.

Methods: Women were eligible for the study if they participated in the ovarian cancer screening program and had an ovarian cyst on multiple TVS scans. A surgery performed for a nonmalignant ovarian tumor was categorized as a false-negative. Data analysis included: MI, change in MI (∆MI) per scan, number of scans, and scan duration.

Results: From 1987-2012, 38,983 women received 218,445 scans. Within the 9,975 eligible subjects, 9,505 ovarian tumors were observed without surgery and 470 were surgically removed. 70% (6,915) of ovarian tumors observed with TVS resolved. For tumors surgically removed, there were 74 ovarian malignancies and 396 nonmalignant tumors. The ∆MI per scan decreased over time for tumors that resolved (∆MI -2.7; ∆MI per scan -1.1) or persisted (∆MI -2.7; ∆MI per scan -1.3) without surgery. For ovaries surgically removed, the ∆MI increased for malignancies (∆MI +3.2; ∆MI per scan +2.4) and remained unchanged over time for benign tumors (∆MI +0.2). On average, women received 3.0 scans over 11.5 months before cyst resolution compared to 2.1 scans over 2.3 months before surgery for an ovarian malignancy. 85% of malignancies had a MI ≥5 at decision for surgery. The preoperative MI was associated with the following risk of malignancy: MI=5 (3%), MI=6 (3.7%), MI=7 (12.6%), MI=8 (26.7%), MI=9 (27.8%), and MI=10 (33.3%). The MI findings were independent of menopausal status.

Conclusions: Malignant tumors have an increasing MI over time, while nonmalignant tumors have a decreasing or stable MI. Serial MI analysis may improve the prediction of malignancy in ultrasound-based screening by reducing false-positive results.

50

An evaluation of molecular markers that predict maximal surgical cytoreduction: A Gynecologic Oncology Group Trial
C. Miller1, A. Miller2, C. Hamilton3, A. Alvarez-Secord4, L. Havrilesky5, F. Muggia2, J. Farley6
1Brooke Army Medical Center, Ft. Sam Houston, TX, 2GOG Statistical and Data Center, Roswell Park Cancer Institute, Buffalo, NY, 3Walter Reed National Military Medical Center: Gynecologic Cancer Center of Excellence, Bethesda, MD, 4Duke University Medical Center, Durham, NC, 5New York University Medical Center, New York, NY, 6St. Joseph’s Hospital and Medical Center, Phoenix, AZ

Objective: To evaluate molecular and clinical markers previously linked to overall survival for their ability to predict residual disease status following primary surgical cytoreduction in advanced-stage epithelial ovarian cancer (EOC) patients enrolled in GOG trials.

Methods: Archival specimens of 106 subjects from GOG0114 and GOG0132 were analyzed with immunohistochemistry and immunoblot techniques for markers of angiogenesis, cell cycle, and protein kinase receptor pathways. A retrospective chart review scrutinized each operative report, pathology report, and protocol data form for residual disease status, the initial extent of disease, and surgical effort. Over 300 clinical and molecular markers were analyzed for association with residual disease status using Fischer’s exact test and the Kruskal Wallis test. Multivariable analysis was used to determine which clinical and molecular characteristics independently influenced residual disease status.

Results: Of 106 patients, 17 had no gross residual disease (NGRD), 36 had minimal (<1 cm) gross residual disease (MGRD), and 53 had bulky (>1 cm) gross residual disease (BGRD). Patients with BGRD had lower expression of MASPIN (P=0.01), bFGF (P=0.009), CD105 (P=0.008), Cyclin D (P=0.013), Cyclin E (P=0.006), and p16 (P=0.001) compared to all patients who were optimally debulked. When analysis separated NGRD patients into their own category, lower expressions of CD105 (P=0.014), MASPIN (P=0.046), and p16 (P=0.001) continued to be associated with BGRD. Below-average CD105 expression was significantly associated with upper abdominal disease (P=0.026), the presence of which most influenced the inability to achieve NGRD on multivariate analysis (P<0.01).

Conclusions: Although clinical absence of upper abdominal disease was most predictive of achieving NGRD, tumor levels of MASPIN, bFGF, CD105, Cyclin...
51

Impact of preoperative and pretreatment CA125 on survival of women with optimal cytoreduced ovarian and primary peritoneal cancer: A Gynecologic Oncology Group ancillary data study

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Objective: The primary use of CA-125 in epithelial ovarian cancer (EOC) and primary peritoneal cancer (PPC) has been to assess response to chemotherapy. Evaluating CA-125 during treatment as a prognostic marker for patients demonstrated improved survival in patients who have a nadir value <10 U/mL. The objective of the current study was to evaluate the prognostic value of preoperative (preop) and pretreatment (preTx) CA-125 in women with advanced stage EOC or PPC.

Methods: Demographic, pathologic, laboratory, surgical, and patient outcome data were collected from GOG 182 records of EOC or PPC patients cytoreduced to <1 cm or no gross residual disease (NGRD). The effects of preop and preTx CA-125 on progression-free survival (PFS) and overall survival (OS) were assessed using Kaplan-Meier and proportional hazards methods.

Results: 998 of 2,655 women with optimal cytoreduction (NGRD, n=328; <1 cm, n=670) had complete data. Median preop and preTx CA-125 was 346 U/mL and 107 U/mL for those with NGRD and 870 U/mL and 249 U/mL for those with <1 cm. 30% had preop CA-125 <35 U/mL and 387 (38.7%) had preop CA-125 >1,000 U/mL. Those with CA-125 <500 U/mL were statistically more likely to achieve NGRD (61% vs 35%, P=0.01). Higher preop and preTx CA-125 values were associated with worse OS and PFS prognosis. Comparing those with preop CA-125 <35 U/mL to those with preop CA-125 >500 U/mL, OS was 80.8 vs 41.1 months (P=0.003) and PFS was 34.3 vs 16.1 months (P<0.01), while OS and PFS for those with preTx CA-125 <35 U/mL compared to those with >500 U/mL was 86.3 vs 35.9 months (P=0.01) and 35.8 vs 12.8 months (P=0.01), respectively. In general, those with lower preop CA-125 had lower preop CA-125 and smaller declines. The median CA-125 decline from preop to preTx was 67% for both NGRD and <1 cm residual. Preop to preTx CA-125 was stable-to-increased in 125 (12.5%) patients; 308 patients (30.8%) had ≥80% decline. Compared to those with ≥80% decline, the hazard ratio for PFS for those with stable-to-increased CA-125 or ≥50% decline was 1.35 (P=0.02) and 1.26 (P=0.03) and OS was 1.70 (P<0.01) and 1.43 (P<0.01).

Conclusions: CA-125 <500 U/mL at presentation was associated with an increased likelihood of NGRD. For women with optimally cytoreduced EOC or PPC, lower preoperative and preTx CA-125 and larger declines in CA-125 were associated with improved PFS and OS. These results suggest that absolute CA-125 value and change in preop to preTx CA-125 may be of value in a model to predict long-term outcomes.

52

Glycomics analysis as a potential diagnostic test for ovarian cancer

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Objective: Glycomics is an emerging area for understanding carcinogenesis; studies in glycobiology have documented that aberrant glycosylation accompanies malignant transformation. We report the use of glycomic profiling of serum to distinguish between serous ovarian cancer cases (OC) versus healthy female controls using nano-liquid chromatography mass spectrometry (nano-LC-MS) and bioinformatics analysis.

Methods: We obtained preoperative sera of serous OC cases and healthy controls from the Gynecologic Oncology Group (GOG). The training set (GOG 1) consisted of 43 stage III-IV serous OC patients and 48 (age-matched) controls for use of biomarker discovery. A more heterogeneous test set (GOG 2) that consisted of 52 stage I-III, 52 stage III-IV serous OC, 52 serous low malignant potential, and 52 controls that were age-matched across the groups and GOG 1 was applied for validation. Nano-LC-MS was used to detect and identify N-glycans in sera. Bioinformatic analysis was performed to evaluate each glycan for its ability to differentiate OC from noncancer controls using feature selection and classification algorithms. We further investigated whether a combination of multiple glycans (i.e., multiplex classifier) could improve predictive performance over individual glycans. Validation studies were conducted to evaluate individual glycans and multiplex classifiers for their classification accuracy in an independent test set (GOG 2).

Results: Of 330 glycans detected in GOG 1 set, 20 significantly differentiated (either over- or underexpressed) between cases and controls at a false discovery rate <0.05. The most informative glycan singly yielded an AUC value of 0.896 with 93% sensitivity and 75% specificity. Multiplex classifiers combining 1 or more glycans together were developed, with the highest accuracy of 91.2% (sensitivity 86.0%, specificity 95.8%) when combining 9 glycans. When testing the multiplex classifiers developed with GOG1 in samples of the independent GOG2 test set, the highest accuracy of 78% was achieved with the top 11 glycans. These results indicate that glycans combinations might lead to improvements in the detection of ovarian cancer.

Conclusions: Serum glycan profiles were capable of discriminating OC cases from controls, showing the great potential for glycomics analysis as a diagnostic test for ovarian cancer. While these preliminary results are promising, extensive validation studies are necessary and in process.
Chi-squared tests, Kaplan-Meier estimates, and Cox regression were used for statistical analyses.

**Results:** Of 52,260 women, 3,932 (7.5%) were Asian and 48,328 (92.5%) were white. The median age of Asians was younger (56 years) compared to whites (64 years) (P<0.001). Of the 2,866 Asians with known place of birth, 780 (27%) were reported as United States-born and the remainder 2,086 (73%) were immigrants, of which 33% were Filipino, 23% Chinese, 10% Korean, 10% Vietnamese, 9% Indian/Pakistani, 7% Japanese, and 10% other. Asians were more likely to be diagnosed at a younger age (P<0.001), undergo primary surgery (P<0.001), and receive lymphadenectomy (P<0.001). Asians were more likely to be diagnosed with earlier stage (P<0.001), non-serous histology (P<0.001), lower grade of disease (P<0.04), and be less likely to have nodal metastasis (P<0.001). The 5-year disease-specific survival of Asians was higher compared to whites (59% vs. 47%, P<0.001). Further, immigrants also had a higher survival compared to US-born women (55% vs. 52%; P=0.03). On subset analysis, the 5-year survivals of Asian subpopulations were: Vietnamese (62%), Filipino (62%), Chinese (61%), Korean (59%), Japanese (55%), and Asian Indian/Pakistani (48%) (P=0.015). On multivariate analysis, Asian race (hazard ratio [HR]=0.92; 95% CI: 0.89 – 0.95; P<0.001) and immigrants (HR=0.91; 95% CI: 0.87 – 0.95; P<0.001) were independent factors associated with improved survival. Further, younger age, primary surgery with lymphadenectomy, earlier stage, and lower grade were also important.

**Conclusions:** Our data suggest that Asian race and immigrants have a better survival compared to whites with ovarian cancer. Asians were also more likely to be diagnosed at a younger age, earlier stage, and with non-serous histologies. Future clinical trials need to consider these differences in the outcomes of ovarian cancer patients.

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54

**Prognostic significance of ethnicity and age in advanced stage ovarian cancer: An analysis of GOG 218**

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**Objective:** Ovarian cancer remains the second most prevalent gynecologic malignancy in the United States, and while novel therapeutic agents are available to treat this disease, overall survival remains poor. Age and ethnicity are among several factors that influence overall survival. This study seeks to evaluate the prognostic significance of ethnicity and age in women enrolled in GOG 218.

**Methods:** An analysis of a randomized phase III clinical trial was conducted in women with advanced-stage ovarian, primary peritoneal, or fallopian tube cancer who underwent surgical staging and received adjuvant chemotherapy with paclitaxel and carboplatin followed by placebo, concurrent bevacizumab, or concurrent and maintenance bevacizumab.

**Results:** A total of 1,873 women were enrolled in GOG 218. 287 minority women and 328 women age ≥70 years were randomized to 1 of 3 regimens. The distribution of age at diagnosis varied by race and ethnicity (P<0.001). The distribution of age also varied by primary site of cancer, with women diagnosed with primary peritoneal cancer being older than women with ovarian or fallopian tube cancers (P<0.001). Multivariate estimates of the hazard ratio (HR) for overall survival showed that women who were 60 to 69 years of age had a 28% increase risk of death and women age ≥70 years had a 47% increased risk of death compared to women <60 years (HR=1.47, 95% CI 1.24-1.74). Women of Asian descent were younger than and had a lower HR than non-Hispanic white women (HR=0.594, 95% CI 0.426-0.829). When survival by country was examined, women enrolled from Japan and Korea had lower HRs than American women of Asian descent after adjusting for age at enrollment, disease stage, performance status, and histology (HR=0.595 and HR=0.498, respectively).

**Conclusions:** Women >70 years had the lowest overall survival. When controlled for age, disease stage, histology, and size of residual disease, there was no statistically significant evidence that the effects of the study treatments depended on racial group. However, clinically significant differences in the HR occurred in women of Asian descent when compared to other racial groups, and the improvement in progression-free survival among Japanese and Korean women was intriguing and may be important in the design of future clinical trials.

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55

**How risky is it to operate on patients with low albumin? Analysis of the patients undergoing surgery for gynecologic cancers**

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**Objective:** Hypoalbuminemia predicts high morbidity and mortality in hospitalized patients with various illnesses. Despite being identified as an independent predictor of poor surgical outcomes in retrospective studies, the precise impact of hypoalbuminemia on various postoperative outcomes in gynecologic oncology patients has not been fully quantified.

**Methods:** Patients included in the National Surgical Quality Improvement Program (NSQIP) dataset who underwent any surgery for gynecologic malignancy between January 1, 2008 and December 31, 2010 were identified. Data on clinical characteristics, comorbidities, operative details, as well as postoperative complications and mortality were collected and analyzed. Patients with preoperative albumin levels <3.5 g/dL were defined as having low albumin.

**Results:** A total of 3,171 patients were identified to have undergone nonemergent surgery for a gynecologic malignancy. Preoperative albumin levels were available for 2,110 patients, with 1,831 (86.7%) having normal albumin levels and 279 (13.3%) having low albumin. Compared to normal albumin group, patients in the low albumin group were more likely to develop at least 1 postoperative complication (36.9% vs. 15.6%, P<0.001; Odds 3.175) or experience 30-day mortality (4.3% vs. 0.8%, P<0.001; Odds 10.2) on the univariate analysis. On multivariate analysis, after controlling for age, complexity of surgery, cancer site, Charlson morbidity index, tobacco use, body mass index, operative time, preoperative chemotherapy, preoperative radiotherapy, American Society of Anesthesiology (ASA) physical status classification scores, localized vs. metastatic disease, and preoperative weight loss of >10%, the low albumin group was more likely to develop at least 1 postoperative complication (odds ratio [OR] -2.03, P<0.0001), organ space infection (OR -2.61, P=0.02), urinary tract infection (OR -2.26, P=0.002), septic shock (OR -9.59, P<0.001), pneumonia (OR -2.8, P=0.03), pulmonary embolism (OR -2.97, P=0.01), or bleeding requiring transfusion (OR -2.23, P=0.001) or die within 30 days (OR -6.28, P<0.001) (Figure).

**Conclusions:** Preoperative hypoalbuminemia in patients undergoing nonemergent surgery for gynecologic malignancy is an independent predictor of increased postoperative morbidity and mortality. Although the causes of low albumin are multifactorial, identification of this subset of patients and aggressive optimization of nutritional status preoperatively may improve surgical outcomes in this high-risk population.
Objective: Previous reports in ovarian, breast, and colorectal cancer using the Surveillance Epidemiology and End Results database have demonstrated negative outcomes associated with delays in delivery of adjuvant therapy. Using prospectively collected data, we sought to determine whether the interval from surgery to initiation of chemotherapy (SIT) affects survival in advanced ovarian carcinoma.

Methods: This is a posttrial ad hoc analysis of Gynecologic Oncology Group protocol 218, a phase III randomized, double-blind, placebo-controlled, 3-arm trial designed to study the impact of incorporating the antiangiogenesis agent bevacizumab in primary and maintenance therapy for patients with newly diagnosed advanced-stage ovarian carcinoma. Cox regression models were used to determine the impact of SIT on progression-free survival (PFS, the primary endpoint) and overall survival (OS). The survival impact of SIT as stratified by clinicopathologic factors, including age, performance status, histology, residual disease, and treatment allocation, was also examined.

Results: A total of 1,718 patients were randomized to chemotherapy alone (arm 1, n=580), chemotherapy plus bevacizumab (arm 2, n=570), or chemotherapy plus bevacizumab and maintenance bevacizumab (arm 3, n=568). Surgical outcome was described as: microscopic residual (n=85), optimal (n=701), and suboptimal (n=932). For the entire study population, SIT had a weak effect on PFS (P=0.155). The risk of adverse outcome on OS, however, increased sharply beyond 25 days (95% CI 16.6-49.9 days, P=0.0003). SIT had a strong impact on surgical outcome (P=0.003), with the microscopic residual group most affected by long interval (Figure). The racial subgroup(s) of patients that appeared to be negatively affected by increasing SIT (P=0.004) were Asian/other. Although SIT did not vary significantly with treatment allocation, a trend for decreased PFS with prolonged SIT for patients on arm 1 was observed (P=0.0891).

Conclusions: These data suggest that outcome may be adversely affected when initiation of adjuvant therapy occurs >25 days following surgery. Our results are consistent with Gompertzian first-order kinetics in that patients with microscopic residual are most vulnerable. Given the hierarchy of angiogenesis pathways and plasticity of oncogene addiction, the potential to favorably exploit SIT by incorporating targeted therapy is implicit.

Survival in early stage endometrioid endometrial cancer risk groups: A Gynecologic Oncology Group ancillary data study

Objective: Management of patients with appropriately staged early-stage endometrial cancer (stage I-II) is often based on single-institution practice patterns. The purpose of this study is to use the previously published GOG LAP2 survival data with a patient cohort of surgical stage I-II endometrioid endometrial cancer and compare endometrial primary characteristics (tumor size, grade, lymph vascular space invasion, and depth of invasion) in regard to disease-free survival (DFS) and overall survival (OS).

Methods: This is a post hoc analysis from the previously identified 2,516 women from 1996-2005 for the institutional review board-approved GOG study LAP2. Inclusion criteria for the patients in this analysis were surgical stage I-II uterine cancer of endometrioid histology on final pathology reports and complete clinicopathologic data. Patients with advanced-stage endometrial cancer were excluded from the analysis. Patients identified as low risk (LR) were modified from Mayo Clinic’s criteria (MMC) on endometrial cancer characteristics with 3 specific criteria on final pathology reports: 1) ≤50% invasion, 2) Tumor size ≤2 cm, and 3) Well or moderately differentiated histology. If the uterine specimen did not meet all 3 criteria, it was viewed as high risk (HR). Modified high intermediate risk (HIR) patients were identified using the GOG 99 criteria involving age, grade, depth of invasion, and lymph vascular space invasion (LVI). Pearson’s χ2 test compared categorical variables, and Wilcoxon rank-sum tests compared continuous variables between the 2 groups. Prognostic factors were included in Cox PH regression models.

Results: The total number of 2009 FIGO stage I-II endometrioid endometrial cancer patients was 1,822. No statistical differences in DFS or OS were found based on myometrial invasion, tumor size, surgical stage (I-II), total lymph nodes resected, performance status, or MMC (Table). GOG 99 HIR, non-white race/ethnicity, increasing age and body mass index, poor tumor differentiation, and positive LVI were associated with worse DFS and OS.

Conclusions: In this multicenter post hoc analysis of GOG LAP2 patients with surgical stage I or II endometrioid endometrial cancer, MMC was not associated with DFS or OS. GOG 99 HIR criteria are associated with DFS and OS, and those patients should receive consideration for adjuvant systemic treatment.

Table. Patient Characteristics Related to Progression-free Survival (PFS) and Overall Survival (OS)

<table>
<thead>
<tr>
<th>Variable</th>
<th>PFS (95% CI)</th>
<th>P value</th>
<th>OS (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race/Ethnicity = Non White</td>
<td>1.86 (1.04-1.07)</td>
<td>&lt;0.001</td>
<td>1.08 (1.06-1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race/Ethnicity = White</td>
<td>1.74 (1.11-2.72)</td>
<td>0.02</td>
<td>1.24 (1.45-3.76)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumor Grade = poor</td>
<td>1.91 (1.18-3.10)</td>
<td>0.01</td>
<td>1.80 (1.02-3.17)</td>
<td>0.04</td>
</tr>
<tr>
<td>Myometrial Invasion ≥50%</td>
<td>2.60 (0.80-8.39)</td>
<td>0.18</td>
<td>2.27 (0.58-8.91)</td>
<td>0.24</td>
</tr>
<tr>
<td>Tumor Size</td>
<td>1.09 (0.54-2.24)</td>
<td>0.20</td>
<td>1.12 (0.49-2.27)</td>
<td>0.79</td>
</tr>
<tr>
<td>2009 FIGO Surgical Stage II</td>
<td>1.36 (0.50-3.73)</td>
<td>0.35</td>
<td>1.40 (0.44-4.50)</td>
<td>0.57</td>
</tr>
<tr>
<td>LVI</td>
<td>1.56 (1.04-2.34)</td>
<td>0.03</td>
<td>1.92 (1.22-3.00)</td>
<td>0.004</td>
</tr>
<tr>
<td>BMI</td>
<td>1.63 (1.00-2.63)</td>
<td>0.02</td>
<td>1.84 (1.02-3.36)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Performance status = symptomatic</td>
<td>1.34 (0.87-2.04)</td>
<td>0.18</td>
<td>1.54 (0.97-2.45)</td>
<td>0.07</td>
</tr>
<tr>
<td>GOG 99 HIR</td>
<td>2.33 (1.62-3.36)</td>
<td>&lt;0.001</td>
<td>2.78 (1.80-4.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMC risk group</td>
<td>1.23 (0.74-2.06)</td>
<td>0.42</td>
<td>1.16 (0.65-2.09)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

LVI, lymph vascular space invasion, BMI, body mass index, MMC, Mayo Clinic’s criteria
Safety and efficacy of aprepitant, ramosetron, and dexamethasone for chemotherapy-induced nausea and vomiting in patients with ovarian cancer treated with paclitaxel/carboplatin

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Objective: Women with ovarian carcinoma treated with paclitaxel/carboplatin are particularly susceptible to chemotherapy-induced nausea and vomiting (CINV). The current study evaluated the new combination (aprepitant/ramosetron/dexamethasone, 20 mg) in ovarian cancer patients receiving multiple cycles of paclitaxel/carboplatin.

Methods: Patients received the following regimen: Day 1: aprepitant 125 mg, ramosetron 0.6 mg, and dexamethasone 20 mg before chemotherapy; Days 2–3: aprepitant 80 mg every day for the prevention of CINV. The primary end point was the proportion of patients with a complete response (CR) in cycle 1. Assessment of toxicity was conducted using the NCI-CTC investigator guide (Version 3.0).

Results: Of the 89 patients enrolled, 85 were evaluable for efficacy and toxicity, and 68 (80%) of them completed all 6 cycles. In cycle 1, the percentage of patients who achieved a CR in the acute, delayed, and overall phases was 98.8%, 89.4%, and 89.4%, respectively. This response continued in cycles 2–6, with maximum decrease of 6.8% in cycle 4. Of the 460 cycles, adverse events, drug-related adverse events, and serious adverse events occurred in 179 cycles (38.9%), 35 cycles (7.6%), and 10 cycles (2.2%), respectively. The most common adverse event was constipation (12.4%) and headache (11.1%), and none of the patients discontinued the study because of adverse events.

Conclusions: The combination of aprepitant, ramosetron, and high-dose dexamethasone represents an advance in treatment options for the prevention of CINV due to MEC over multiple cycles of chemotherapy.

A novel proteomic-based screening method for ovarian cancer using cervicovaginal fluids: A window into the abdomen

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Objective: To develop a site-specific proteomic-based screening test for ovarian cancer using the mucus of the cervix and vagina. Although this location is countere intuitive, the sole purpose of the fallopian tube is to actively transport oocytes from the ovary to the endometrium. This active transport spills a protein-rich fluid that eventually drains down the uterus, through the cervix, and into the vagina. Coupled with this transport mechanism, emerging molecular data demonstrate that most ovarian cancers potentially originate within the fallopian tube itself.

Methods: Cervicovaginal fluid samples were obtained during pelvic exams for liquid chromatography-mass spectrometry (LC-MS) evaluation of differences in proteomic sequencing between ovarian cancer patients and normal controls. Peptide selection was performed using "lasso" modeling, with penalty factor chosen by "leave-one-out" cross-validation to select the most accurate set of predictors. A best subset regression analysis was used to determine the panel with the best detection of disease and highest penetrance across ovarian cancer samples.

Results: A total of 83 consecutive patient samples were collected prospectively (33 ovarian cancer and 50 controls). Using LC-MS, 36 peptides demonstrated independent statistical significance for detecting ovarian cancer. Using statistical modeling, the protein panel that determined the best predictor for detecting ovarian cancer formed an ovarian cancer "fingerprint." This fingerprint consists of 5 known proteins: serine protease inhibitor A1, periplakin, profilin1, apolipoprotein A1, and thymosin beta4-like protein. Thymosin beta4-like protein was "sentinel" in that it was only observed in ovarian cancer patients while being absent in all controls. These peptides have a rationale for carcinogenesis and demonstrate a significant increased probability of detecting ovarian cancer with their receiver operating characteristics curve having an AUC of 0.88 (P= 0.00001) (Figure).

Conclusions: Using novel site-specific collection methods, we have statistically identified a group of peptides that detect ovarian cancer. Statistical modeling detected this ovarian cancer "fingerprint" with adequate sensitivity and specificity to warrant further evaluation in a larger cohort. Combining our results with emerging data suggesting that most ovarian cancers originate within the fallopian tube, this methodology has the potential to detect early-stage ovarian cancer in a screening test.

Serous cancer precursor evolution in the fallopian tube

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Objective: Given the failure of screening programs in improving survival, the limited success of targeted therapy, and the absence of data supporting routine prophylactic salpingectomy in healthy low-risk women, novel paradigms of ovarian cancer prevention are needed. The distal fallopian tube is implicated in the genesis of many of the most lethal high-grade serous carcinomas, and precursors (p53 signatures and tubal intraepithelial carcinomas) to these neoplasms have been proposed. Precisely how these entities emerge from the tubal mucosa and the specific cells targeted remain unclear. Because the distal tube harbors a unique Mullerian-mesothelial junction, we addressed the possibility that this junction harbored unique target epithelial cells.

Methods: Embryonic derived epithelial cells from the cervix squamo-columnar junction were analyzed by array technology to identify embryonic-specific genes. Selected biomarkers were used to probe fallopian tubes to identify region-specific gene expression. Selected markers were then applied to a range of precursor lesions to identify gene expression linking these precursors to potential progenitor cells.

Results: A series of embryonic markers identified a subpopulation of nonciliated cells in the distal oviduct. These markers, by both their presence/absence, were selectively expressed/not expressed in a majority of direct precursors (p53 signatures or serous tubal intraepithelial carcinomas) to high-grade serous
cancer. The same markers were also expressed/not expressed in other secretory cell outgrowths (SCOUTs) that have not been described in significantly higher frequency in the tubes of women with ovarian cancer.

**Conclusions:** A specific immunophenotype identifies both a subpopulation of nonciliated epithelial cells in the normal distal oviduct and serous cancer precursors. This suggests that a certain population evolving during embryogenesis is a frequent if not exclusive target for clonal expansions, including some that could eventuate in malignancy. Regional differences in serous cancer precursor distribution could reflect the distribution of this population as well as genotoxic stimuli. Variations in the latter may explain the variable forms of clonal expansion seen in the oviduct. The link between the shared features of these early lesions, the relationship of some to serous cancer, and the role of the proximity of the distal tube to a müllerian-mesothelial junction as the underpinning of this process merit further study.

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**61 Brush cytology of the fallopian tube**

G. Linnemeier, G. Sutton, A. Moriarty, M. Callahan, H. Fornalik, R. McCarthy

1St. Vincent Gynecologic Oncology, Indianapolis, IN, 2St. Vincent Hospital, Indianapolis, IN

**Objective:** Recent evidence suggests that many high-grade “ovarian” serous carcinomas (HGSC) are associated with epithelial precursors in the fallopian tube (FT). Such tubal intraepithelial carcinomas are observed in salpingectomy specimens obtained at risk-reducing surgery in BRCA-positive women. The purpose of this study was to evaluate the cytomorphology of cells obtained from the FT.

**Methods:** Women undergoing salpingo-oophorectomy (SO) for risk reduction or for pelvic masses were selected for study. Immediately after surgical removal, the FT was transected at its midpoint and a cytobrush was introduced into the lumen, advanced toward the fimbria, and withdrawn. The specimen was rolled onto a glass slide, fixed in 95% ethanol and stained with Papanicolaou stain. An expert cytopathologist examined the slides, and all cases had pathologic correlation.

**Results:** 91 FTs from 58 patients (pts) were examined. Epithelial cells characteristic of the FT were identified in 87/91 (96%) specimens. In pts with benign disease and no personal or family history of breast cancer, atypia was reported in one of 19 FTs. Malignant or atypical cells were identified in 12/15 FTs from 8 pts with untreated HGSC and in 0 of 6 FTs from 3 pts treated with neoadjuvant chemotherapy. 5 pts undergoing prophylactic SO had known BRCA mutations at the time of surgery. Atypical cells, nuclear enlargement, or “naked” (stripped) nuclei were observed in 3/9 FTs in this high-risk group. Naked nuclei were observed in 22/58 pts (38%). These myoepithelial cells of stromal origin, previously described in association with proliferations of the breast, were observed in 11/14 FTs from 8 pts with breast cancer or a family history of breast cancer, 8/9 FTs from 6 pts with endometriosis, 6/8 FTs from 4 pts with HGSC, 2/2 FTs from 2 pts with other adenocarcinoma, and 2/3 FTs from 2 pts with benign findings.

**Conclusions:** If a precursor lesion exists in the FT, a cytologic screening technique might be developed for women at risk for HGSC. This study demonstrates that adequate FT cytology specimens can be obtained at the time of SO. These findings suggest that cytologic study of the FT using hysteroscopy may be feasible. The nature of myoepithelial cells of stromal origin arising from the FT needs elucidation.

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**62 The impact of tubal sterilization techniques on the risk of serous ovarian and primary peritoneal carcinoma: A Rochester Epidemiology Project (REP) study**

C. Lessard-Anderson, R. Molitor, J. St. Sauver, K. Steckelberg, A. Weaver, J. Bakkum-Gamez, S. Dowdy, B. Cliby

Mayo Clinic, Rochester, MN

**Objective:** Evidence is emerging that implicates tubal epithelium as the source of serous epithelial ovarian cancer (EOC). We aimed to determine the impact of tubal sterilization, specifically excisional methods, on subsequent development of serous EOC or primary peritoneal cancer (PPC).

**Methods:** This was a population-based case-control study utilizing individuals residing in Olmsted County, Minnesota. Cases included females diagnosed with either serous EOC or PPC between 1/1/1966 and 12/31/2010. Controls consisted of age-matched females seen in the same time period without either diagnosis identified from Olmsted County using the resources of the Rochester Epidemiology Project (REP). Cases were matched 1:2 with controls. Reproductive, surgical, and medical data prior to the index date were abstracted.

**Results:** Over the 45-year period, 194 cases of serous EOC and PPC (mean [SD] age, 61.4 [15.2] years) were diagnosed among Olmsted County residents. Cases were matched with 388 controls. Among cases, 7.2% had a history of tubal sterilization compared to 11.6% of the controls. The adjusted overall risk of serous EOC or PPC was lower after any tubal sterilization (odds ratio [OR] 0.58; 95% CI 0.29-1.14; P=0.11). Cases had a lower rate of excisional tubal
sterilization compared to controls (2.6% vs 6.2%, respectively). The risk of serious EOC and PPC after excisional tubal sterilization was reduced by more than 60% (OR 0.38; 95% CI, 0.14-1.06; P=0.063) when compared to all those without sterilization and those who had nonexcisional tubal sterilization.

**Conclusions:** Serous ovarian and primary peritoneal cancers may arise from the fallopian tube. We present the first population-based study investigating the impact of excisional tubal sterilization procedures on EOC and PPC risk reduction. Excisional methods may be driving the overall impact of tubal sterilization on EOC and PPC risk reduction. Larger population-based studies are needed to validate these findings.

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**Featured Poster Session I**

**Sunday, March, 10, 2013, 6:30 a.m. -7:30 a.m.**

Petree Hall C (Los Angeles Convention Center)
Moderator: Laura Havrilesky, MD, Duke University Medical Center, Durham, NC

**63 Cervical cytology and HPV infection: A study of 15,565 women**

*E. Dickson, R. Vogel, L. Downs*

University of Minnesota, Minneapolis, MN

**Objective:** To determine the rates of single- and multiple-type human papillomavirus (HPV) infection in women in the United States with known cervical cytology results.

**Methods:** Type-specific HPV analyses from the first adequate samples of women were performed as part of cervical cancer screening from July 2007 to May 2011. Women were 18-65 years at testing. Only those samples with associated cytology results were analyzed. The odds of abnormal cytology (compared to normal results) for multiple- vs. single-type HPV infections were calculated for each cytology subtype and odds ratio (OR) and 95% confidence intervals (CI) are reported.

**Results:** 15,565 women were included in the analysis. The samples represented all geographic regions of the United States (North Central, 50.0%; Western, 35.8%; Southern, 10.3%; Eastern, 3.9%). The majority of the women (67.2%) had atypical squamous cells of unknown significance (ASCUS) cervical cytology. Of those analyzed, 7.3% were positive for 2 or more HPV types. For all cervical cytology subtypes with adequate sample sizes (ASCUS, ASCUS-H, low-grade squamous intraepithelial lesion [LSIL], and high-grade squamous intraepithelial lesion [HSIL]), women with multiple-type infections were more likely to have abnormal cytology, with ASCUS, ASCUS-H, LSIL, and HSIL having ORs of 1.52 (1.34-1.72), 2.09 (1.41-3.09), 2.19 (1.92-2.51), and 2.22 (1.65-2.97), respectively.

When analyzing HPV type 16 alone, women with multiple-type infections were more likely to have abnormal cytology, with ASCUS-H and HSIL having the highest ORs of 2.81 (1.51-5.24) and 2.96 (1.85-4.73), respectively. Few women had infections including HPV type 18 and no results reached statistical significance. Results focused on the alpha 9 phylogenetic family showed similar results as HPV type 16.

**Conclusions:** Women with multiple-type HPV infections were more likely to have abnormal cytology than those with single-type infections.
Results: The study included 577 women: 274 with partners assigned to the control group and 303 assigned to the intervention group. At enrollment, the frequency of high-intensity LA bands (3 or 4) for HR-HPV® genotypes was similar in the intervention arm (42%) and the control arm (44%) (P=0.713). At 24 months follow-up, the prevalence of LA band signal (3 or 4) was significantly lower in the intervention arm (35%) than the control arm (45%) (PRR=0.77; 95% CI 0.62-0.95; P=0.015). In adjusted analyses, HR-HPV® linear array band intensity (3 or 4) was significantly reduced in female partners of circumcised men compared to female partners in the control group (adjusted PRR 0.80; 95% CI 0.67-0.97; P=0.02).

Conclusions: Male circumcision reduces shedding of HR-HPV® in infected female partners. This may provide benefit for prevention of cervical neoplasia.

Table. Cost Components and Complication Estimates for PDS and NACT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Average Cost</th>
<th>PDS</th>
<th>NACT</th>
<th>Savings associated with NACT</th>
<th>Cost considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>$2,712</td>
<td>$1,691</td>
<td>$1,021</td>
<td></td>
<td>Lower debulking cost for NACT group and lower rates of additional procedures</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>$13,698</td>
<td>$14,526</td>
<td>-$828</td>
<td></td>
<td>Increased complication rates contribute to length of stay, decreased care utilization and reduced overall costs</td>
</tr>
<tr>
<td>Hospital Stay</td>
<td>$24,087</td>
<td>$21,233</td>
<td>$2,854</td>
<td></td>
<td>Overall care costs</td>
</tr>
<tr>
<td>TOTAL</td>
<td>$40,498</td>
<td>$37,450</td>
<td>$3,048</td>
<td></td>
<td>Overall care costs</td>
</tr>
</tbody>
</table>

Rate of Complications

<table>
<thead>
<tr>
<th>Examples of Complications</th>
<th>0≤1 minor, no major</th>
<th>1 major</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary embolus, myocardial infarction, stroke, wound dehiscence, bowel perforation, fistula</td>
<td>25.0%</td>
<td>51.3%</td>
</tr>
</tbody>
</table>

Objective: The treatment for patients with advanced-stage epithelial ovarian cancer (AOEC) may include primary debulking surgery (PDS) or neoadjuvant chemotherapy (NACT). Previous studies have reported similar outcomes for these cohorts, yet the optimal treatment is controversial. Studies have reported higher complication and chemotherapy non-completion rates in patients ≥65 years after PDS. The objective of this study was to compare the cost of PDS to NACT for initial treatment of AQOC in patients ≥65 years.

Methods: A cost model, from the perspective of the health care system, was used to compare surgical, hospital, and chemotherapy costs among patients undergoing PDS or NACT. Arm 1 included patients undergoing PDS followed by 6 cycles of carboplatin and paclitaxel (CT). Arm 2 included patients receiving NACT with 3 cycles of CT, followed by interval debulking surgery (IDS) and 3 additional cycles of CT. Surgical complications for debulking and add-on procedures (e.g., bowel resection) were estimated from national Medicare reimbursements rates. The model accounted for differences in surgical complexity across the 2 arms by weighting add-on procedure costs by the published rate for each procedure and inclusion of a more complex base cost for PDS (radical debulking vs. debulking). Hospital cost in each arm was a weighted average of diagnosis-related group costs for ovarian cancer (debulking surgery with no, minor, or major complications) weighted by a composite estimate of published complication rates among patients ≥65 years undergoing PDS and NACT (Table). Chemotherapy costs were based on institutional cost. Non-completion of treatment was estimated at 5.7% for arm 1 and 9.5% for arm 2. Sensitivity analyses were performed.

Results: Relative to PDS ($40,498), NACT ($37,450) is associated with $3,048 in cost savings per patient (Table). Given an average reported charge-to-cost ratio for the diagnostic-related group codes included of 3.3, the overall estimated charge savings per patient would be $10,058. The cost savings conclusion is robust to variation in the model parameter estimates.

Conclusions: In this model, NACT has an estimated cost savings of 7.5% when compared with PDS for patients ≥65 years with AEOC. In 2012, approximately 6,350 women ≥65 years will be diagnosed with AEOC for an estimated cost savings of $19 million with NACT. Cost savings may be underestimated as costs of complications are conservative and readmissions are not included in this model. Assumptions regarding survival may also affect the cost benefit.

Objective: Controversy exists regarding the best chemotherapy regimen for women with low-risk gestational trophoblastic neoplasia (GTN) with World Health Organization scores of 0–4. Since virtually all patients are cured, cost and quality of life are important factors. We constructed a probabilistic decision analysis model to evaluate the cost and outcomes for 4 commonly used chemotherapy regimens.

Methods: A decision-tree model was used to compare biweekly actinomycin-D (Act-D) 1.25 mg/m2 intravenous (IV) q 14 days, weekly methotrexate (MTX) 30–50 mg/m2 intramuscular (IM) q 7 days, 5-day MTX 0.4 mg/kg (maximum, 25 mg) IV daily for 5 days q 14 days, and 8-day MTX with folinic acid (FA) (MTX 1 mg/kg IM days 1, 3, 5, 7 and FA 15 mg oral [PO] days 2, 4, 6, 8 q 14 days). Women failing their first regimen were switched to an alternative single-agent, followed by multiagent chemotherapy for a second treatment failure. A systematic review of MEDLINE and EMBASE identified prospective studies using the 4 regimens, and outcomes were pooled using the generic inverse variance methodology to inform model inputs. The model used a societal perspective, true costs from 3 tertiary centers in Canada, and a 1-year time-horizon, at which point all patients achieved a complete response. Outcomes included quality-adjusted life years (QALYs) and treatment-free days (TFDs). All model inputs were described using probability distributions to account for parameter uncertainty with probabilistic sensitivity analysis.

Results: 1,000 probabilistic Monte Carlo simulations were performed (Table). In both the cost-utility and cost-effectiveness analyses, Act-D dominated all other regimens, resulting in the lowest costs, the highest QALYs, and the most TFDs. Among the MTX regimens, weekly MTX dominated the 5-day MTX and
A population-based study to evaluate SGO criteria for the identification of Lynch syndrome among endometrial cancer patients

A. Bruegl1, B. Djordjevic1, B. Fellman1, D. Urbauer1, R. Luthra3, K. Lu1, R. Broaddus1

1The University of Texas, MD Anderson Cancer Center, Houston, TX, 2University Hospitals Case Medical Center, Cleveland, OH, 3The Cleveland Clinic

Objective: The Society of Gynecologic Oncology (SGO) published a statement in 2007 with recommendations regarding which patients would benefit from further risk assessment via genetic evaluation for Lynch syndrome (LS). These criteria are a clinically based risk assessment tool analogous to the Revised Bethesda Criteria. The primary objective of this study was to evaluate the ability of SGO criteria to predict women at risk for LS in a population of unselected endometrial carcinoma (EC) patients.

Methods: 408 consecutive, unselected EC cases were evaluated for immunohistochemical expression of the 4 DNA mismatch repair (MMR) proteins. Tumors with loss of MLH1, MSH2, or PMS2 were designated asprobable LS (PLS). Tumors with loss of MLH1 and absence of MLH1 promoter methylation were also designated PLS. Clinical and pathologic data were collected from the electronic medical record.

Results: Of these unselected EC cases, 43/408 (10.5%) of the patients had PLS. 97/408 (23.7%) of EC cases met SGO criteria, but only 14/97 (14.4%) had tumor testing results consistent with LS. In our cohort, 29/43 (67.4%) of EC cases with PLS did not meet SGO criteria. As shown in the Table, the overall sensitivity for predicting LS was 32.6%, with a marginally greater sensitivity for detecting tumors lacking MLH1 and MSH2 protein expression. The Table also summarizes known LS risk factors for the 43 PLS patients. Those who met SGO criteria were younger, had tumor arising in the lower uterine segment, and more frequently had a family history of colorectal cancer. Note that the majority of EC cases with PLS in both groups did not have these historical risk factors.

Conclusions: A recent study showed that SGO criteria correctly identified 93% of individuals with EC among a population with a known germline DNA MMR mutation (mean age of diagnosis = 47.3 years). In our cohort of unselected EC patients, SGO criteria correctly identified only 32.6% of women with PLS, resulting in 67% of EC patients missing the opportunity for further cancer risk assessment and heightened screening for colorectal cancer. These results suggest that while SGO criteria may be adequate in successfully identifying younger EC patients with family/personal histories of colorectal cancer as having LS, these same criteria lose substantial efficacy when applied to the general EC patient population.

Table. Performance of SGO Criteria: Sensitivity, Specificity, and Selected Characteristics Among Those Who Do and Do Not Fulfill Criteria

<table>
<thead>
<tr>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable Lynch syndrome (n=43)</td>
<td>32.6 (19.1-48.5)</td>
</tr>
<tr>
<td>MLH1 (n=15)</td>
<td>40.0 (16.3-67.7)</td>
</tr>
<tr>
<td>MSH2 (n=12)</td>
<td>42.7 (15.2-72.3)</td>
</tr>
<tr>
<td>MSH6 (n=9)</td>
<td>22.2 (3.0-60.0)</td>
</tr>
<tr>
<td>PMS2 (n=7)</td>
<td>14.3 (0.3-57.9)</td>
</tr>
</tbody>
</table>

Meets SGO Criteria n=14 Does Not Meet SGO Criteria n=29

Table. Average of 1,000 Probabilistic Model Simulations

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cost (CANS)</th>
<th>QALYs</th>
<th>Treatment-free days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinomycin-D</td>
<td>5,445</td>
<td>0.95</td>
<td>293</td>
</tr>
<tr>
<td>Weekly MTX</td>
<td>8,685</td>
<td>0.94</td>
<td>286</td>
</tr>
<tr>
<td>8-day MTX-FA</td>
<td>17,804</td>
<td>0.92</td>
<td>271</td>
</tr>
<tr>
<td>5-day MTX</td>
<td>18,669</td>
<td>0.89</td>
<td>272</td>
</tr>
</tbody>
</table>

69 Evaluation of the cost of CA-125 measurement, office visit and CT scan in the diagnosis of recurrent ovarian cancer

A. Armstrong1, B. DeBernardo2, J. Knight1, B. Otvos2

1University Hospitals Case Medical Center, Cleveland, OH, 2University McDonald Women’s Hospital, Cleveland, OH, 3The Cleveland Clinic Foundation, Cleveland, OH

Objective: To determine the cost of common methods of surveillance of women with ovarian cancer in first clinical remission. Recurrence rates are approximately 80% in those diagnosed with advanced disease, most occurring within 2 years. The current standard for posttreatment surveillance is the National Comprehensive Cancer Network (NCCN) guidelines. However, the cost and effectiveness of surveillance in the first clinical remission has not been studied. We retrospectively determined how recurrence was initially detected at our institution. A cost model was created and applied to the United States (US) population to calculate surveillance costs using the Surveillance Epidemiology & End Results (SEER) database.

Methods: We retrospectively identified all patients with initial recurrence of ovarian malignancy treated at our institution from 2002-2009. 410 patients were identified and 105 patients had complete medical records. Method of recurrence detection was recorded; office visit, computed tomography (CT) scan, or CA-125 level. Medicare reimbursements were applied to the data to create a cost model. This was applied to the US population using SEER data. We calculated the theoretical costs and efficacy associated with 4 surveillance approaches: CA-125 alone, NCCN guidelines, NCCN with annual CT scan, and NCCN with biannual CT scan.

Results: 57% (n=60) of first recurrences were identified by increasing CA-125 level. Routine office visit identified 27% (n=29) of recurrences, and 15% (n=16) were diagnosed initially with CT scan. In 5% (5/105), CT abnormality was the only finding. 95% (100/105) of patients had either elevated CA-125 or office visit findings at time of recurrence regardless of the initial method of detection. Costs were calculated using 2010 Medicare reimbursements: $34 (CA-125), $151 (office visit), and $993 (CT scan). Of the 22,000 women diagnosed with ovarian cancer yearly, 60% (n=13,266) will have advanced disease and are likely to recur. The surveillance cost for this population for 2 years using our model is $32,500,000 using NCCN guidelines and $58,000,000 if one CT scan is obtained (Table). Our data suggest that following NCCN guidelines will detect 95% of recurrences. An additional $26 million will be needed to identify the 5% of women with recurrence seen on CT only.

Conclusions: Posttreatment surveillance of ovarian cancer patients contributes significantly to health care costs. Use of CT scan to follow these patients largely increases cost with only a small increase in recurrence detection.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

70

Addressing comfort-care in the ambulatory setting is associated with improved end-of-life quality measures among women with ovarian cancer

M. Lopez-Acevedo1, L. Havrilesky, A. Abernethy, A. Kamal, G. Broadwater, A. Berchuck, P. Lee

Duke University Medical Center, Durham, NC

Objective: To evaluate: 1) conformance with end-of-life (EOL) quality care measures in patients with progressive/recurrent ovarian cancer; and 2) the impact of the setting of comfort-care discussions on EOL quality measures and hospitalizations near the end of life.

Methods: This retrospective study involved women who died of ovarian cancer diagnosed between 2000 and 2008 in a single academic center. Patients who never received chemotherapy or who had incomplete clinical information regarding the last 3 months of life were excluded. Outcomes: hospitalizations near the end of life and conformance to EOL quality measures. The National Quality Forum’s EOL quality measures were defined as: chemotherapy in the last 14 days of life, >1 hospitalization in the last 30 days, >1 emergency department visit in the last 30 days of life, dying in an acute care setting (intensive care unit), admitted to hospice ≤3 days, and not admitted to hospice. Wilcoxon signed-rank test and Fisher’s exact test were used to compare outcomes between those who received a documented comfort-care discussion as outpatient vs. inpatient and between those who received chemotherapy in the last 3 months of life vs. those who did not.

Results: 169 patients met inclusion criteria; 41 (24%) failed to meet at least one EOL quality measure. Nonconformance with EOL quality measures was distributed as (Table): chemotherapy in the last 14 days: 11/169 (6.5%); >1 hospitalization in the last 30 days: 26/169 (15.5%); >1 emergency department visit in the last 30 days: 26/169 (15.5%); dying in an acute care setting: 15/169 (8.8%); admitted to hospice ≤3 days: 9/89 (10%); and not admitted to hospice: 80/169 (47%). Comfort-care was discussed with 103 patients (72%). Chemotherapy in the last 3 months of life was administered to 105 patients (62%). Discussion of comfort-care as an outpatient was associated with fewer hospitalizations in the last 3 months (P<0.0001) and fewer hospital days in the last 30 days (P<0.0001). Discussion of comfort-care in the ambulatory setting was associated with fewer hospitalizations in the last 3 months (P=0.0001) and fewer hospital days in the last 30 days (P=0.0001), higher likelihood of being hospitalized in the last month (P<0.0001), and lower likelihood of being admitted to hospice (P=0.01).

Conclusions: Our findings suggest that conformance with EOL quality measures and reduction in the number of end-of-life hospitalizations may be achieved by addressing comfort care in the ambulatory setting and by avoiding administration of futile chemotherapy.

Table. Comparative Costs of Surveillance

<table>
<thead>
<tr>
<th>Time Since Treatment (months)</th>
<th>Number of Recurrences (SEER data, n=13266)</th>
<th>NCCN</th>
<th>+ Annual CT</th>
<th>+ 6 Months CT</th>
<th>CA-125</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1459</td>
<td>$2,448,638</td>
<td>$2,448,638</td>
<td>$2,448,638</td>
<td>$445,472</td>
</tr>
<tr>
<td>6</td>
<td>1725</td>
<td>$1,149,529</td>
<td>$1,149,529</td>
<td>$1,287,422</td>
<td>$792,958</td>
</tr>
<tr>
<td>9</td>
<td>1591</td>
<td>$5,368,807</td>
<td>$5,368,807</td>
<td>$5,297,258</td>
<td>$3,015,661</td>
</tr>
<tr>
<td>12</td>
<td>2654</td>
<td>$6,269,075</td>
<td>$4,730,185</td>
<td>$2,317,293</td>
<td>$1,140,511</td>
</tr>
<tr>
<td>15</td>
<td>1459</td>
<td>$5,368,967</td>
<td>$11,184,859</td>
<td>$16,982,751</td>
<td>$980,032</td>
</tr>
<tr>
<td>18</td>
<td>1327</td>
<td>$4,945,547</td>
<td>$9,197,214</td>
<td>$17,894,548</td>
<td>$882,079</td>
</tr>
<tr>
<td>21</td>
<td>1061</td>
<td>$3,942,075</td>
<td>$6,892,633</td>
<td>$15,033,750</td>
<td>$717,168</td>
</tr>
<tr>
<td>24</td>
<td>398</td>
<td>$2,938,513</td>
<td>$6,891,847</td>
<td>$10,845,181</td>
<td>$534,593</td>
</tr>
<tr>
<td>Total at 2 Years</td>
<td></td>
<td>$32,566,151</td>
<td>$58,130,712</td>
<td>$112,816,843</td>
<td>$6,508,474</td>
</tr>
</tbody>
</table>

71

Cost-effectiveness of early palliative care intervention in recurrent platinum-resistant ovarian cancer

W. Lowery1, A. Lowery1, J. Barnett2, M. Lopez-Acevedo1, P. Lee1, A. Alvarez-Secord1, L. Havrilesky1

1Duke University Medical Center, Durham, NC, 2Brooke Army Medical Center, Fort Sam Houston, TX

Objective: Early palliative care intervention has been shown to reduce hospital admissions, emergency department (ED) visits, and chemotherapy administration in the last 30 days of life in patients with metastatic non-small cell lung cancer. Platinum-resistant ovarian cancer and metastatic non-small cell lung cancer share an aggressive clinical course. The purpose of our study was to determine if early palliative care intervention (EPC) in patients with recurrent, platinum-resistant ovarian cancer has the potential to be cost-saving or cost-effective.

Methods: A decision model with a 6-month time horizon was constructed to evaluate routine care versus routine care plus early referral to a palliative medicine specialist (EPC) in patients with recurrent platinum-resistant ovarian cancer. The primary outcome was the average cost of each strategy. Model parameters included rate of inpatient admissions, ED visits, and chemotherapy administration as well as quality-of-life (QOL) scores. Based on published ovarian cancer data, we assumed baseline event rates over the last 6 months of life as: hospitalization, 70%; chemotherapy, 60%; ED visit, 30%. Data from a previous randomized trial evaluating EPC in patients with metastatic lung cancer was used to model odds ratios (ORs) for reductions in hospitalization (OR 0.69), chemotherapy (0.77), and ED care (OR 0.74). The costs of hospitalization ($5,302), ED visit ($784), chemotherapy ($3,923 per cycle liposomal doxorubicin), and 6 monthly palliative care visits ($471) were based on published national data. Ranges of each estimate were used for sensitivity analysis. QOL was modeled for sensitivity analysis using published data from the lung cancer randomized controlled trial to estimate effectiveness in quality adjusted life years (QALYs); survival was assumed equivalent.

Results: EPC intervention was associated with a cost savings of $1,285 per patient over routine care. In sensitivity analysis incorporating QOL, EPC was cost-effective, with an incremental cost-effectiveness ratio (ICER) <$100,000/QALY, unless the cost of the palliative intervention exceeded $3,000 (Figure). Assuming no clinical benefit other than QOL (no change in chemotherapy administration, hospitalizations, or ED visits), EPC remained highly cost-effective, with an ICER of $37,440/QALY.
Conclusions: EPC intervention has the potential to reduce the cost associated with end-of-life care in patients with ovarian cancer.

72

Is a home-based palliative care treatment strategy preferable to standard chemotherapy in recurrent cervical cancer?

N. Phippen1, C. Leahy2, C. Miller1, W. Lowery1, L. Havrilesky1, J. Barnett1
1Brooke Army Medical Center, Fort Sam Houston, TX, 2University of Alabama at Birmingham, Birmingham, AL, 3Duke University Medical Center, Durham, NC

Objective: Recurrent cervical cancer (RCC) has a poor prognosis. Despite questionable benefit, treatment is often given at the expense of substantial toxicity. A panel of poor prognostic factors recently identified a high-risk group with an even worse prognosis. A prominent lung cancer study showed improved survival and quality of life (QOL) with treatment incorporation of home-based palliative care. We evaluated the comparative effectiveness of 4 management strategies for RCC: 1) standard combination chemotherapy for all (STD); 2) selective standard chemotherapy for low- to intermediate-risk patients, while high-risk patients receive home-based palliative care (SC); 3) single-agent chemotherapy plus home-based palliative care for all (C); and 4) home-based palliative care for all (H).

Methods: A cost-effectiveness decision model was constructed. A Gynecologic Oncology Group (GOG) pooled analysis identified prognosis risk profiles for RCC (high-risk overall survival [OS]: 5.5 months, intermediate-risk OS: 9.2 months, low-risk OS: 11.1 months). A survival reduction of 24% was assumed for C compared to STD based on phase III single-agent platinum data, while a 40% reduction was assumed for H and varied in sensitivity analysis (SA). Using these assumptions, survival was modeled as follows: STD: 8.9 months; SC: 8.7 months; C: 6.7 months; H: 5.3 months. Costs for STD and SC were based on cervix cancer final year of life expenditure data for Medicaid beneficiaries, while palliative care costs were based on Medicare reimbursement data. Equal QOL was assumed for base case. SA was used to vary OS, QOL, and cost.

Results: The least effective, least costly strategy was H at 5.3 months (median cost, $11K). With OS of 6.7 months and 8.7 months and median costs of $15K and $29K, respectively, C and SC were both potentially cost-effective compared to H with incremental cost-effectiveness ratios (ICERs) of $40K and $81K per quality-adjusted life-year (QALY). STD was most effective (8.9 months), most costly ($33K), and not cost-effective over SC, with an ICER of $276K/QALY; STD remained cost-ineffective in all SA. When high-risk patients receiving home-based palliative care (chemotherapy withheld) lived longer than 4.5 months, SC became the most effective strategy. Both C and SC became cost-ineffective, with small QOL decreases compared to H.

Conclusions: Strategies incorporating home-based palliative care into the treatment of RCC are likely more cost-effective and possibly even more effective than standard treatment and warrant evaluation in prospective trials.

73

Symptoms of posttraumatic stress disorder in women who have undergone exenterative pelvic surgery for treatment of gynecologic malignancy

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Objective: The aim of this study was to determine the rate of clinically significant symptoms of posttraumatic stress disorder (PTSD) 1 or more years after exenterative pelvic surgery for gynecologic cancer.

Methods: Participants completed a validated self-report instrument (PTSD Checklist-Specific [PCL-S]) as part of a larger study of quality of life after anterior, posterior, or total pelvic exenteration. Two previously published scoring methods for the PCL-S were used to determine the rate of clinically significant PTSD symptoms in this sample. One scoring method uses an empirically derived cutoff for the total score (sum) of items, whereas the other method screens for items corresponding to positive Criteria B, C, and D for the diagnosis of PTSD, as specified in the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Data were analyzed using descriptive statistics and Spearman rank-order (nonparametric) correlations.

Results: Participants (n=17) had a mean age of 58 years at the time of surgery. Surveys were completed at a mean of 5 years after the date of surgery (range, 1-17 years). 6 participants (35.3%) endorsed moderate-to-extreme bother related to surgery. 4 (23.5%) participants screened positive for PTSD using both scoring methods for the PCL-S item responses. Those who screened positive for PTSD symptoms were survivors of cervical (n=1), vaginal (n=2), and ovarian (n=1) cancers. Age at time of surgery was negatively correlated with PCL-S score (rho=-.50, P=0.04). There was no relationship between PCL-S score and time elapsed since surgery.

Conclusions: Nearly one-fourth of participants endorsed items suggestive of probable PTSD. Participants who were older at the time of surgery appeared to endorse less severe symptoms of PTSD. Our small sample size limited our ability to detect other demographic or clinical predictors of PTSD symptoms. However, the psychological stress and morbidity resulting from pelvic exenteration have the potential to contribute to poor mental health status in any population. As empirically supported treatments for PTSD exist, screening for PTSD should be considered in the routine follow-up care of women who have undergone exenterative pelvic surgery.

74

Changes in perceptions of screening over time among average-risk women undergoing ovarian cancer screening using the risk of ovarian cancer algorithm

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Objective: Ovarian cancer screening (OCS) trials are currently ongoing in the United States and United Kingdom. As we await those results, it is important to determine how OCS may affect women. The objective of this study was to identify how perceptions toward OCS change over time in women enrolled in an OCS trial with the risk of ovarian cancer algorithm (ROCA).

Methods: Postmenopausal women with the same ovarian cancer risk as the general population were surveyed prospectively between 2001 and 2011 upon their entry into a large, multicenter, prospective OCS study utilizing the ROCA. The survey queried ovarian cancer worry (Cancer Worry Scale [CWS]), anxiety (State-Trait Anxiety Inventory [STAI]), health and well-being (SF-36), and acceptability of OCS. Surveys were readministered in 2012 to women who had completed a baseline survey and had participated in the OCS study >1 year.

Results: Of the 594 women who completed a baseline survey, 64.5% completed a follow-up survey. Median age of respondents was 65 years (range, 52-84 years), 92% were white, and median time between surveys was 65 months (range, 15-
124 months). Compared to baseline, follow-up CWS scores (6 vs. 7, P<0.001) and STAI-S scores (26 vs. 30, P<0.001) were significantly lower, meaning cancer worry and situational anxiety decreased during the OCS trial. STAI-T and SF-36 scores were not significantly different from baseline (all P >0.05). Follow-up responses indicated OCS was acceptable and were not significantly different from baseline, with 97.9% agreeing that "the benefits of screening outweigh the difficulties," and few women reporting reluctance to undergo OCS because of time constraints (1.3%), pain (1.6%), or embarrassment (2.1%). During the OCS study, some women had elevated CA-125 values that prompted additional blood work and/or ultrasound. When follow-up responses of these women were compared to those who always had normal CA-125 values, there were no significant differences in cancer worry, anxiety, or OCS acceptability (all P >0.05). Surveys were completed at various times after the abnormal tests, suggesting there are no long-term differences.

Conclusions: OCS did not lead to increased anxiety or cancer worry in our population of average-risk women. Furthermore, women who required additional testing, as determined by the ROCA, did not have any long-term differences in cancer worry or anxiety. These findings suggest that OCS with the ROCA would be acceptable to the general population and would be unlikely to lead to undue distress.

75

Improved outcomes with beta blocker use in epithelial ovarian cancer patients
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Objective: Preclinical evidence suggests that sustained adrenergic activation can promote ovarian cancer growth and metastasis. Beta-1 receptors are primarily found in the heart, and selective beta-1 antagonists have negative inotropic and chronotrophic effects. In contrast, beta-2 receptors are located in many different tissues. Nonselective agents work on both beta-1 and beta-2 receptors. We examined the impact of beta-adrenergic blockade on clinical outcomes of women with epithelial ovarian, primary peritoneal, or fallopian tube cancers (collectively called EOC).

Methods: A multicenter review of 1,425 women with histopathologically confirmed EOC was performed. Comparisons were made between patients with documented beta-blocker use during their chemotherapy and those without beta-blocker use.

Results: Median age of patients in this study was 61 years (range, 31-93 years). Among all cases, 1,304 (91.5%) patients had tumors of serous histology and 90.2% of patients had advanced-stage (III or IV) disease. The sample included 501 (35.2%) patients with hypertension, 269 (18.9%) of whom were on beta-blockers. Of those, 195 (13.7%) were on beta-1-selective agents and the remaining were on nonselective beta-antagonists. Indications for beta-blocker use included hypertension, arrhythmia, and postmyocardial infarction. Median disease-specific survival (DSS) for patients with hypertension was 41.4 months compared to 47.4 months for those without hypertension (P=0.004). For those patients on beta-blockers, the median DSS was 48.6 vs. 42.4 months (P=0.02). The median DSS based on beta-blocker receptor selectivity was 90 months for those on nonselective beta-blockers versus 38.2 months for those on beta-1-selective agents (P<0.001).

Conclusions: Use of beta-blockers in patients treated for EOC was associated with improved survival compared to that of those not using beta-blockers. Our findings of improved survival for those on nonselective beta-antagonists have implications for new therapeutic approaches.

76

Pelvic pain, quality of life (QOL), and exercise in gynecologic cancer patients: A single institution study
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Objective: To explore the correlation between QOL and body mass index (BMI), self-reported diet, and exercise in cancer patients. In addition, to describe the specific relationship with pelvic pain and the previously noted factors.

Methods: A single-institution cross-sectional study was undertaken consisting of a 6-page survey distributed to a random sample of patients receiving cancer care at a comprehensive cancer center. The anonymous survey, which contained self-reported demographic, treatment, lifestyle, QOL, and pelvic pain characteristics, was randomly distributed to cancer patients. The QOL data collected were the Functional Assessment of Cancer Therapy-General (FACT-G) in addition to a previously validated female pelvic pain survey. FACT-G, pelvic pain scores, and subdomains were compared by patient descriptive variables (exercise, diet, BMI, stage, disease status, treatment) using 2-group t-tests or analysis of variance.

Results: From January to August 2012, 95 cancer patients completed the survey; 85 (89.5%) were female and included in the analysis. The majority of patients were in the 31-70 years age range (n=75), with roughly 80% being English-speaking (n=67), 72% having primary gynecologic cancers (n=61), and the mean BMI being 28.4±8.3. Over half of the patients reported receiving chemotherapy and/or radiation. 54 (64%) patients had stage data available and were distributed as follows: 24% stage I, 26% stage II, 30% stage III, 20% stage IV; 31 patients did not report stage. 24% of the patients reported never exercising and 45% reported eating 1-2 servings of fruits and/or vegetables per day. In multivariate analysis, higher pelvic pain scores and never exercising were significantly associated with worse QOL (P<0.05). BMI, stage (early versus advanced), and treatment type were not significantly associated with QOL. Mean scores for the FACT-G and Functional Well-being (FWB) subdomain were significantly higher in patients who exercised daily/weekly versus never, (FACT-G: 78.7 vs. 68.2, P=0.036 and FWB: 18.8 vs.14.5, P=0.018).

Conclusions: Data collected in this study demonstrate that pelvic pain scores are the most influential variable on QOL in this population, where almost three quarters have a gynecologic malignancy. However, preliminary analysis also demonstrates an association between exercise and QOL. After adjusting for pain, exercise was the only other factor that was found to have significance as a predictor for QOL.
The number of these truly eligible cases enrolled on a protocol was noted. Appropriate statistical tests were used.

Results: Five-hundred eighty-four cases were identified as potentially eligible for 21 GOG protocols. Three-hundred ninety-five (68%) were truly eligible after careful review of all eligibility criteria. Of these 395 truly eligible cases, 85 (22%) were enrolled onto a protocol. Whether a trial was either placebo-based, therapeutic or not, or randomized was not associated with enrollment rates. Enrollment for vaccine-based protocols was significantly higher than for other types of protocols (61% vs. 19%; P<0.0005). Enrollment rates for phase I, II, and III and longitudinal protocols were 36%, 27%, 15%, and 19%, respectively (P<0.0005). Enrollment rates based on primary disease site were: ovary (28%), endometrium (10%), uterine leiomyosarcoma (15%), cervix (24%), and preventive (6%) (P<0.0005). The enrollment rate for protocols containing a biologic targeted agent was 30% compared to 10% for protocols not containing such an agent (P<0.0005). The enrollment rate for protocols chaired by institutional faculty was 27% compared to 17% for protocols not nationally chaired by institutional faculty (P=0.03).

Conclusions: Approximately one quarter of patients eligible for cooperative group protocols will be enrolled. There is an apparent need to enhance protocol enrollment. Enrollment rates appear to be higher for protocols that are vaccine-based, are phase I and II, and incorporate targeted therapies. Enrollment for protocols chaired nationally by institutional faculty also appears to be higher. Incorporation of placebo arms and randomization do not appear to affect patient enrollment.

Table. Toxicity Profiles

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79

The lead-in phase I/II trial design to interrogate novel biological agents

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Objective: Novel target discovery from genomic interrogation is rapidly outpacing drug development, which has placed a premium on patient resources. The mismatch has also led to a call for more efficient trial designs, which are optimized to deliver insight into multiple research questions without increasing sample size. In addition, some targeted agents are better suited as partners in therapeutic combinations. We propose a “lead-in” phase I study design that provides an opportunity to evaluate early target engagement effects both as a single agent and in combination with a therapeutic partner as one option to address this clinical conundrum.

Methods: The standard design of the lead-in phase I combination trial is a shortened exposure window (also called cycle 0), which is centered around administration of the novel single agent, followed by cycle 1 of combination or standard treatment. The window provides an opportunity to evaluate target-specific effects on the tumor and microenvironment (pharmacodynamics [PD] effects, target and bystander engagement, imaging, biomarker discovery) as well as agent-specific parameters (toxicity, pharmacokinetics [PK]), both alone and in combination with a desired therapeutic partner (e.g., chemotherapy or other biologic therapy). The duration of cycle 0 depends on anticipated target modulation time frames; early biomarker development provides opportunities to test early discontinuation strategies.

Results: We have used this trial design to evaluate several new compounds in patients with gynecologic cancers. On the basis of preclinical data, a current trial is evaluating modulation of EphA2 and other biomarkers in response to dasatinib, a small-molecule multi-tyrosine kinase inhibitor, in women with advanced or recurrent endometrial cancer. The trial design is depicted in the Figure. The duration of the dasatinib lead-in is 14 days and is accompanied by paired tissue biopsies and blood to evaluate impact on potential predictive biomarkers. Cycle 1 initiates the therapeutic partner (paclitaxel/carboplatin), and tolerance and efficacy is examined in this phase Ib trial. Recruitment/analysis is ongoing, but we have been able to serially capture EphA2-staining circulating tumor cells and circulating nucleic acids for quantitative assessment in cycle 0 (and subsequent cycles).

Conclusions: The “lead-in” trial design for early drug development affords comprehensive evaluation of single agent and combination short exposure PK, PD, and toxicity effects.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

81

Characteristics and outcomes of gyn-oncology patients treated on phase I trials (1999-2012)
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Objective: Phase I trials evaluate dosing characteristics, safety, and adverse effects of novel agents or unique combinations and new delivery methods of conventional therapies. This study examined the characteristics and outcomes of patients (pts) with gynecologic malignancies treated on phase I trials.

Methods: We reviewed records for 410 pts participating in 43 different phase I trials at a single institution from 1999-2012. Demographic, pathologic, and treatment-related information was abstracted and analyzed.

Results: Phase I trials included: 17 Phase Ib, 17 Phase Ia dose escalation, and 9 dose expansion. Nine trials (21%) investigated unique cytotoxic delivery methods, 15 (35%) conventional cytotoxics plus novel agents, and 19 (44%) novel agents alone. Six required prescreening of molecular targets for eligibility. The median age was 57 years. 64% of pts were treated in an upfront setting and 36% with recurrent disease (dz). The most common dz site was ovary (n=239), followed by cervix (n=92), uterus (n=69) and vagina/vulva (n=6). Median number of prior therapies for pts with recurrent dz was 3 (range, 1-14). Of pts treated in the upfront setting, 74% achieved complete response (CR), 16.5% partial response (PR), 7.4% stable disease (SD), and 1.7% progressive disease (PD). 23% of these pts discontinued trials due to toxicity. The median progression-free survival (PFS) was 18.5 months. For recurrent dz, 2 achieved CR, 11 PR, and 57 SD, for an overall clinical benefit rate of 57%. 28% of these pts discontinued trials due to toxicity. Median survival from time of referral to the phase I program was 8.9 months. Thirty pts were treated with agents requiring tissue screening, all in the recurrent setting. The overall response rate was 46.2%. There was no difference in median PFS for pts with screened (3.73 months) vs. non-screened (3.16 months) therapies (P=0.93). Pts with platinum resistance had a clinical benefit rate of 57%, and a median PFS of 4.6 months. Recurrent endometrial cancer pts had a median PFS of 3.5 months and an overall clinical benefit rate of 59%.

Conclusions: Phase I trials demonstrate excellent response rates in the primary treatment setting and offer clinically meaningful outcomes for recurrent dz. Pts with recurrent ovarian and endometrial cancers have comparable response rates to phase II trials. Agents requiring tissue screening did not perform better than those open to all tumor types. Phase I trials are a promising therapeutic option for selected pts, and increased referral to phase I programs will identify promising agents earlier in drug development.
Homologous recombination defects are common in non-serous ovarian, fallopian tube, and peritoneal carcinomas

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Objective: Cells that are defective in homologous recombination (HR) DNA repair demonstrate increased sensitivity to poly-ADP-ribose polymerase inhibitors (PARPis). 50% of serous ovarian carcinomas may have defects in HR, which are targeted in several clinical trials of PARPis. The rate of HR deficiency in nonserous cases is unknown. We sought to determine the rate of germline and somatic mutations in HR genes in an unselected series of women with nonserous ovarian carcinoma.

Methods: Neoplastic and germline DNA from 65 nonserous ovarian, fallopian tube, or peritoneal carcinomas were evaluated for germline and somatic mutations in 30 tumor suppressor genes, including BRCA1, BRCA2, and 13 other HR genes, using targeted capture and massively parallel genomic sequencing. All cases underwent centralized pathology review to confirm histology. Cases of low malignant potential and cases referred due to genetic risk were excluded. All suspected deleterious mutations were verified with Sanger sequencing and only clear loss-of-function mutations were included.

Results: Overall, 20 of 65 (31%) nonserous cases had a germline (20%) and/or somatic (14%) loss-of-function mutation in one or more of the following genes: BRCA1 (10.8%), BRCA2 (4.6%), CHEK2 (7.7%), ATM (3%), BRRP1 (3%), RAD50 (1.5%), RAD51C (1.5%), RAD51D (1.5%), and FAM175A (1.5%). Specifically, somatic or germline HR mutations were noted in 5 of 17 (29%) clear cell, 6 of 24 (25%) endometrioid, 3 of 13 (23%) carcinosarcoma, 3 of 7 (43%) mixed (all predominantly endometrioid) histologies, and in 3 of 8 (38%) grade 1 carcinomas. Additionally, 2 of 3 (67%) small cell and 1 transitional cell carcinoma had germline mutations in RAD50, CHEK2, and FAM175A, respectively. In comparison, 87 of 291 (30%) serous carcinomas had mutations in HR genes, including 68 germline (23%) and 21 somatic (7%).

Conclusions: Approximately 30% of nonserous histologic subtypes have a germline or somatic HR gene mutation, a similar rate to that of serous carcinomas using the same gene panel. Therefore, we do not find evidence that HR deficiency is more prevalent in high-grade serous compared to nonserous carcinomas. The HR deficiency caused by these loss-of-function mutations would theoretically make these carcinomas sensitive to PARPis. Current clinical trials of PARPis in sporadic ovarian carcinoma should include cases with nonserous histology, and testing for mutations in HR genes might inform patient selection.

Etiologic heterogeneity in endometrial cancer: Evidence from a Gynecologic Oncology Group trial

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Objective: Although the epidemiology of typical endometrial carcinomas (grades 1-2 endometrioid or type I) is well established, less is known about higher-grade endometrioid or nonendometrioid carcinomas (type II). Within a large Gynecologic Oncology Group trial (GOG-210), which included central pathology review, we investigated the etiologic heterogeneity of endometrial cancers by comparing risk factors for different histologic categories.

Methods: Based on epidemiologic questionnaire data, risk factor associations, expressed as odds ratios (OR) with 95% CI, were estimated comparing grade 3 endometrioid and type II cancers (including histologic subtypes) to grades 1-2 endometrioid cancers.

Results: Compared with 2,244 grades 1-2 endometrioid cancers, women with grade 3 endometrioid cancers (n=354) and those with type II cancers (321 serous, 232 mixed epithelial, 141 carcinosarcomatous, 77 clear cell, 60 other malignancies) were older; more often non-white, multiparous, and current smokers; and less often obese. Risk factors for grade 3 endometrioid carcinomas were similar to type II cancers, with the exception that the latter were more strongly influenced by a history of breast cancer and prior tamoxifen use. These differences largely reflected higher rates of these exposures for serous cancers and carcinosarcomas.

Conclusions: Risk factors for aggressive endometrial cancers, including grade 3 endometrioid and nonendometrioid tumors, appear to differ from lower-grade endometrioid carcinomas. Our findings support etiologic differences between type I and II endometrial cancers as well as additional heterogeneity within type II cancers. These findings may have value for improving cancer surveillance and support the need for molecular profiling of endometrial cancers.

Towards personalized PARP therapy: XRT-induced Rad51 predicts response to ABT-888 in ovarian cancer

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Objective: Ovarian cancer patients with BRCA mutations derive benefit from poly-ADP-ribose polymerase (PARP) inhibitor therapy. As many as 50% of ovarian cancer tumors have homologous recombination (HR) deficiencies defined by genetic analysis, raising the possibility that these patients may also benefit from PARP inhibition. However, genetic analysis does not necessarily predict functional deficits that would be more predictive of response. We sought to develop and validate a clinically feasible functional assay, XRT-induced Rad51 formation (XR51a), that would allow prediction of PARP therapy in ovarian cancer.

Methods: Because cells with HR defects have reduced activation of Rad51 in response to XRT, we sought to correlate this functional response to PARP therapy. Established ovarian cancer cell lines and freshly collected ovarian tumor samples were irradiated and probed for Rad51 foci. Baseline Rad51 expression without XRT exposure was also assessed by Western blot and immunohistochemistry. Cell lines were then exposed to the PARP inhibitor ABT-888 to determine effects on growth, both alone and in combination with carboplatin. Microarray data for the cell lines were compared with an established 60-gene “BRCA-ness” signature to determine if this signature also correlated with ABT-888 response.

Results: Three of seven cell lines were found to be sensitive to PARP inhibition. In each of these lines, 5- to 7-fold sensitization to carboplatin was demonstrated. The most PARP-sensitive line, A2780ip2, also had the lowest rate of Rad51 foci formation. Four of eight freshly collected patient tumors had impaired Rad51 foci formation, consistent with published rates of HR deficiency based on genetic profiling in ovarian cancer. Rad51 expression at the protein level was present in all cell lines but only detectable in 1 patient sample. This demonstrates that functional assessment of HR defects must be examined to differentiate between responsive cancers. Cross-matching data from a 60-gene “BRCA-ness” signature revealed a strong correlation between the signature and diminished Rad51 foci formation.

Conclusions: Rad51 foci formation after irradiation correlates with PARP inhibitor sensitivity in ovarian cancer, whereas protein analysis of total Rad51 expression is not a reliable substitute. Functional assessment of HR defects is feasible in primary patient samples and is consistent in frequency with predictions from genomic data.
85 Interleukin-stimulated cellular therapy: Effectiveness against ovarian cancer using in vitro and in vivo models

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1Florida Hospital Cancer Institute, Orlando, FL, 2University of Central Florida, Orlando, FL, 3CTI Clinical Trial and Consulting Services, Cincinnati, OH

Objective: To compare the ex vivo expansion potential and cytotoxic responses elicited by cytokine-induced killer cells (CIK) from ovarian cancer (OC) patients and healthy donors (HD) in the presence or absence of interleukin (IL)-7. To assess the therapeutic efficacy of immune cell therapy using an in vivo xenograft mouse model of OC.

Methods: Peripheral blood mononuclear cells isolated from 12 OC patients and 6 HD were expanded in our previously reported cocktail (IL-2, IL-12, and anti-CD3 antibody) with and without IL-7 (10 ng/mL). Ex vivo expanded CIK cytotoxicity was assessed against an OC cell line (SKOV3-AP2) in the presence of IL-2 and interferon (IFN)α-2b. To determine in vivo activity, OC cells (1x106) were injected intraperitoneally (IP) into athymic nude mice (n=80). Day -7 after OC cell injection, mice were injected IP with mononuclear cells (MC) from HD in triplicate experiments (MC; 5x106 and IL-2 [4,000 U]; n=7/group). IL-2 injections were continued thrice weekly. Control mice with and without MC and with and without IL-2 were also included. One group of mice received a second dose of MC on day -21. Mice were sacrificed when they became moribund due to tumor burden, at which time solid tumor and ascitic fluid were measured/collected.

Results: CIK expanded exponentially in both culture conditions over 3 weeks, but average fold expansion doubled in the presence of IL-7 (159-fold) compared to cultures without IL-7 (81-fold) (P<0.05). Expansion cultures consisted primarily of T cells (>98%) by day 8. There was no difference in cytotoxicity elicited against OC cells by CIK expanded in IL-7 (25.8%) compared to CIK expanded without IL-7 (28.5%) (P=0.57). No cytotoxicity was observed in negative controls lacking CIK (0.8%). In the in vivo experiments, animals tolerated all MC and cytokine dosages. Mice receiving MC+IL-2 treatment had improved survival at 9 weeks (60%) (P<0.05) compared to untreated mice (20%) or mice treated with IL-2 alone (0%) or MC alone (20%). Mice that received a second dose of MC did not show a survival advantage compared to those receiving a single dose.

Conclusions: IL-7 augments the expansion of CIK from OC patients and HD in vitro without a decrease in cytotoxic effect and, therefore, may be useful for development of immune therapy for OC. OC-bearing mice treated with MC+IL-2 showed improved survival. Both MC and CIK cells showed effectiveness against OC. Animal studies are underway to test CIK, MC, and their combination. Data generated will provide the basis for development of an immunotherapy-based phase I trial for OC.

86 Intraperitoneal delivery of human natural killer cells for treatment of ovarian cancer

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Objective: Dramatic clinical antitumor effects have been observed with interleukin (IL)-2 activated natural killer (NK) cells. However, to date intravenous (IV) delivery of NK cells in ovarian cancer patients has not been successful in ameliorating disease. We investigated in vivo expansion and persistence of intraperitoneally (IP) delivered NK cells in an ovarian cancer xenograft model to determine if delivery mode can affect tumor cell killing and circumference lack of NK cell expansion.

Methods: NOD/SCID/γc-/- (NSG) mice were sublethally irradiated (225 cGy) (Day -5) and xenografted with firefly luciferase-expressing MA-148 tumor cells IP (Day -4). On Day 0, mice were given 20x106 CD3/CD19-depleted IL-2-activated human NK cells IP followed by IP injections of IL-15 or IL-2. Tumor burden was monitored by bioluminescent imaging. NK cell engraftment and trafficking were evaluated. Transplanted NK cells were evaluated by flow cytometry and cytotoxicity assays. Differences between groups were compared using a paired T-test; results were considered significant at P values of 0.05 or less.

Results: NK cells remained IP 54 days following injection and had markers of maturation. Tumor-only mice had significant tumor burden (34.3% GFP+/MA-148 cells) (Figure). NK cell-treated mice had significantly reduced levels: NK + IL-2 group = 0.375% GFP+ (P=0.005) and NK + IL-15 group = 19.11% GFP+ (P=0.008). High levels of NK cells were found in peritoneal washings, with higher numbers in the IL-2 (19.8%) vs. IL-15 (4.07%) group. Peripherally circulating NK cells were seen in both IL-2 and IL-15 groups on days 7, 14, and 21. Surviving NK cells killed ovarian cancer cells in vitro at a rate similar to preinfusion levels, supporting that in vivo functionality of human NK cells can be maintained following IP infusion.

Conclusions: IP delivery of NK cells leads to stable engraftment, expansion, and antitumor response in an ovarian cancer xenograft model. These data support further preclinical and clinical evaluation of IP delivery of allogeneic NK cells in ovarian cancer.

87 18F-fluorodeoxyglucose positron emission tomography (PET) and computed tomography (CT)-based nomogram for prediction of incomplete cytoreduction in patients with advanced ovarian cancer

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Objective: Complete cytoreduction (no macroscopic residual disease) is known to be one of the most important prognostic factors in advanced-stage EOC. The aim of this study was to develop a preoperative 18F-FDG PET/CT-based nomogram predicting for incomplete cytoreduction (macroscopic residual disease) in patients with advanced-stage epithelial ovarian cancer (EOC).

Methods: One hundred fifty-nine patients with AEOC who underwent PET/CT before primary cytoreduction in our institution between 2004 and 2009 were retrospectively reviewed. Possible variables, including 10 PET/CT features for prediction of incomplete cytoreduction, were analyzed using a logistic regression model. Ratio between the highest standardized uptake value (SUVmax) in the upper abdomen and lower abdomen divided at the level of umbilicus was expressed as UA/LA SUVmax. A nomogram based on this model was developed and internally validated by bootstrapping. Its performance was assessed by using the concordance index and a calibration curve.

Results: The median age and follow-up period were 55 (range, 27–80) years and 28 (range, 1–83) months, respectively and 133 and 26 patients had stage III and IV disease, respectively. There were 114 and 50 cases of recurrence and disease-specific death, respectively. Complete cytoreduction was achieved in 44 (27.7%) patients. Multivariate regression analysis (Table and Figure) revealed
that 4 PET/CT features, including diaphragm disease ($P=0.022$, odds ratio [OR] 3.579, 95% CI 1.025–10.628), peritoneal carcinomatosis ($P=0.013$, OR 8.224, 95% CI 1.558–43.456), lymph node outside abdomen ($P=0.011$, OR 4.145, 95% CI 1.382–12.429), and UA/LA SUVmax ($P=0.002$, OR 6.284, 95% CI 1.965–20.091), were independent predictors of incomplete cytoreduction. A nomogram predicting for incomplete cytoreduction incorporating these 4 significant variables was constructed. The concordance index was 0.844 (95% CI 0.778–0.910). The predictive ability of the nomogram proved to be superior to that of the traditional predictors (CA-125 and albumin) ($P<0.05$).

**Conclusions:** The nomogram based on 4 preoperative PET/CT features (diaphragm disease, peritoneal carcinomatosis, lymph node outside abdomen, UA/LA SUVmax) resulted in the accurate prediction of incomplete cytoreduction in patients with AEOC. If externally validated, it could be used in patients with AEOC for establishing a more meticulous preoperative plan or considering neoadjuvant chemotherapy.

**Table. Univariate and Multivariate Analyses of Predictors of Incomplete Cytoreduction**

<table>
<thead>
<tr>
<th>Variables</th>
<th>n</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (as a continuous variable)</td>
<td>159</td>
<td>1.020 (0.990–1.051) 0.186</td>
<td>OR (95% CI) 1.051 (0.962–1.148) 0.270</td>
</tr>
<tr>
<td>Parity (as a continuous variable)</td>
<td>159</td>
<td>1.167 (0.924–1.474) 0.194</td>
<td>OR (95% CI) 1.167 (0.924–1.474) 0.194</td>
</tr>
<tr>
<td>Menopause</td>
<td>No (62)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes (96)</td>
<td>0.580 (0.286–1.180) 0.599</td>
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<tr>
<td>Diaphragm disease</td>
<td>No (105)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes (54)</td>
<td>5.791 (2.127–15.768) 0.001</td>
<td>OR (95% CI) 3.579 (1.205–10.628) 0.022</td>
<td></td>
</tr>
<tr>
<td>Large bowel mesentery implants</td>
<td>No (95)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes (64)</td>
<td>2.565 (1.182–5.565) 0.017</td>
<td>OR (95% CI) 1.653 (0.101–4.224) 0.655</td>
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<tr>
<td>Pleural effusion</td>
<td>No (136)</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Yes (23)</td>
<td>2.877 (0.810–10.220) 0.102</td>
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<tr>
<td>Ascites</td>
<td>No (33)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes (126)</td>
<td>3.294 (1.478–7.342) 0.004</td>
<td>OR (95% CI) 1.661 (0.539–5.116) 0.377</td>
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<tr>
<td>Peritoneal carcinomatosis</td>
<td>No (15)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes (144)</td>
<td>9.250 (2.762–30.975) &lt;0.001</td>
<td>OR (95% CI) 8.228 (1.558–43.456) 0.013</td>
<td></td>
</tr>
<tr>
<td>Small bowel mesentery implants</td>
<td>No (95)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes (64)</td>
<td>3.010 (1.360–6.662) 0.007</td>
<td>OR (95% CI) 2.182 (0.325–14.628) 0.422</td>
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<tr>
<td>Rectal implants</td>
<td>No (146)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes (13)</td>
<td>5.010 (0.632–39.733) 0.127</td>
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<tr>
<td>Pelvic lymph nodes &gt;1 cm</td>
<td>No (99)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes (60)</td>
<td>1.910 (0.893–4.085) 0.095</td>
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<tr>
<td>Retropertioneal lymph nodes &gt;1 cm</td>
<td>No (87)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes (72)</td>
<td>2.909 (1.363–6.206) 0.006</td>
<td>OR (95% CI) 1.813 (0.704–4.667) 0.217</td>
<td></td>
</tr>
<tr>
<td>Inguinal lymph nodes &gt;1 cm</td>
<td>No (153)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes (6)</td>
<td>2.018 (0.228–17.773) 0.527</td>
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<tr>
<td>Lymph nodes outside abdomen &gt;1 cm</td>
<td>No (100)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes (59)</td>
<td>5.414 (2.124–13.802) &lt;0.001</td>
<td>OR (95% CI) 4.145 (1.382–12.429) 0.011</td>
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</tbody>
</table>

**SUV\_\text{max}** in the primary tumor (as a continuous variable)

<table>
<thead>
<tr>
<th></th>
<th>159</th>
<th>1.051 (0.962–1.148) 0.270</th>
</tr>
</thead>
<tbody>
<tr>
<td>UA/LA SUV_\text{max} (as a continuous variable)</td>
<td>17.469 (5.753–53.048) &lt;0.001</td>
<td>6.284 (1.965–20.091) 0.002</td>
</tr>
<tr>
<td>Log of preoperative CA-125 (as a continuous variable)</td>
<td>2.075 (1.173–3.670) 0.012</td>
<td>0.978 (0.430–2.225) 0.978</td>
</tr>
<tr>
<td>Preoperative albumin (as a continuous variable)</td>
<td>0.376 (0.189–0.746) 0.005</td>
<td>0.954 (0.390–2.330) 0.917</td>
</tr>
<tr>
<td>Preoperative platelet count (as a continuous variable)</td>
<td>1.003 (0.999–1.006) 0.163</td>
<td></td>
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</tbody>
</table>

**SUV\_\text{max}**, maximum standard uptake value; OR, odds ratio; CI, confidence interval

\*UA/LA SUV\_\text{max} = (highest SUV\_\text{max} among the lesions in the upper abdomen divided at level of umbilicus)/(highest SUV\_\text{max} among the lesions in the lower abdomen divided at level of umbilicus).

88

**Risk-scoring system for the individualized prediction of lymphatic dissemination in unstaged patients with endometrioid endometrial cancer**

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**Objective:** The indications for definitive surgical staging in patients diagnosed with occult endometrial cancer (EC) following simple hysterectomy remain ambiguous. We propose a risk-scoring system (RSS) for individualized prediction of lymphatic dissemination after hysterectomy with or without bilateral salpingo-oophorectomy.

**Methods:** Patients who underwent surgery for EC from 1/1/1999 through 12/31/2008 were prospectively evaluated. Patients with nonendometrioid histology, synchronous cancers, insufficient follow-up, or receiving adjuvant therapy (excluding brachytherapy) without pelvic and/or paraaortic (P/PA) lymphadenectomy (LND) were excluded. Lymph node dissemination was defined as nodal metastasis when P/PA LND was performed, P/PA lymph node recurrence after negative LND, or no LND performed. Logistic regression analysis was used to identify clinical and pathologic predictors for lymphatic dissemination and develop an RSS and nomogram. Patients with inherently high risk for lymphatic metastasis, including stage IV with gross extrauterine disease and uterine serosal and adnexal involvement, were not included in RSS.
The RSS was verified for discrimination and calibration using bootstrapping to obtain unbiased estimates.

Results: Overall, 883 patients were included in the RSS, of whom 521 (59.0%) underwent PA LND and 57 (10.9%) had positive lymph nodes. Among patients who did not undergo P/PA LND (n=362) or had negative nodes (n=464), 10 (1.2%) had P/PA lymph node recurrence. Median follow-up was 5.2 years. Lymphovascular space invasion (odd ratio [OR] 1.64; 95% CI 0.84, 3.23), FIGO grade (OR 1.53; 95% CI 0.77, 3.02) and cervical tumor diameter > 2 cm (OR 5.30; 95% CI 1.22-23.12), and cervical stromal invasion (OR 1.79; 95% CI 0.66-4.83), were significant on univariate analysis (P<0.05). All preceding variables were included in a multivariable logistic model. Individualized estimates of lymphatic dissemination are illustrated in a nomogram (Figure). The unbiased estimate of the concordance index was 0.88. The model had excellent calibration.

Conclusions: Pending results of independent validation, our RSS can be used to quantify the probability of lymphatic dissemination after hysterectomy with high accuracy in patients with endometroid EC. This information is valuable in guiding postoperative counseling and surgical reintervention decisions.

89 Predictors and incidence of radical vulvectomy complications in the modern era: A National Surgical Quality Improvement Program study J. Lin1, M. Yu1, S. Beriwal1, T. Krivak1, G. Huang1, P. Sukumvanich1
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Objective: To determine radical vulvectomy complication rates in the modern era and identify prognostic indicators for complications.

Methods: All patients who underwent radical vulvectomy from 1/2005 to 12/2010 were identified from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database. This database tracks detailed preoperative and postoperative data based on medical chart review and phone and letter follow-up, with 95% success rate in capturing 30-day outcomes. Exploratory analysis of perioperative characteristics using chi-square tests with Bonferroni correction was performed to identify pre-/perioperative factors associated with postoperative complications, and binary logistic regression was used to identify factors that independently predict improved outcomes.

Results: 178 patients were identified with a mean age of 64 years. A total of 3.9% and 1.7% of patients received radiotherapy and chemotherapy within 90 and 30 days before surgery, respectively. 85 radical partial vulvectomies were performed, and an additional 24 were performed with unilateral lymphadenectomy (LND) and 24 with bilateral LND. 23 radical total vulvectomies were performed, and an additional 7 were performed with unilateral LND and 14 with bilateral LND. Skin flap/graft was used in 9% of patients. The risk of any complication was 22.5%. Wound and medical complications accounted for 14.6% and 5.6%, respectively. The risk of reoperation was 6.7%. Controlling for pre-/perioperative risk factors (e.g., age, comorbidities, laboratory values) found that active smoking within the past year (25.0% vs. 9.8%, P<0.01) and radiation therapy for malignancy within 90 days preoperatively (71.4% vs. 12.3%, P=0.0005) independently predicted wound complications, while active smoking within the past year (32.1% vs. 18.0%, P<0.05) was the only factor that independently predicted overall complications. Diabetes, increased body mass index, and low preoperative albumin levels were not independently associated with overall or wound complications.

Conclusions: This report describes patient comorbidity and complications rates in those undergoing radical vulvectomy in the modern era. Historical wound complication rates of 40% to 50% are much higher than the 22.5% observed in this cohort, suggesting that decreased complication rates may be due to improved postoperative care in recent years. Active smoking within 30 days of surgery appears to worsen outcomes while smoking history per se does not.

90 Laparoscopic single site versus conventional laparoscopic surgical staging for early-stage endometrial cancer J. Park, D. Kim, J. Kim, Y. Kim, Y. Kim, J. Nam
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Objective: To analyze the feasibility, safety, and efficacy of laparoscopic single-site (LESS) surgical staging for early-stage endometrial cancer compared to conventional laparoscopic surgical staging.

Methods: The prospective cohort consisted of 37 consecutive patients with early-stage endometrial cancer who underwent LESS surgical staging, including hysterectomy, bilateral salpingo-oophorectomy (BSO), and pelvic lymph node dissection (PLND). A control group consisted of 74 consecutive patients with early-stage endometrial cancer who underwent 4-port laparoscopic surgical staging, including hysterectomy, BSO, and PLND before the study period. Surgical outcomes were compared between the 2 groups.

Results: No one in the LESS or conventional laparoscopic surgery group required additional trocar or conversion to laparotomy. There were no between-group differences in mean age, menopause, parity, body mass index, comorbid medical disease, or previous history of abdominal surgery. There also were no between-group differences in number of total (LESS vs. conventional, 25±10.6 vs. 24.6±0.9, P=0.497), pelvic (24.6±11.4 vs. 23±7.7, P=0.459), and para-aortic (4.9±2.5 vs. 6.9±7.3, P=0.494) lymph nodes retrieved; the operating time (183±50 min vs. 173±58 min, P=0.388); estimated blood loss (194±149 mL vs. 173±106 mL, P=0.394); transfusion (5.4% vs. 8.1%, P=0.717); postoperative hospital stay (5.0±1.8 days vs. 5.1±1.8 days, P=0.911); intraoperative complication (2.7% vs. 0%, P=0.333); or postoperative complications (0% vs. 1.4%, P=0.999). After surgery, 2.7% and 4.1% in each group were upstaged due to lymph node metastasis, respectively (P=0.999).

Conclusions: LESS surgical staging that includes hysterectomy and PLND was a feasible, safe, and effective surgical management in patients with early-stage endometrial cancer. Further evaluation of LESS surgical staging in a prospective randomized trial is required.

Special Interest Session V: International Symposium
Monday, March, 11, 2013, 5:00 p.m.-6:30 p.m.
Concourse Hall (Los Angeles Convention Center)
Moderators: Byoung-Gie Kim, MD, PhD, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea. Jae-Hoon Kim, MD, PhD, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea. Jae-Weon Kim, MD, PhD, Seoul National University College of Medicine, Seoul, South Korea
Invasive endocervical adenocarcinoma – How a new proposal for a pattern-based classification can influence clinical management decisions

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1University Health Network, Toronto, Ontario, Canada, 2Memorial Sloan-Kettering Cancer Center, New York, NY, 3Mexican Oncology Hospital, Mexico City, Mexico, 4Texas Children’s Hospital, Houston, TX, 5Long Beach Memorial Hospital, Long Beach, CA, 6Cedars-Sinai Medical Center, Los Angeles, CA, 7Cleveland Clinic, Cleveland, OH, 8Kyoto University Hospital, Kyoto, Japan, 9Wayne State University, Detroit, MI

Objective: Clinically relevant pathologic criteria affecting the subsequent management of invasive endocervical adenocarcinoma (ECA) have not been effectively established, unlike those for invasive cervical squamous cell carcinoma. A critical issue in the current assessment of ECA is accurate determination of depth of invasion (DOI), a parameter widely used for staging. More than 97% of patients undergoing lymph node dissection (LND) have negative lymph nodes (LN). This study evaluated other pathologic parameters or patterns that predict risk of LN metastasis and overall patient survival and, therefore, can guide therapy.

Methods: Collated data on EAC cases from 14 international institutions were reviewed, including patient age, tumor size, grade of differentiation, DOI, presence of lymphovascular invasion (LVI) or of LN metastases, recurrences, stage, and follow-up. The cases were also classified using the new proposed system, which is based on the pattern of tumor invasion: Pattern A: well-demarcated glands (regardless of DOI); Pattern B: early stromal invasion arising from well-demarcated glands; and Pattern C: diffuse, destructive invasion.

Results: A total of 410 cases with LND were identified (stage I=1 to IVB). Patient ages ranged from 20 to 83 years, tumor size was 0.5 to 65 mm, and DOI ranged from 0.5 to 40 mm but did not exceed 20 mm in pattern B cases. LVI was present in 41.5% of cases: pattern A=0%, pattern B=34%, and pattern C=63.3%. Despite the nearly identical DOI in patients with patterns A and B (4.7 and 4.6 mm, respectively), 66% of pattern B patients were LN-positive and 2 had tumor recurrence, whereas no pattern A patients had positive LN or recurrence. Among pattern C patients, 27% had positive LNs and 21% had recurrence (Table).

Conclusions: Analysis of additional cases following our initial study further validates our observation of the clinical utility of the pattern-based classification. All pattern A cases had stage I disease and did not need LND. Few patients with pattern B had LN metastases or recurrences. Pattern C patients had the highest rate of LN metastasis and tumor recurrence and could benefit from LND. Our proposed pattern-based method is reproducible and correlates well with the status of LVI and LN metastases and with patient outcome. The clinical utility of sentinel LN assessment should be evaluated as a potentially safe alternative for pattern B and possibly for pattern C patients without clinical or imaging suspicion of LN involvement.

Table. Patient Characteristics Based on Pattern of Tumor Invasion

<table>
<thead>
<tr>
<th>Method</th>
<th># Cases</th>
<th>Stage I</th>
<th>Stage II IV</th>
<th>LVI</th>
<th>LN</th>
<th>Recurrence</th>
<th>DOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>410 (100%)</td>
<td>372 (91%)</td>
<td>38 (9%)</td>
<td>174 (41%)</td>
<td>66 (16%)</td>
<td>40 (11.7%)</td>
<td>19 (4.6%)</td>
</tr>
<tr>
<td>Pattern A</td>
<td>86 (21%)</td>
<td>86 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Pattern B</td>
<td>106 (26%)</td>
<td>104 (98%)</td>
<td>2 (1.9%)</td>
<td>31 (34%)</td>
<td>7 (6.6%)</td>
<td>2 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Pattern C</td>
<td>218 (53%)</td>
<td>182 (84%)</td>
<td>36 (16.5%)</td>
<td>238 (63%)</td>
<td>59 (27%)</td>
<td>46 (21%)</td>
<td></td>
</tr>
</tbody>
</table>

Accuracy of detection of high-grade cervical intra-epithelial neoplasia using electrical impedance spectroscopy with colposcopy

J. Tidy1, J. Healey1, B. Brown1
1Royal Halamshire Hospital, Sheffield, United Kingdom, 2University of Sheffield, Sheffield, United Kingdom

Objective: To determine if electrical impedance spectroscopy [EIS] improves the diagnostic accuracy of colposcopy when used as an adjunct.

Methods: Prospective, comparative, multicenter clinical study of women referred with abnormal cytology to 2 colposcopy clinics in England and 1 in Ireland. In phase I, EIS was assessed against colposcopic impression and histopathology of the biopsies taken. A probability index and cutoff value for the detection of high-grade cervical intraepithelial neoplasia (HG-CIN) (CIN2+) was derived to indicate sites for biopsy in phase II. EIS data collection and analyses were performed in real time and blinded to the clinician. The phase II data were analyzed using different cutoff values to assess performance of EIS as an adjunct.

Results: 474 women were recruited, 214 were eligible for analysis in phase I, and 215 were eligible in phase II. Average age was 33.2 years (median age, 30.3 years; range, 20–64 years). 48.5% (208/429) had high-grade cytology. Using the cutoff from phase I, the accuracy of colposcopic impression to detect HG-CIN when using EIS as an adjunct at the time of examination improved positive predictive value (PPV) from 78.1% (95% CI 67.5–86.4%) to 91.5%. Specificity was also increased from 83.5% (95% CI 75.2–89.9%) to 95.4%, but sensitivity was significantly reduced from 73.6% (95% CI 63.0–82.5%) to 62.1%, and negative predictive value (NPV) was unchanged. The positive likelihood ratio for colposcopic impression alone was 4.46. This increased to 13.5 when EIS was used as an adjunct. The overall accuracy of colposcopy when used with EIS as an adjunct was assessed by varying the cutoff applied to a combined test index. Using a cutoff set to give the same sensitivity as colposcopy in phase II, EIS increased the PPV to detect HG-CIN from 53.3% (95% CI 45.0–61.8%) to 67%, and specificity increased from 38.5% (95% CI 29.4–48.3%) to 65.1%. NPV was not significantly increased. Alternatively, applying a cutoff to give the same specificity as colposcopy alone, EIS increased sensitivity from 88.5% (95% CI 79.9–94.4%) to 96.6% and NPV from 80.8% (95% CI 67.5–90.4%) to 93.3%, PPV was not significantly increased. Receiver operator characteristic to detect HG-CIN had an AUC of 0.887 (95% CI 0.840–0.934).

Conclusions: EIS used as an adjunct to colposcopy improves colposcopic performance. The addition of EIS could lead to more appropriate patient management with lower intervention rates.

The Chinese Cervical Cancer Prevention Study (CHICAPS) - The development of a new model for population based cervical cancer screening

J. Belinson1, R. Wu2, G. Wang3, H. Du4, J. Zou5, J. Shen6, S. Belinson7, X. Qu1
1Preventive Oncology International/The Cleveland Clinic Foundation, Cleveland Heights, OH, 2Peking University Shenzhen Hospital, Shenzhen, Guangdong, China, 3BGI Shenzhen, Shenzhen, Guangdong, China, 4Preventive Oncology International, Cleveland Heights, OH, 5Preventive Oncology International, Shenzhen, Guangdong, China

Objective: To develop and implement a community-based preventive health care model using cervical cancer screening as the target medical intervention.

Methods: In multiple communities in rural Guangdong Province, China, using the concepts founded in community-based participatory research (CBPR), 10,000 women between the ages of 30 and 59 will be screened. The goal is the development of a model that allows the communities to totally manage the screening and results reporting process and the available health care resources to focus on management of patients. A CBPR-based system should allow massive acquisition of samples to take full advantage of the technologies of self-collection, solid transport media, and centralized high throughput to allow highly sensitive, low cost per case processing with good quality control. Positive patients will be randomized between immediate cryotherapy after VIA.

Table. Patient Characteristics Based on Pattern of Tumor Invasion

<table>
<thead>
<tr>
<th>Method</th>
<th># Cases</th>
<th>Stage I</th>
<th>Stage II IV</th>
<th>LVI</th>
<th>LN</th>
<th>Recurrence</th>
<th>DOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current</td>
<td>410 (100%)</td>
<td>372 (91%)</td>
<td>38 (9%)</td>
<td>174 (41%)</td>
<td>66 (16%)</td>
<td>40 (11.7%)</td>
<td>19 (4.6%)</td>
</tr>
<tr>
<td>Pattern A</td>
<td>86 (21%)</td>
<td>86 (100%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Pattern B</td>
<td>106 (26%)</td>
<td>104 (98%)</td>
<td>2 (1.9%)</td>
<td>31 (34%)</td>
<td>7 (6.6%)</td>
<td>2 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Pattern C</td>
<td>218 (53%)</td>
<td>182 (84%)</td>
<td>36 (16.5%)</td>
<td>238 (63%)</td>
<td>59 (27%)</td>
<td>46 (21%)</td>
<td></td>
</tr>
</tbody>
</table>
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

94 First experience of enhanced recovery in a tertiary gynecologic oncology centre in the UK

M. Doohan, J. Bailey
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Objective: Enhanced recovery is a novel approach to elective surgery that ensures that patients are in the optimal condition for the surgical treatment, thus minimizing complications, offering more effective rehabilitation and a shorter length of stay. The main aim of this project was to prospectively assess the effectiveness of this approach in patients undergoing major surgery for gynecologic cancers.

Methods: Patients were recruited between March and August 2012, from the outpatient clinic following an initial consultation with an option to refuse participation. Data were collected prospectively from the selected patients at the outset, soon after the surgery, and 28 days later using specially designed questionnaires. In addition, patients were asked to complete a daily diary documenting their care, pain control, number of walks, nutrition, and their overall experience, which they handed in at the time of discharge. Data were compared to previous studies on length of stay from within the department.

Results: From March to August 2012, 75 patients were recruited, but data were available for 50 patients who underwent surgery. The mean age of the sample was 62 years (range, 32-82 years), 92% of the cases were operated for cancer or suspected cancer. 86% of the patients were graded as ASA grade 2 or 3. Of the sample, 48% had laparoscopic surgery, 44% had laparotomy, and 6% had vaginal hysterectomy. The average length of stay following laparotomy was 5 days (range, 2 - 15 days) and following laparoscopic procedure was 2 days (range, 1-6 days), making overall average length of stay of 3.5 days. In comparison, the length of stay in cases of endometrial cancer from the same hospital in 2007 following laparotomy was 4.7 days and following laparoscopic procedures was 4.6 days. The overall complication rate was 16%, reoperation rate was 6%, and readmission rate within 4 weeks was 4%. Of all the patients responding to the patient experience questionnaire, 100% were satisfied with care provided.

Conclusions: This initial analysis of the data following the introduction of the enhanced recovery approach has confirmed a significant reduction in the length of stay after laparoscopic surgery (2 days vs. 4.6 days) while enhancing patient empowerment, involvement, and satisfaction and without any increase in the complication or readmission rates. If further analysis supports these findings, this approach should be implemented for all cancer patients.

95 The impact of cancer policy: Specialist surgery for ovarian cancer in England 2000 to 2009

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Objective: To investigate the proportion of women with ovarian cancer in England undergoing surgery in gynecologic cancer centers (GCCs) or by specialist gynecological oncologists (GOs) since the publication of the Improving Outcomes Guidance in Gynaecological Cancers (1999) and the National Health Service Cancer Plan (2000).

Methods: We conducted a retrospective analysis of English cancer registry records, Hospital Episode Statistics (HES), and General Medical Council (GMC) subspecialty accreditation. All English NHS providers from 2000 to 2009 were reviewed, and study participants were patients with ovarian cancer (ICD10 C56, C57) undergoing major gynecologic surgery within 13 months of their diagnosis (-1 to +12). The primary outcome measures were annual proportion of patients undergoing surgery at GCCs and operated on by GMC-accredited GOs or high caseload surgeons in England and by each Strategic Health Authority (SHA) area.

Results: From 2000 to 2009, 2,428 consultants were responsible for surgery on 30,753 ovarian cancer patients. There was a significant increase in the proportion of ovarian cancer patients undergoing surgery at GCCs (43% to 76%, P = 0.001), by GMC-accredited gynecological oncology surgeons (5% to 36%, P = 0.001), and by high ovarian cancer caseload (>18 cases) surgeons (22% to 56%, P <0.001) (Figure). Centralization and specialization of surgery for ovarian cancer patients has increased in England since the NHS cancer plan. In 2009, there remained room for improvement, with many patients still receiving nonspecialist surgery and large variations apparent by SHA. Although, more than half of the ovarian cancer patients were operated on by high-volume surgeons and in specialist cancer centers by 2009, the majority of patients were not operated on by GMC-accredited gynecologic oncologists. Systems of accreditation should be reviewed and trusts should ensure that HES data accurately record clinical activity and procedures.

96 The wait time creep: Changes in the surgical wait time for women with uterine cancer in Ontario, Canada during 2000-2009

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Objective: 1) To describe the wait times for uterine cancer surgery for women living in Ontario from 2000-2009 and 2) to understand demographic, tumor, and structural variables related to wait times.

Methods: We conducted a population-based study involving women in Ontario, Canada, who had uterine cancer diagnosed histologically and then treated with hysterectomy between April 2000 and March 2009. Wait time was defined as the time from diagnosis by histology to the date of hysterectomy, as reported in the Canadian Institute for Health Information (CIHI) database. Cancer diagnosis was documented using the Ontario Cancer Registry. Demographic information was identified from the registered persons database (RPDB),

triage vs. “standard of care” of colposcopy/biopsy/loop electrosurgical excision procedure. Secondary screens of cytology and genotyping will also be reported.

Results: Five thousand, seven hundred and sixty-two women have been screened in the developmental phases of the project. We now believe that our model, which can be communicated through a 1-hour workshop conducted with "poster showing" and "role playing," is ready and will be tested in the completion of the study. Fifty-three percent of the census-based eligible population has participated in the villages already screened. Accurate evaluation of those truly available (within the census) is the target for the final test. We anticipate the remaining 4,338 women will be screened by their villages over a period of 7-10 days. Eighty-four percent of those who had positive results returned for evaluation and treatment. Satisfaction in the process is >95.

Interim results of the 6 month follow-up will be reported.

Conclusions: We have a community-based model involving a self-collection, a solid media transport system (for cervical cancer screening), and "public health affordable" assays, and most patients can be treated in their community. We understand the contribution of genotyping and cytology as secondary screens, and we have developed a manual to guide communities in developing their own framework for cervical cancer screening. We believe we have demonstrated that the community can successfully conduct the screenings themselves after attending the 1-hour workshop.
A systematic review of economic evaluations on the treatment of ovarian cancer: What have we learned in the past 10 years?

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Objective: Results of economic evaluations, which compare costs and consequences of alternative treatment strategies, are more commonly being used in funding and policy decision-making. Our objective was to systematically review the literature for economic evaluations on ovarian cancer treatments published in the past 10 years, to summarize these studies qualitatively, and to evaluate their methodologic quality.

Methods: We searched MEDLINE and MEDLINE in-process and non-indexed citations from January 1, 2002 to July 27, 2012. Eligible studies were complete economic evaluations, considering both costs and clinical outcomes for at least 2 treatment alternatives for patients with ovarian cancer. Bibliographies were screened for additional eligible studies. Two reviewers independently screened studies for eligibility and assessed study quality. A validated tool, the Quality of Health Economic Studies (QHES), was used to subjectively assess study quality.

Results: We identified 21 eligible economic evaluations spanning all aspects of treatment of ovarian cancer patients, including the setting in which care is provided, chemotherapy, surgery, treatment of adverse effects, prevention of complications, and methods to diagnose recurrent disease. Five studies were trial-based and 16 studies were model-based evaluations. Although appropriate incremental analyses were presented in 18 of 21 studies (86%), 6 studies (29%) provided average cost-effectiveness ratios, which are considered inappropriate and can be misleading. Uncertainty was properly evaluated using a probabilistic sensitivity analysis or non-parametric bootstrapping in 10 studies (48%) and was displayed using a cost-effectiveness acceptability curve (CEAC) in 5 studies (24%). The average QHES score was 65 out of 100 points. When the QHES scores were compared for studies published prior to and as of 2008, overall quality did not improve (t=0.02, P=0.98). In addition, the use of CEACs and probabilistic sensitivity analysis was not more prevalent in the most recent studies.

Conclusions: Economic evaluations covered a broad range of therapeutic modalities in the treatment of ovarian cancer, but the quality of these studies was lacking and did not improve over the past 10 years. The low quality of economic evaluations in this field reduces their ability to contribute meaningfully to decision-making. Quality improvement and adoption of newer methodologies for quantifying uncertainty are urgently needed.

Robot-assisted total preservation of pelvic autonomic nerve with extended lymphadenectomy as part of nerve-sparing radical hysterectomy for cervical cancer

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Objective: To evaluate short-term clinical outcomes of robot-assisted total preservation of pelvic autonomic nerve with extended lymphadenectomy as part of nerve-sparing radical hysterectomy for early and locally advanced cervical cancer.

Methods: Between March 2011 and June 2012, we observed prospectively 28 consecutive cervical cancer patients who underwent robot-assisted autonomic nerve-sparing extended lymphadenectomy that included the superior and inferior gluteal, hypogastric vein, presacral (subaortic), common iliac, and lower para-aortic nodes.

Results: The mean age of patients was 47.1 years and body mass index was 24.1. FIGO staging was IA2 in 3, IB1 in 15, IB2 in 5, IIA1 in 3, and IIA2 in 2. The mean total operating time was 308.8±54.9 minutes, and the mean console time was 280.0±46.0 minutes. The mean blood loss was 102.7±153.8 mL. The mean number of acquired pelvic lymph nodes was 27.1±9.3, and the mean number of extended lymph nodes was 19.2±9.6 (total 46.3±14.5). 13 patients (46.4%) had node metastasis, including 9 (32.1%) who had pelvic nodal metastasis and 4 (14.3%) who had extended nodal metastasis. No intraoperative complications that required treatment occurred, although ischemic ureterovaginal fistula occurred in 4 patients (14.3%) 3-4 weeks after operation and ureter stenosis were identified in 4 patients (14.3%) as late complication after radiotherapy. The mean self-voiding time was 10±5 days. Mean follow-up time was 10 months (range, 1-16 months). There were no pelvic recurrences, but 1 patient had recurrence at the transposition of the ovary.

Conclusions: With the advantage of delicate movement of the robotic instrument, robot-assisted total preservation of pelvic autonomic nerves without compromise of the radicality is technically feasible and safe in patients with early and locally advanced cervical cancer. By using this approach, we could harvest more lymph nodes and achieved a high rate of metastatic nodes harvest while preserved voiding function. However, there was increased rate of ischemic ureter complications. Moreover, long-term survival benefit after an extended lymphadenectomy must be evaluated.

The expression of makorin ring finger protein 1 (MKRN1), pAKT, pmTOR, and PTEN in cervical neoplasia

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Objective: The protein kinase B (AKT) pathway plays a key role in the regulation of cell death and survival, and has been proposed as a central signaling event in carcinogenesis. We investigated the expression of MKRN1, which is a transcriptional coregulator and an E3 ligase, and sought to define the role of the AKT pathway in cervical neoplasia.

Methods: One hundred eighty-three cervical cancer, 415 cervical intraepithelial neoplasia, and 400 matched nonadjacent normal tissues were arrayed into tissue microarrays. MKRN1, phosphorylated AKT(pAKT), phosphorylated mammalian target of rapamycin (pmTOR), and total phosphatase and tensin homolog deleted on chromosome 10 (PTEN) protein expressions were assessed by immunohistochemistry (IHC) and the relationship between MKRN1 expression and clinicopathologic parameters, including survival data, was studied.
Results: MKRN1, pAKT, and pmiTOR expressions were significantly increased in cervical cancer cases compared with normal epithelia (P<0.001 for all markers), and this increased expression of MKRN1 was significantly associated with tumor stage (P=0.018) and tumor grade (P=0.001). Expression of MKRN1 was positively associated with pAKT expression (Spearman’s rho=0.167, P=0.030), while negatively associated with PTEN expression (Spearman’s rho=-0.260, P=0.016) in cervical cancer specimens. In multivariate analysis, MKRN1+ (hazard ratio [HR]=4.11 [1.12-15.03], P=0.033), MKRN1+/pAKT+ (HR=5.94 [2.08-16.93], P=0.001), MKRN1+/PTEN- (HR=4.59 [1.64-12.80], P=0.004), and lymph node metastasis (HR=5.28 [1.08-25.69], P=0.039) were independent prognostic factors for overall survival.

Conclusions: This study provides evidence of an association between the AKT pathway and cervical carcinogenesis and shows that MKRN1/pAKT expression predicts poor prognosis in cervical cancer. Our findings also suggest that future research assessing its clinical usefulness would be worthwhile.

100
The incidence of endometrial cancer in women with BRCA1 and BRCA2 mutations
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1Women’s College Research Institute, Familial Breast Cancer Research, Toronto, Ontario, Canada, 2Princess Margaret Hospital, Toronto, Ontario, Canada

Objective: To evaluate the risk of endometrial cancer in BRCA1 and BRCA2 mutation carriers.

Methods: Women with a BRCA1 or a BRCA2 mutation were identified through a registry of mutation carriers in North America and Europe. Women completed a questionnaire at baseline and were followed up for 2 years. Women were eligible for the study if they had an intact uterus at study entry and had not been diagnosed with any cancer other than breast cancer. Women were included if they had completed a questionnaire at study entry and at least 1 questionnaire during the follow-up. The women were followed from age 30 years until either: 1) age 75 years, 2) the diagnosis of endometrial cancer, 3) the diagnosis of ovarian cancer 4) hysterectomy for a reason other than endometrial cancer, 5) death due to any cause, or 6) date of completion of the last follow-up questionnaire. The expected number of endometrial cancers was calculated from the person-years at risk and the annual age-specific incidence rates for North America and Europe. The relative risk of endometrial cancer in the BRCA cancers was estimated by using this standardized incidence ratio (SIR): the ratio of observed cancers to the expected number of cancers. The Globocan 2008 statistics were used to estimate age-standardized rates.

Results: A total of 4,893 carriers were found eligible and were included in the cohort. Eighteen endometrial cancers were diagnosed among all BRCA carriers after a mean follow-up of 3.7 years. The observed number of endometrial cancer was 18 vs. 7.3 cancers expected (SIR 2.47, 95% CI 1.51-3.83, P<0.001). The observed number of endometrial cancer in BRCA1 carriers was 14 vs. 5.4 cancers expected (SIR 2.47, 95% CI, 1.47-4.22, P=0.002). The observed number of endometrial cancer in BRCA2 carriers was 4 vs. 1.8 cancers expected (SIR 2.16, 95% CI, 0.69-5.21, P=0.15). Among the cases, 44% used tamoxifen compared to 14% of the controls (P<0.001). Among the subjects who used tamoxifen, the mean duration of tamoxifen use was 5.7 years for case vs 2.7 years among the controls (P<0.001).

Conclusions: The risk of endometrial cancer is increased in BRCA2 mutation carriers compared to women in the general population. Tamoxifen use might contribute to the increased risk for endometrial cancer among BRCA2 carriers. Women who use tamoxifen might wish to consider hysterectomy at the time of preventive salpingo-oophorectomy.

102
An open label trial of SMK treatment of advanced metastatic cancer
S. Hoffman1, H. Bruckner2, G. Del Priore3, M. Demurjian1, K. Frankel1, J. Malanowiska-Stega1
1Luminant Biosciences, West Caldwell, NJ, 2Bruckner Oncology, New York, NY, 3Indiana University, School of Medicine, Indianapolis, IN

Objective: To determine the safety, tolerability, and efficacy of SMK on patients with advanced metastatic breast cancer. SMK is a novel therapy that creates alterations in defenses to oxidative stress and increases free radical availability to the cancer cell. SMK is designed to penetrate the living cancer cells and introduce multiple mechanisms to kill the cell. The liberation of electrons in the cancer cells promotes oxidative stress, and simultaneously the mitigation of the cancer cell-created defense allows catalyzed external free radicals to react. SMK is a combination of low-dose agents that are generally recognized as safe for typical use other than in cancer treatment.

Methods: This was an institutional review board-approved, open-label pilot study. SMK was administered orally and subcutaneously, 5 days/week for 6 weeks (1 cycle). More than 200 patients were screened. Criteria included all metastatic cancers. 30 patients meeting criteria were consented, 14 of whom had breast cancer.
Results: The average age of the female patients was 55 years (range, 40-70 years); 93% were Caucasian. 4/14 declined routine treatment before enrolling in the study; 10/14 had used all available treatment and were considered incurable. 11/14 (79%) had 1- to 3-point improvements in Eastern Cooperative Oncology Group (ECOG) rating, and 10/14 (71%) had 1- to 5-point improvements in European Organization for Research and Treatment of Cancer (EORTC) (scale 1-7) rating. 4/14 gained weight (1-5 lbs), 6/14 (43%) maintained the same weight, and 4/14 (28.5%) lost weight (1-2 lbs). 8/14 (57%) had reduction in pain levels (1-9 points on scale of 1-10); 6/14 (43%) entered with no pain and maintained the same level; and of the 6/14 (43%) who entered study on pain medication, 5/6 (83%) no longer needed pain medication at the end of cycle 1. 3/14 (21%) were disease-free with normal findings on physical examination and review of systems and imaging. 5/14 (36%) had significant reduction in quantity and/or size of the largest tumor, 2/14 (14%) had reduction in quantity and/or size of the largest tumor, 4/14 (29%) and had no progression of disease. 14/14 (100%) are alive, with median survival 28 weeks: 4/14 (29%) at 33-37 weeks, 5/14 (36%) at 27-29 weeks, and 5/14 (36%) at 12-19 weeks. 3/14 (21%) went home, and 11/14 (89%) continue with the treatment. All patients developed hyperpigmentation. Overall, all patients tolerated the SMK compounds well, with no adverse events reported related to the product, and all have had responses documented to the treatment.

Conclusions: SMK is a very promising treatment for all types of metastatic breast cancer.

Cervical Cancer

103 Utility of risk-weighted surgical-pathological factors in early-stage cervical cancer

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Objective: Surgical-pathological risk factors have been used in determining the indications for adjuvant treatment and the survival of surgically treated early-stage cervical cancer. We further evaluated the surgical-pathological risk factors by weighting the magnitude of significance of multiple risk factors correlating to survival and treatment response.

Methods: Multivariate analysis was performed for survival outcomes entering high-risk factors (nodal metastasis, parametrial invasion, and positive margin), intermediate-risk factors (lymphovascular space invasion [LVSI], deep stromal invasion, and large tumor), and histology. Hazard ratio (HR) in each variable was determined, and the sum of HR scores for corresponding risk factors was determined per case. Survival curves and treatment response (concurrent chemoradiotherapy [CCRT] or radiotherapy [RT] alone) were evaluated based on the extent of HR-weighted scores.

Results: Five hundred forty cases were examined. HRs for risk factors relating to disease-free survival (DFS) were: LVSI 3.95, nodal metastasis 3.88, adenocarcinoma/adenosquamous 3.40, large tumor 2.36, positive margin 1.99, deep stromal invasion 1.29, and parametria invasion 1.21. Median of HR-weighted scores was 5.24. The HR-weighted scoring method showed a high predictive value for recurrence (AUC 0.836, P < 0.001) and correlated well with traditional low-, intermediate-, and high-risk classifications (Spearman’s r = 0.83, P < 0.001). HR-weighted scores were negatively correlated to DFS, and the cases with scores > 2.5 showed a 5-year DFS rate of 23.8% (upper Figure). Survival benefits of CCRT over RT alone for DFS were diminishing as HR-weighted score went high (P < 0.001, lower Figure).

Conclusions: Surgical-pathological risk factors provide valuable information for survival and management of early-stage cervical cancer when number and significance of risks are weighted.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

105
The multicenter collaborative study of small cell carcinoma of the uterine cervix in Japan
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S. Kuji1, H. Nakayama2, S. Nishio3, O. Takeo4, Y. Nagamitsu5, N. Tanaka6, K. Ito7, Y. Hirashima8, N. Teramoto9, T. Yamada10

Objective: A retrospective study to accumulate cases of small cell carcinoma of the uterine cervix (SmCC) to clarify its clinical and clinicopathologic features and prognosis and to obtain findings to establish future individualized treatment.

Methods: This study enrolled patients who were diagnosed with SmCC between 1997 and 2007 at medical centers participating in the Kansai Clinical Oncology Group/Intergroup. A total of 71 patients were registered from 25 medical centers throughout Japan. At least 1 hematoxylin-eosin (HE)-stained slide was collected from each medical center. Whenever possible, chromogranin-, synaptophysin-, and CD56-stained slides were also obtained. In surgical cases, the resected specimens were obtained. In cases of preoperative anticancer drug treatment, the surgical specimens and pretreatment biopsy specimens were obtained. In nonsurgical cases, the pretreatment local biopsy specimens were obtained. In all cases, a histopathologic review was conducted by 2 pathologists from different medical centers. Patients diagnosed with SmCC based on agreement of the 2 pathologists were analyzed.

Results: A total of 71 patients were registered, and 52 patients (73%) were diagnosed with SmCC based on pathologic review. These 52 patients diagnosed with SmCC were analyzed. The median follow-up period was 57 months. The 4-year progression-free survival (PFS) was: stage IB1, 59%; stage IB2, 68%; stage IB, 13%; and stage IIIB, 17%. The median DFS was: IB1, 83 months (mo); IB2, 5 mo; and IIIB, 8 mo. The 4-year overall survival (OS) was: IB1, 63%; IB2, 67%; IB, 30%; IIIB, 29%; and IVB, 25%. The median OS was: IB2, 15 mo; IIIB, 15 mo; IVB, 2 mo. Initial recurrence was hematogenous in 14 cases (67%), lymphogenous in 7 (34%), and local in 2 (10%) (some overlap). Of these, 28 patients who had no preoperative treatment and underwent as initial treatment radical hysterectomy with retropertioneal lymphadenectomy were analyzed (FIGO IB1, IB2, IB, 7, IIIB, 6). As postoperative adjuvant therapy, with the addition of chemotherapy (including a platinum drug in all cases) vs. no chemotherapy, the 4-year DFS was 65% vs. 14% and the 4-year OS was 65% vs. 29%. The log-rank test showed a significantly prolonged DFS (P=0.002), and the OS tended to be different (P=0.073).

Conclusions: Even in patients with early-stage SmCC, the prognosis is poor. However, in early-stage patients, the prognosis may improve by adding postoperative chemotherapy.

106
Cervical cancer prognosis in women aged 35 and younger
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Objective: Age has been evaluated as a prognostic factor in cervical cancer in hospital- and population-based studies. Results on the relationship of age and cervical cancer prognosis have been conflicting. This study pursued a contemporary assessment of the effect of age on survival during a time period that may begin to capture meaningful historic cancer-specific changes in care.

Methods: Institutional review board approval was obtained and retrospective data collection performed. Inclusion criteria involved women younger than 35 years diagnosed with cervical cancer between 1990 and 2012. Data included demographic and prognostic information pertinent to survival and progression. Characteristics of younger (<25 years) and older women (≥25-35 years) were compared. Kaplan-Meier estimates and the log-rank test were used to compare progression-free survival (PFS) and overall survival (OS) between the groups for age, race, smoking, and marital status as well as tumor histology, grade, stage, and parametrial involvement.

Results: One hundred twenty-six incident cases of cervical cancer in women ≤35 years of age were identified of which complete clinical information was available for 119. Over 14% (17 of 119) were 25 years or younger, with the remaining 85% (102 of 119) belonging to the older group. Race, smoking status, and marital status were comparable between the 2 groups. Squamous histology dominated overall (81 of 119 [68%]) with adenocarcinoma contributing approximately one quarter (31 of 119 [26%]) of cases. The majority (n=100 [84%]) had either stage IA (n=31 [26%]) or IB (n=69 [58%]) disease. There was no evidence to infer a difference in either PFS or OS between the age groups (P=0.439 and P=0.257). Presence of parametrial involvement and stage significantly affected both PFS (P=0.002, P=0.001) and OS (P=0.002, P=0.00007). Grade and histologic cancer type significantly affected PFS (P=0.01, P=0.001).

Conclusions: Progression and survival outcomes are age-independent in women ≤35 years of age suffering from cervical cancer. Tumor histology, parametrial involvement, and stage continue to be strong prognosticators for these measures. Ongoing multi-institutional studies may yield different results.

107
Clinical correlation of nodal yield and disease recurrence in patients with early-stage cervical cancer
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Objective: To evaluate the clinical impact of nodal yield on recurrence in patients with early-stage cervical cancer.

Methods: Retrospective chart review was performed for 137 women with early-stage (FIGO stage IB1 to IB2) cervical cancer who underwent radical hysterectomy and pelvic node dissection between 2003 and 2011.

Results: Mean nodal yield was 27.9 (±10.8). According to the cutoff value (nodal yield ≥27), which had been determined by the receiver operating characteristic curve, patients were divided into group A (nodal yield ≤27, n=71) and group B (nodal yield ≥27, n=63). Group B was significantly associated with more advanced stage (FIGO stage IB2), nonsquamous cell carcinoma, and larger tumor size (>4 cm) than group A (P=0.020, 0.042, and 0.007, respectively). In addition, patients in group B were correlated with recurrence (P=0.014). The mean disease-free survival did not differ between the 2 groups (83.1±4.13 months for group A vs. 73.6±5.09 months for group B, P=0.148) (Figure). Logistic regression analysis revealed that a higher amount of nodal yield, older age, and deep stromal invasion were independent risk factors for disease recurrence (P=0.042, 0.018, and 0.045, respectively) (Table).

Conclusions: Our findings show that a higher amount of nodal yield (>27) had no benefit in reference to disease recurrence and survival. Therefore, excessive pelvic node dissection does not seem to be rational in early stage cervical cancer.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

Table. Assessment of Risk Factors for Disease Recurrence

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hazard ratio</th>
<th>95% Confidence interval</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age (&gt;50 years)</td>
<td>4.507</td>
<td>1.294-15.691</td>
<td>0.018</td>
</tr>
<tr>
<td>Clinical stage (FIGO IB2)</td>
<td>3.677</td>
<td>0.618-21.933</td>
<td>0.153</td>
</tr>
<tr>
<td>Tumor size (&gt;4 cm)</td>
<td>0.533</td>
<td>0.017-26.55</td>
<td>0.443</td>
</tr>
<tr>
<td>Deep stromal invasion (&gt;2/3)</td>
<td>3.119</td>
<td>1.025-9.492</td>
<td>0.045</td>
</tr>
<tr>
<td>Lymphovascular space invasion</td>
<td>1.466</td>
<td>0.462-4.650</td>
<td>0.516</td>
</tr>
<tr>
<td>Removed number of pelvic lymph nodes (&gt;27)</td>
<td>3.089</td>
<td>1.039-9.178</td>
<td>0.042</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td>1.109</td>
<td>0.263-4.884</td>
<td>0.888</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>1.225</td>
<td>0.381-3.936</td>
<td>0.733</td>
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</table>

Table. Overall Survival Comparing Consecutive 2-year Groups

<table>
<thead>
<tr>
<th>Index Group</th>
<th>n</th>
<th>Median OS (months)</th>
<th>5-year OS</th>
<th>Compari-</th>
<th>Log rank</th>
<th>P value</th>
<th>HR for death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y95-96</td>
<td>917</td>
<td>37</td>
<td>42.8%</td>
<td>Y97-98</td>
<td>0.799</td>
<td>0.985</td>
<td>(0.877-1.107)</td>
</tr>
<tr>
<td>Y97-98</td>
<td>841</td>
<td>38</td>
<td>43.8%</td>
<td>Y99-00</td>
<td>0.001</td>
<td>0.828</td>
<td>(0.741-0.926)</td>
</tr>
<tr>
<td>Y99-00</td>
<td>1,394</td>
<td>63</td>
<td>50.6%</td>
<td>Y01-02</td>
<td>0.692</td>
<td>1.019</td>
<td>(0.928-1.119)</td>
</tr>
<tr>
<td>Y01-02</td>
<td>2,060</td>
<td>61</td>
<td>50.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

108 Surveillance Epidemiology and End Results (SEER) analysis confirms overall survival benefit with concurrent chemoradiotherapy for cervical cancer

H. Hsu, J. Curtin, P. Schiff
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Objective: In early 1999, the National Cancer Institute (NCI) issued a clinical alert based on 5 randomized trials in locoregional cervical cancer showing better overall survival (OS) with concurrent chemoradiotherapy (CCRT) than with surgery or radiation alone. This study seeks to confirm whether OS did change significantly after the alert was issued.

Methods: SEER 18-Registry data (2011 submission) were queried using SEER*Stat 7.1.0 software. Cases were selected using the following criteria: cervix uteri, FIGO stages IB2-IVA, diagnosis years 1995-2002, radiotherapy given, and no other malignancy. Kaplan-Meier (K-M) OS curves with diagnosis year as the independent variable were generated for the following 3 comparisons: 1995-1996 (Y95-96) vs. 1997-1998 (Y97-98), 1997-1998 vs. 1999-2000 (Y99-00), and 1999-2000 vs. 2001-2002 (Y01-02). Log rank tests for significance and hazard ratios (HR) for death were calculated. Cox multivariate model was used to account for other risk factors for death. In the Cox model, treatment years were aggregated into 2 levels (95-98 vs. 99-02). All tests were 2-tailed, with alpha P<0.05 and 95% CI reported. Data were analyzed with IBM SPSS Statistics v.20.

Results: K-M OS improved significantly for Y99-00 compared to Y97-98 (log rank P=0.001, HR=0.828). OS was not significantly different for Y95-96 vs. Y97-98 (log rank P=0.799). Similarly, OS was not significantly different for Y99-00 vs. Y01-02 (log rank P=0.692). Cox multivariate model revealed the following significant variables: time period, age group, race, histology, grade, FIGO stage, tumor size, lymph node status, surgery extent, and radiation type. After adjusting for other variables, the multivariate HR for death for patients treated after vs. before the 1999 alert was 0.806 (CI 0.747-0.871).

Conclusions: Adoption of CCRT within 2 years of the 1999 NCI alert resulted in higher OS for stage IB2-IVA cervical cancer patients (Table). While SEER data did not explicitly include information on chemotherapy usage, the specific and narrow time frame of the OS improvement in patients treated with radiotherapy is indirect evidence of the increased use of CCRT. The magnitude of the 5-year OS benefit of approximately 7% reflects nationwide outcomes of CCRT and is consistent with the results seen in the selected populations treated on the randomized clinical trials.

109 The socioeconomic and fiscal burden of cervix cancer in a modern era

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Objective: Given the prevalence of cervix cancer (ccxa) in patients (pts) of lower socioeconomic (SEC) stature, we sought to explore social aspects and costs associated with treatment (tx).

Methods: A retrospective chart review of pts treated for ccxa at a single institution during 2006-2011 was performed. Demographic, onologic, tx, and SEC characteristics were recorded, as were visits, admissions, procedures, and recurrence. Hospital charges were available beyond January 2010 and were summed. SAS 9.2 was used for statistical analysis.

Results: 219 pts had tx for primary ccxa during the study period. Median age was 46 years (range, 17-87 years). 75% were Caucasian, 9% Native American, 6% Hispanic, and 5% African American. 51% were stage I, 39% stage II/III, and 10% stage IV. 49% were ever-users of tobacco, with 29 median pack-years. 4% reported drug abuse; 49% were unemployed. 50% lived >30 miles ("rural") from tx hospital. Insurance (ins) type was 46% private, 25% Medicaid, 20% Medicare, and 9% uninsured. 26% had surgery alone; 74% had chemoradiation (chemoRT). 24% of pts were treated on a clinical trial (CLT). Within 12 months of tx completion, 19% required hospital visits, 21% were admitted, 71% had procedures, and median number (no.) of office visits was 6 (range, 0-17). Most frequent reason for admission was urinary tract infection or percutaneous nephrostomy. Most common procedure was CT scan. After median follow-up of 23 months, 26% of stage I, 31% of stage II, and 41% of stage III pts recurred. Median duration to recurrence was 19 months. 77% of pts had salvage tx (41% chemotherapy, 17% chemoRT, 6% surgery, 4% RT). No. of hospital visits, admissions, and procedures were not associated with rural residence. Government ins was associated with stage (P=0.003), drug use, (P=0.02), race (P=0.03), unemployment (P<0.001), admission at primary diagnosis (P=0.0145), primary chemoRT (P=0.036), and no. of hospital visits (P=0.0045) but not with CLT enrollment, RT completion, or salvage tx. Cost data were available for 100% of pts beyond 1/2010. Cost of inpatient tx of 83 ccxa pts in 2010-2011 was $2,592,537 (49% admissions, 25% RT, 8% hospital visits, 6% procedures). Most common procedure was CT scan. After median follow-up of 23 months, 26% of stage I, 31% of stage II, and 41% of stage III pts recurred. Median duration to recurrence was 19 months. 77% of pts had salvage tx (41% chemotherapy, 17% chemoRT, 6% surgery, 4% RT). No. of hospital visits, admissions, and procedures were not associated with rural residence. Government ins was associated with stage (P=0.003), drug use, (P=0.02), race (P=0.03), unemployment (P<0.001), admission at primary diagnosis (P=0.0145), primary chemoRT (P=0.036), and no. of hospital visits (P=0.0045) but not with CLT enrollment, RT completion, or salvage tx. Cost data were available for 100% of pts beyond 1/2010. Cost of inpatient tx of 83 ccxa pts in 2010-2011 was $2,592,537 (49% admissions, 25% RT, 8% hospital visits, 6% surgery, and 12% other). Medical cost per pt was $24,795. Cost was associated with government ins (P=0.006), salvage tx (P=0.0033), and recurrence (P=0.005) but not stage, parity, distance, primary chemoRT, or CLT enrollment.

Conclusions: Despite similar tx, morbidity of ccxa pts with government ins is high and costly. Prevention with prospective study is warranted and will soon be underway.
110 Cervical cancer post-treatment follow-up: Critical analysis

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Objective: To evaluate the role played by follow-up tests and examinations (physical examination, cytology, and imaging examinations) in diagnosing symptomatic and asymptomatic relapses after treatment for neoplasms of the cervix.

Methods: Data were collected from medical records for all patients diagnosed with cervical cancer from 1985 to 2010. There were a total of 359 eligible patients during that period, 64 of whom had tumor relapses. The significance level adopted was 5%.

Results: Sixty-four (17.8%) of the 359 patients investigated suffered tumor relapse. Thirty-four (53.1%) were symptomatic and 30 (46.9%) were asymptomatic. A majority of patients had tumor relapse diagnosed during physical examination, both among the symptomatic patients (50%), and the asymptomatic patients (66.7%) (P=0.274). Cytopathology was responsible for detecting relapse in just 1 case in each group, corresponding to 2.9% and 3.3%, respectively (P=0.999). Imaging detected 10 (29.4%) relapses among symptomatic patients and 8 cases (26.6%) among asymptomatic patients (P=0.770). There were no statistically significant differences between the 2 groups or between the different methods of detecting relapses. There was still no association after adjustment for potential confounding factors such as age and type of treatment.

Conclusions: Physical examination was the preeminent method for detecting tumor relapse in this study. None of the other tests or examinations were capable of detecting relapses in both symptomatic and asymptomatic patients. These results highlight the urgent need for prospective studies that compare the efficacy of different follow-up regimes, analyzing factors such as global survival and quality of life.

111 Twists predict cervical carcinoma prognosis and promote metastasis through blocking senescence and inducing epithelial-mesenchymal transition

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Objective: Cervical carcinoma is associated with a high propensity for local invasion and lymph node metastasis. The molecular alterations that drive invasion and metastasis in cervical cancer and predict prognosis are still unclear. Recently, two closely related transcription factors, Twist1 and Twist2, have been linked to the development and progression of several human solid tumors through the regulation of senescence and epithelial-mesenchymal transition (EMT). In this study, we examined whether expression of Twist1/2 had prognostic value and therapeutic potential in cervical carcinoma. We determined the effects of Twist1/2 up- and downregulation in cellular senescence and EMT of cervical cancer cell lines and in promoting the invasion and metastasis of cervical carcinoma in nude mice.

Methods: We examined the predictive role of Twist1/2 and the correlation between Twist1/2 and clinicopathologic characteristics in cervical cancer specimens with different FIGO stages and lymph-node metastasis status. We explored the mechanism of Twist1/2 on disease progression by examining the expression of Twist1/2, CBX3 (senescence marker), and E-cadherin (EMT marker) in serial sections of normal cervical tissues and early/late-stage cervical cancer tissues. We identified the potential oncogenic functions of Twist1/2 on cell senescence by performing SA-hyaluronidase staining and flow cytometry analysis on cervical cancer cell lines. We further confirmed the connection between Twist1/2 and EMT program by using migration and invasion assays to study the role of Twist1/2 in regulating cervical carcinoma metastasis in vitro. We finally explored the clinical therapeutic potential of targeting Twist1/2 by examining the effects of Twist1/2 on tumor growth and metastasis in nude mice.

Results: Twist1/2 correlated with prognosis and was significantly associated with invasion and metastasis in cervical carcinoma. Cervical cancer tissues with high Twist1/2 expression tended to exhibit lesser degrees of senescence and state of EMT. Twist1/2 overrode cell senescence in cervical cancer cells. Twist1/2 induced EMT and regulated migration and invasion in vitro. Twist1/2 linked senescence bypass and EMT and was an effective molecular target for repressing cervical carcinoma.

Conclusions: Twist1/2 is both a candidate biomarker for the prognosis of cervical carcinoma and a viable therapeutic target that promotes cervical carcinoma metastasis through overriding senescence and inducing EMT.

112 Platinum-based combination chemotherapy ± consolidation versus weekly cisplatin during adjuvant concurrent chemoradiation after radical hysterectomy in early cervical cancer patients with pelvic lymph node metastasis

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1Samsung Medical Center, Seoul, Republic of Korea, 2Samsung Changwon Hospital, Changwon, Republic of Korea

Objective: Adjuvant concurrent chemoradiation (CCRT) should be considered in surgically treated patients with early-stage cervical cancer (ECC) who exhibit pelvic lymph node (LN) metastasis. Platinum-based chemotherapy is usually recommended during adjuvant CCRT, but it is unclear which regimen has better prognostic outcomes.

Methods: We reviewed electronic medical records to find patients with primary ECC (FIGO stages IB-IIA) who underwent type III radical hysterectomy and adjuvant CCRT due to pelvic LN metastasis at Samsung Medical Center, Sungkyunkwan University School of Medicine in Seoul, Korea, between November 1997 and September 2007.

Results: Among the 75 patients, 34 received weekly cisplatin. Combination chemotherapy was performed without consolidation in 21 patients and with consolidation in 20 patients. The mean follow-up period was 59.0 months and the 5-year survival rate was 84.4%. In multivariate analysis, combination chemotherapy ± consolidation was associated with improved disease-free survival (hazard ratio [HR], 0.23; 95% CI, 0.06-0.88; P=0.032 and HR, 0.29; 95% CI, 0.09-0.91; P=0.034). Combination chemotherapy with consolidation significantly improved overall survival (HR, 0.11; 95% CI, 0.02-0.87; P=0.037) when compared to weekly cisplatin.

Conclusions: We observed that platinum-based combination chemotherapy during adjuvant CCRT after surgery promoted better survival than a weekly cisplatin regimen in ECC patients with pelvic LN metastasis (Table). Consolidation chemotherapy after adjuvant CCRT may contribute to the increased overall survival in these patients.

Table. Univariate and Multivariate Analysis for Disease-free Survival in Patients With Early Cervical Carcinoma With Pelvic Lymph Node Involvement

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th>Multivariable</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Chemotherapy*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Group 2</td>
<td>0.35 (0.11-1.06)</td>
<td>0.064</td>
</tr>
<tr>
<td>Group 3</td>
<td>0.73 (0.30-1.81)</td>
<td>0.497</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>1.00 (0.96-1.04)</td>
<td>0.990</td>
</tr>
<tr>
<td>FIGO stage</td>
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<td></td>
</tr>
<tr>
<td>IB1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IB2</td>
<td>2.56 (0.97-6.71)</td>
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</tr>
<tr>
<td>IIA</td>
<td>1.52 (0.35-4.23)</td>
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</tr>
<tr>
<td>Pelvic LN</td>
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<tr>
<td>positive count</td>
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</tbody>
</table>
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

113
Genetic profiling to predict recurrence of early cervical cancer

Y. Lee1, A. Yoon1, J. Park1, W. Kim1, M. Kim1, C. Choi1, T. Kim1, J. Lee1, B. Kim1, D. Bae1
1Samsung Medical Center, Seoul, Republic of Korea, 2Kangbuk Samsung Hospital, Seoul, Republic of Korea, 3Samsung Changwon Hospital, Changwon, Republic of Korea

Objective: To compare the prediction powers for disease recurrence between a gene set prognostic model and clinical prognostic model developed in a single large population to see whether a genetic quantitative approach will have a significant prognostic role in early cervical cancer patients who underwent radical hysterectomy with or without adjuvant therapies.

Methods: A gene set model to predict disease-free survival of early cervical cancer was developed using DASL assay dataset from the cohort of early cervical cancer patients who were treated with radical surgery with or without adjuvant therapies at the Samsung Medical Center of Sungkyunkwan University School of Medicine in Seoul, Republic of Korea, between January 2002 and September 2008. A clinical prediction model was also developed in the same cohort, and the ability to predict recurrence from each model was compared.

Results: Adequate DASL assay profiles were obtained in 300 patients, and we selected 12 genes for the gene set model. When the proportions of patients were categorized as having a low or high risk by the prognostic scoring using these genes, the Kaplan-Meier curve showed significant different recurrence rates between the 2 groups. A clinical model was developed using FIGO stage as well as postsurgical pathologic findings. In multivariate Cox regression analysis of prognostic models, the gene set prognostic model showed higher hazard ratio for recurrence of 9.95 with 95% CI of 5.46-18.1 compared with the clinical prognostic model, which showed the hazard ratio of 1.96 with 95% CI of 1.29-2.97 (Table).

Conclusions: A genetic quantitative approach may have better performance of predicting recurrence in early cervical cancer patients.

<table>
<thead>
<tr>
<th>Table. Univariate and Multivariate Cox Regression of the Predicted Scores for Recurrence With Clinical and/or Gene Set Models</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis</strong></td>
</tr>
<tr>
<td>Clinical model using 2 variables*</td>
</tr>
<tr>
<td>Clinical model using 5 variables†</td>
</tr>
<tr>
<td>Gene set model†</td>
</tr>
<tr>
<td>Multivariate analysis 1</td>
</tr>
<tr>
<td>Clinical model using 2 variables*</td>
</tr>
<tr>
<td>Gene set model†</td>
</tr>
<tr>
<td>Multivariate analysis 2</td>
</tr>
<tr>
<td>Clinical model using 5 variables†</td>
</tr>
<tr>
<td>Gene set model†</td>
</tr>
</tbody>
</table>

*2 variables (lymph node status, largest tumor size) selected by stepwise variable selection method, †5 variables (lymph node status, largest tumor size, microscopical parametrial invasion, lymphovascular space invasion, deep stromal tumor invasion) with univariate Cox P value <0.05, ‡Gene set=12 probes included in the prediction model fitted by the whole tumor dataset

114
Comparison of laparoscopic-assisted radical vaginal hysterectomy and laparoscopic radical hysterectomy in the treatment of cervical cancer

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Objective: To compare the surgical and oncologic outcomes of laparoscopic-assisted radical vaginal hysterectomy (LARVH) with that of laparoscopic radical hysterectomy (LRH) for early-stage cervical cancer.

Methods: Patients affected by invasive cervical cancer (FIGO stage I – IIA) who had received LARVH (n=89) in our institute between September 2004 and December 2010 were compared to patients treated by LRH (n=105) during the same period. All patient information, surgical and pathological data, and oncological results were prospectively collected. Patients undergoing abdominal radical hysterectomy (ARH) were included for comparison of safety, morbidity, and recurrence rate.

Results: The mean estimated blood loss (EBL) and return of bowel activity were significantly reduced in the LRH group compared to the LARVH group (P=0.011 and P=0.002, respectively). Intraoperative complications occurred in 10 patients (11.2%) in the LARVH group, 6 (5.7%) in the LRH group, and 3 (3.0%) in the ARH group. Forest plot analyses of the previous studies showed a higher incidence of intraoperative complication in the LARVH group than in LRH group (P=0.02). Despite the similar overall recurrence rate, stump recurrence seems to be high in the LRH group in the forest plot analysis of previous studies (P=0.08).

Conclusions: Both LARVH and LRH are safe and effective therapeutic procedures for the management of early-stage cervical cancer, although LRH is characterized by less blood loss and shorter bowel recovery time. Possible higher stumps in the LRH group should be further evaluated.

115
Clinical evaluation of early (stage I-II) cervical adenocarcinoma and adenocarcinoma of non-squamous cell carcinoma (non-SCC) of the cervix?

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Objective: In 2000, Peters et al. reported that the addition of concurrent cisplatin-based chemotherapy (CT) to radiation therapy (RT) significantly improves the progression-free survival and overall survival (OS) of high-risk patients (pN1, except common iliac lymph nodes) with early carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy. Also, patients with non-SCC achieved the same prognosis as those with SCC after concurrent chemoradiation therapy (CCRT). At present, CCRT is the gold standard as adjuvant therapy for high-risk patients after radical surgery. According to JGOG 1069 (the national report about treatment of uterine cervical cancer), non-SCC (especially adenocarcinoma) is distinguished from SCC in 70% of institutions, and paclitaxel plus carboplatin (TC therapy) is selected as adjuvant chemotherapy at 70 institutions. This approach to non-SCC is unique to Japan. Our aim was to evaluate adjuvant therapy for SCC and non-SCC after radical surgery.

Methods: Between January 1976 and December 2010, 194 patients (SCC: 138, adenocarcinoma [AD]: 48, adenosquamous cell carcinoma [ADSCC]: 8, except neoadjuvant CT and RT) with stage I-II disease and pelvic lymph node metastasis underwent radical hysterectomy and pelvic lymphadenectomy at various centers, including Tokai University Hospital, and were enrolled. We analyzed prognostic factors based on the histologic type and adjuvant therapy.
The one-sided log-rank test (P=0.05 for significance) was used to assess progression-free and OS, and Cox regression analysis was performed.

**Results:** In the multicenter study, the following prognostic factors were identified: histologic type (P=0.012) and metastasis to more than 3 lymph nodes (P=0.002). Among patients with more than 3 metastatic lymph nodes, the following prognostic factors were identified: adjuvant therapy (P=0.03) and histologic type (P=0.002). Compared with operation plus chemotherapy (OC) and operation, chemotherapy plus radiation therapy (OCR) cases of non-SCC, OC patients had significantly better overall survival (P=0.011). In OC patients, more pelvic lymph nodes were dissected (P=0.023), and para-aortic lymph node dissection (P=0.077) was also performed more often.

**Conclusions:** We suggest that the combination of adjuvant chemotherapy and radical hysterectomy with pelvic and para-aortic lymph node dissection is very useful for operable patients with metastasis to more than 3 lymph nodes in early (stage I-II) non-SCC.

116

**Nanog-Tcl1a-Akt axis-induced tumor stem-like phenotype with immune evasion**


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**Objective:** Adaptation of tumor cells to the host is a major cause of cancer progression, failure of therapy, and ultimately death. We report that immune selection drives this adaptation in human cancer by enriching for tumor cells with a phenotype resistant to cytotoxic T lymphocyte (CTL)-mediated apoptosis and resembling that of cancer stem cells (CSCs).

**Methods:** 6- to 8-week-old female NOD/SCID mice were used. To generate pMSCV/Nanog, cDNA encoding human Nanog was amplified from pSinEF2-Nanog-Pur (Addgene). The QuickChange XL site-directed mutagenesis kit was employed for site-directed mutagenesis. Synthetic siRNA targeting GFP, Nanog, or Tcl1a was constructed. CaSki, CUMC6, MCF7, MDA-MB-231, MDA-MB-453, H1299, HepG2, OVCA13, SKOV3, A2780, HT29, SN1C4, SW620, and HCT116 cells were obtained commercially. CaSki-D8 p0 cells were produced by retroviral transduction of CaSki cells with pMSCV-H2-D8 using pMSCV vector-Phoenix packaging cell line system. NOD/SCID mice were inoculated subcutaneously with HCT116/SCT-E7 cells and administered with siNanog- or siGFP-loaded chitosan nanoparticles (5 µg/animal). Study participants encompassed 431 patients diagnosed with CIN (n=193), carcinoma in situ (CIS) (n=68), or cervical cancer (n=170). Tissue microarrays (TMAs) were produced from formalin-fixed, paraffin-embedded tumor and nonadjacent normal cervical tissue. Some of the paraffin blocks were provided by the Korea Gynecologic Cancer Bank through Bio & Medical Technology Development Program of the Ministry of Education, Science and Technology.

**Results:** This phenotype arises through the Akt signaling pathway via transcriptional induction of Tcl1a by Nanog. High expression of Nanog in human cervical tumor tissue is correlated with advanced stage of disease and poor prognosis. Furthermore, hyperactivation of the Nanog-Tcl1a-Akt signaling axis is conserved across multiple types of human cancer. Inhibition of Nanog in a preclinical model of colon cancer renders tumor cells susceptible to immune-mediated clearance and leads to successful, long-term control of disease.

**Conclusions:** Our findings establish a firm link between immune selection, disease progression, and development of a stem-like tumor phenotype in human cancer and implicate the Nanog-Tcl1a-Akt pathway as a central molecular target in this process.

117

**Single CpG Site hypomethylation of MAL gene might be associated with human papillomavirus persistent infection**

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**Objective:** It has been well known that cervical intraepithelial neoplasia is preceded by persistent infections with human papillomavirus (HPV) types that carry a high oncogenic risk. About 80% of young women who become infected with HPV have transient infections that clear within 12-18 months. Only a small fraction of women with HPV infection eventually develop persistent infections. No definitive molecular evidence is associated with persistent infection. In this study, we aimed to determine the difference of promoter methylation level in cervical cell genes (ADCYAPI, PAX1, CAMDI, and MAL) between persistence and clearance of HPV infection.

**Methods:** Exfoliated cervical scrap samples from the HPV-persistent group (n=25) and the HPV clearance group (n=25) in the Korean HPV Cohort Study were used to interrogate the methylation patterns of 4 host nuclear genes (ADCYAPI, PAX1, CAMDI, and MAL) in each group at 6- and 12-month follow-up. DNA isolated from exfoliated cervical scrap samples was treated with bisulfite, specific regions of host genome were polymerase chain reaction amplified, and CpG methylation was quantified using pyrosequencing.

**Results:** The HPV-persistent infection group was not significantly different from the HPV clearance group in global methylation level over time. When comparing a single CpG methylation level of each gene, CADM1(-338bp), MAL(-190bp), MAL(-186bp), and MAL(-173bp) CpG site methylation levels were significantly lower in the HPV-persistent infection group than the HPV clearance group at 6 month follow-up. Methylation level of only CADM1(-338bp) CpG site was significantly increased in the HPV-persistent group compared with the HPV clearance group from 6 months to 12 months. In analysis of the high-risk HPV infection subgroup, MAL(-190bp) CpG site methylation level of high-risk HPV-persistent infection group (n=16) at 6 months follow-up was significantly lower than the level of the high-risk HPV infection clearance group (n=11) at that time. Sensitivity and specificity of MAL(-190bp) CpG site methylation level predicting high-risk HPV-persistent infection were 75.0%, 90.9%, respectively, with under cutoff value 2.1.

**Conclusions:** Relative but significant hypomethylation of MAL(-190bp) CpG site might play a crucial role in initiating high-risk HPV-persistent infection.

118

**Loss of ARID1A/BAF250a expression is associated with cervical carcinogenesis and predicts shorter overall survival**


1Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, 2National Cancer Institute, Bethesda, MD, 3Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, 4Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

**Objective:** ARID1A, the tumor suppressor gene, encodes BAF250a, which is a component of human SWI/SNF chromatin-remodeling complexes and has recently been reported as loss of expressions in several tumor types. We investigated the expression levels of the BAF250a during the sequential steps of cervical carcinogenesis and assessed its prognostic value.

**Methods:** One hundred ninety-one cervical intraepithelial neoplasias and 376 matched nonadjacent normal tissues from 147 cervical cancer patients were arrayed into tissue microarrays. BAF250a expressions were assessed by immunohistochemistry (IHC) and the relationship between BAF250a expression and clinicopathologic parameters, including survival data, was studied. The transcriptional level of BAF250a was also evaluated by SYBR Green real-time polymerase chain reaction in 5 cell lines and 10 clinical specimens.
Results: The mRNA expression levels of BAF250a decreased in cervical cancer cell lines (P=0.013) and tissues (P=0.010) compared with normal cervical epithelial tissues, respectively. BAF250a was detected in nuclear fractions of HeLa cells and nucleus of cervical cancer tissue samples by western blotting and IHC, respectively. The expression level of BAF250a gradually decreased during the normal to tumor transition of cervical carcinoma (P=0.001), and this loss of the expression was significantly associated with tumor stage (P=0.005), tumor grade (P=0.029), tumor size (P=0.003), and lymph node metastasis (P=0.020). In multivariate analysis, overall survival in cervical cancer was significantly shorter in cases with the loss of BAF250a expression (hazard ratio = 2.78 [1.01-7.63], P=0.047).

Conclusions: Our results suggest that BAF250a expression has the potential to provide valuable prognostic information to clinicians for risk assessment in cervical cancer.

Methods: We identified all pts who underwent SLN mapping with cervical conization for stage 1 cervical cancer between 9/2005 and 8/2012. Relevant demographic, clinical, and pathological information was collected. All pts underwent laparoscopic lymphatic mapping and biopsy of identified SLNs followed by selective pelvic lymphadenectomy of any suspicious lymph nodes. Pathologic ultrastaging was performed on SLNs.

Results: We identified 10 eligible pts. The median age was 28 years (range, 18-36 years). Nine pts (90%) were nulliparous. None of the pts had a grossly visible tumor, and in all cases, the initial diagnosis was made either on a loop electrosurgical excision procedure or a cone biopsy performed prior to transfer to our institution. All outside pathology specimens were reviewed preoperatively. All patients underwent comprehensive preoperative radiologic evaluation that included MRI and PET-CT. None of the patients had evidence of residual tumor seen on MRI or suspicion of lymph node metastasis on PET-CT. Stage distribution included: IA1 with lymphovascular invasion (LVI), 7 pts (70%); IB1, 3 pts (30%). Histology included: squamous, 8 pts (80%); adenocarcinoma, 1 pt (10%); clear cell, 1 pt (10%). Nine patients underwent repeat cervical conization with SLN mapping, and 1 pt underwent postconization cervical biopsies and SLN mapping. None of the patients had residual tumor identified on the final specimen. Bilateral mapping was achieved in all cases. The median number of SLNs examined was 4 (range, 2-8). The median number of non-SLNs examined was 2 (range, 0-9). All SLNs and non-SLNs were negative for metastasis. After a median follow-up of 17 months (range, 1-83 months), none of the patients were diagnosed with recurrent disease and 3 patients (30%) achieved pregnancy.

Conclusions: Cervical conization and SLN mapping may be an acceptable treatment strategy for select pts with microscopic stage 1 disease. A larger sample size and longer follow-up is needed to establish the long-term outcomes of this procedure.

Objective: To determine feasibility and safety of a novel, less morbid fertility-preserving surgery for early-stage cervical cancer patients. A loupes assisted nerve-sparing abdominal radical trachelectomy was accomplished to minimize nerve plexus trauma and preserve uterine vessels.

Methods: We conducted a retrospective review of patients undergoing fertility-sparing radical abdominal trachelectomy at our institution from 2002 to 2011.

Results: Fifty-eight patients who underwent abdominal radical trachelectomy with pelvic lymphadenectomy were followed up for 59 months (range, 18-92 months). The characteristics of the patients included stage IB1 disease in all cases, tumor diameter 8-37 mm, a mean age of 32 years (range, 26-41 years), and a mean operative time of 162 minutes (range, 142-202 minutes). Uterine vessels preservation was feasible in all cases but one. There was no case of parametrial lymph node involvement, and no patient needed postoperative adjuvant treatment. Urinary and anorectal morbidity were minimal. Urinary Foley catheter was removed on the 6th day in 55 patients and on the 10th day for the remaining 3 patients. There was 1 recurrence on the para-aortic area treated with chemoradiation. One patient developed a CIN2 lesion that was successfully treated by loop excision. Forty women attempted to conceive and 30 pregnancies were recorded. All of the pregnancies resulted in live births. Nineteen were full term and 1 was preterm.

Conclusions: Nerve-sparing procedures using microsurgical techniques could be applied in fertility-preserving abdominal trachelectomies to minimize morbidity and potentially improve obstetric outcome by preserving the uterine vessels.

Objective: Radical trachelectomy is an accepted treatment option for select stage I cervical cancer patients (pts). Tumor size in pts considered for trachelectomy ranges from microscopic disease up to 4 cm. For pts with small-volume disease, parametrial extension is rare. The objective of this study was to report on our initial experience using sentinel lymph node (SLN) mapping with cervical conization in the treatment of stage I cervical cancer.

Methods: A subset of women who underwent cesarean hysterectomy between 1999 and 2002 were identified from a national maternal fetal medicine database consisting of 19 academic centers. We compared women undergoing cesarean hysterectomy for cervical cancer to those undergoing the same procedure for a different indication and compared perioperative maternal and neonatal outcomes.

Results: Sixteen women had a cesarean hysterectomy for cervical cancer, and 275 women underwent cesarean hysterectomy for another indication. In the cervical cancer group, 37.5% had a history of previous cesarean delivery, and most were Caucasian (56.3%). 43.8% received antenatal steroids. Compared to patients who underwent cesarean hysterectomy for another indication, those who underwent the procedure for cervical cancer were significantly less likely to need an intraoperative or postoperative blood transfusion or to be admitted to an intensive care unit setting postoperatively (Table). There were no instances of cystotomy, bowel injury, or ureteral injury at the time of surgery in the cervical cancer group. With respect to neonatal outcomes, there were no significant differences between the 2 groups in gestational age, birthweight, or Appgar score. There were no maternal or neonatal deaths in the cervical cancer cohort and 3 maternal deaths among the 275 women who had a cesarean hysterectomy for reasons other than cervical cancer.

Conclusions: Patients who underwent cesarean hysterectomy for cervical cancer fared better with respect to maternal perioperative morbidity and fared no worse with respect to neonatal outcomes than patients who required...
cesarean hysterectomy for other indications. These findings may be explained by the surgical expertise of the gynecologic oncologist performing the surgery as well as the high morbidity of cesarean hysterectomy performed for indications such as abnormal placentaion or refractory uterine atony.

### Table. Patient and Procedure Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cesarean Hysterec-tozy for Cervical Cancer</th>
<th>Cesarean Hysterectomy for Other Indication</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative blood transfusion</td>
<td>5/16 (31.2%)</td>
<td>204/275 (74.2%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Postoperative blood transfusion</td>
<td>2/16 (12.5%)</td>
<td>121/275 (44%)</td>
<td>0.017</td>
</tr>
<tr>
<td>&lt;3 units transfused intraoperatively</td>
<td>1/5 (20%)</td>
<td>133/204 (65.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Intensive care unit treatment postoperatively</td>
<td>0/16 (0%)</td>
<td>78/275 (28.4%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Smoking</td>
<td>8/16 (50%)</td>
<td>45/275 (16.4%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Composite comorbidities</td>
<td>2/16 (12.5%)</td>
<td>65/275 (23.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Intraoperative cystotomy</td>
<td>0/16 (0%)</td>
<td>31/275 (11.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Intraoperative bowel injury</td>
<td>0/16 (0%)</td>
<td>2/275 (0.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Intraoperative ureteral injury</td>
<td>0/16 (0%)</td>
<td>9/275 (3.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Postoperative wound complication</td>
<td>2/16 (12.5%)</td>
<td>11/275 (4%)</td>
<td>NS</td>
</tr>
<tr>
<td>5-minute Apgar score &gt;9</td>
<td>11/16 (68.8%)</td>
<td>180/275 (65.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean delivery gestational age (wks)</td>
<td>35.2</td>
<td>36.3</td>
<td>NS</td>
</tr>
<tr>
<td>Mean birthweight (g)</td>
<td>2681</td>
<td>2838</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Conclusions:
Although the combination of CIS and SFU causes more toxicity, this analysis suggests that there may be a role for this chemotherapy regimen in patients with positive lymph nodes.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

124
TRIO amplification and over-expression was associated with progression and prognosis of squamous cervical carcinoma

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Objective: Globally, cervical cancer remains the second most frequent cancer among women around the world. High-risk human papillomavirus (HPV) infection is the most important factor, with other factors contributing to the progression to cervical cancer, such as genetic susceptibility of host. Recently, studies on genetic background transformed to genomewide study from candidate gene screening, and there are many studies of solid cancer adopting the CNV marker. However, it is little information available on susceptible genes from CNV study and the underlying mechanism in cervical cancer. This study aims to search the new CNV aberrant in squamous cervical carcinoma (SCC) tissues by assay-CGH and investigate whether TRIO overexpression, which is located in application DNA fragment 5p15, was correlated with development and poor prognosis of SCC. Furthermore, the molecular mechanism involved was explored.

Methods: CNV polymorphism was screened by assay-CGH with tissues of SCC, and fragments of loss and gain were validated by real-time polymerase chain reaction (PCR). Additionally, a series of 119 samples were detected with real-time PCR and immunohistochemistry to explore TRIO expression and its role in progression and prognosis. Wound healing and Transwell assay were studied to identify the effect of TRIO in migration and invasion. Furthermore, Western blot, immunofluorescence staining, and GTPase activity assay were used to prove whether the pathway TRIO was involved in SCC.

Results: Array-CGH mapping displayed chr.5p15.2 genomic gains in 90% samples on which the TRIO gene was located. In another 36 cases study, TRIO gene amplification was validated. TRIO was highly expressed in cervical cancer compared with normal cervical tissues, both in mRNA and protein level. Furthermore, significant correlation was observed between TRIO protein expression level and advanced-stage SCC (parametrium invasion) (P<0.001) and lymph node metastasis (P<0.001), respectively. TRIO protein expression level was associated with poor prognosis and serves as an independent prognostic factor. TRIO depletion by siRNA suppressed the capability of invasion and cell migration in Siha cells. TRIO suppression displayed that the level of GTP-RhoA was significantly decreased and the stress fiber formation was hindered.

Conclusions: These results indicate that the TRIO gene was frequently amplified in SCC. Moreover, TRIO overexpression was significantly related to invasion and metastasis in SCC. Decreased expression of TRIO implied an activating effect of TRIO on cytoskeletal contractility.

125
HPV16 E6/E7 induces EMT via Twist and promotes carcinogenesis and metastasis of cervical cancer

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Objective: Human papillomaviruses (HPVs) are recognized as the etiologic agents of cervical cancer, with local invasion and metastasis as the major way to development. P53 and retinoblastoma proteins are well-characterized targets of the HPV16 E6/E7 oncoproteins. However, recent studies showed that the alterations of additional pathways are equally important for transformation. Meanwhile, cancer-associated epithelial-to-mesenchymal transition (EMT) has been considered as a critical phenomenon in carcinogenesis and development in other solid tumors, such as mammary cancer and prostate cancer, but little involvement has been shown in cervical cancer. This study aimed to investigate whether EMT program participates in cervical cancer tumorigenesis and metastasis and whether EMT associates with HPV oncoproteins or known EMT inducers.

Methods: We screened the differential expression genes correlated with HPV16 E6/E7 by RNA-seq based on the information from the endocervical epithelial cell with stable expression of HPV16 E6/E7 compared to normal cervical epithelial cells. We validated the relationship among HPV16 E6/E7, Twist, and E-cadherin in tissue microarray with normal cervical tissues, cervical intraepithelial neoplasia (CIN), and cervical cancer tissues by immunohistochemistry. We validated the relationship among HPV16 E6/E7, Twist, and E-cadherin in cervical cancer cells by examining the effect of Twist on EMT induced by HPV16 E6/E7 through Western blot and real time polymerase chain reaction. We then sought to investigate the mechanism of HPV16 E6/E7 interacting with Twist in cervical cancer cells by ChIP-seq and Co-immunoprecipitation. We finally explored the role of Twist on the action of HPV16 E6/E7 in carcinogenesis and metastasis both in vitro and vivo.

Results: HPV16 E6/E7 modulated expression of genes involved in EMT and differentiation-associated processes in human cervical epithelial cells. HPV16 E6/E7 and Twist were frequently coexpressed in human cervical cancer and correlated with E-cadherin. Induction of the transcription factor Twist was required for HPV16 E6/E7-induced EMT. HPV16 E6/E7 interacted with Twist directly in inducing EMT in cervical cancer cells. Twist played a vital role in carcinogenesis and metastasis of cervical carcinoma promoted by HPV16 E6/E7.

Conclusions: HPV16 E6/E7-induced EMT is Twist-dependent and can promote carcinogenesis and metastasis of cervical cancer.

126
Comparison of laparoscopic versus abdominal radical hysterectomy for bulky (≥3 cm) FIGO stage IB and IIA cervical cancer

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Objective: Laparoscopic radical hysterectomy (LRH) is an alternative surgery to abdominal radical hysterectomy (ARH). There have been many comparative reports on laparoscopic vs. abdominal radical hysterectomy for early-stage cervical cancer. However, most of these studies included patients with FIGO stage IA2 and small (≤2 cm) IB1 disease. The purpose of this study was to compare the safety, morbidity, and recurrence rate of LRH and ARH with pelvic lymphadenectomy for bulky (≥3 cm) FIGO stage IB and IIA cervical cancer.
Methods: We conducted a retrospective analysis of 85 consecutive patients with bulky (≥3 cm) stage IB and IIA cervical cancer who underwent LRH or ARH with pelvic and/or para-aortic lymphadenectomy between May 2006 and July 2012.

Results: Among 85 patients, 37 received LRH and 48 underwent ARH. There were no differences in demographic data between the 2 groups. Mean estimated blood loss was 580 mL for the ARH group compared to 444 mL for the LRH group (P=0.001). Mean operative time was 246 minutes for the ARH group compared to 254 minutes for the LRH group (P=0.589). Return of bowel motility was observed earlier after LRH (P=0.012). A mean 23 pelvic lymph nodes were obtained during ARH compared with 22 during LRH (P=0.573).

The median duration of hospital stay was significantly shorter for the LRH (P=0.017) group. No statistically significant difference was found between the 2 groups when the recurrence rate was compared. 5-year disease-free survival rates were 94.0% in the ARH group and 100% in the LRH group (P=0.284). With a median follow-up of 43 months, all patients were alive, with no disease-related deaths.

Conclusions: LRH is a safe and effective therapeutic procedure for management of bulky (≥3 cm) FIGO stage IB and IIA cervical cancer, with reduced blood loss, postoperative morbidity, and postoperative hospital stay, and oncologic results of this procedure are comparable to ARH with the limitation of a short follow-up period. Further randomized studies are necessary to evaluate long-term clinical outcome.

127
Radical vaginal trachelectomy-fertility outcomes and significance of the lower uterine segment presence in the superior margin of the pathologic specimen

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Objective: To report if the presence of lower uterine segment (LUS) in the superior margin of the pathologic trachelectomy specimen is associated with a higher likelihood of preterm birth.

Methods: We retrospectively reviewed data from 355 patients (median age, 40 years; range, 21-68 years) with CIN 2-3, AIS, and MICA treated by CKC at a single institution. Clinicopathologic variables, including age, parity, severity of the disease in cone specimens, number of quadrant involved, and ecto- and endocervical involvement, were evaluated as possible predictors of residual disease.

Results: Among the 355 patients, 26 (7.3%) had residual disease demonstrated by colposcopically-directed biopsy and subsequent loop electrosurgical excision procedure (LEEP) or hysterectomy. In 244 patients (68.7%), the specimen was assessed as complete excision, and in 111 patients (31.3%), the excision was incomplete. There were no significant differences in demographic data between the 2 groups. The patients who demonstrated positive margins had more severe disease of CKC specimens (P<0.01), glandular involvement (P<0.01), number of involved quadrants (P<0.01), and residual disease (P<0.01). Of 244 patients, 238 (97.5%) were found to have been cured of disease in the negative-margin group. The cure rate for incomplete excision at the ectocervical margin was 91.5%; incomplete excision at the endocervix was 76.7% and only 44.4% if excision was incomplete at both margins. In univariate analysis, severity of the disease in CKC specimens (20.4% [11/54] of patients with AIS and MICA vs. 5.0% [15/301] of patients with CIN 2-3, P<0.01) and positive resection margin (18.0% [20/111] vs. 2.5% [6/244], P<0.01) were significant risk factors for the residual disease. Multivariate analysis demonstrated that age (>50 years) (P<0.01), severity of the disease in CKC specimens (P<0.01), and positive ecto- and endocervical resection margin (P<0.01) were significantly associated with higher risk of residual disease.

Conclusions: CKC performed for CIN2-3, AIS, and MICA is likely to be curative when the lesion is completely excised. Most cases of incompletely excised CIN 2-3, AIS, and MICA would also be curative, even in the positive ectocervical margin. Age (>50 years), severity of the disease in CKC specimens, positive ecto- and endocervical resection margin could be significant risk factors for developing residual disease after CKC.
(Group B, historical control group). Survival rates were calculated using the Kaplan–Meier product-limit method.

**Results:** One hundred ninety-eight patients were evaluated and underwent NACT. After 3 cycles, 41 patients with no clinical responses and 36 node-positive patients were excluded from the study. Of the remaining 121 patients, 35 (Group A) underwent modified radical hysterectomy and were compared to 86 (Group B) who had classic radical hysterectomy. The rate of bladder dysfunction was significantly lower in the patients who had less radical surgery (14% vs 72% in Groups A and B respectively; P=0.0001). Median follow-up time was 45 months. 5-year overall survival was 92% for Group A and 94% for Group B.

**Conclusions:** The overall survival of node-negative patients with favorable prognostic factors submitted to type B radical hysterectomy is comparable to that of patients submitted to type C radical hysterectomy. Less aggressive surgery is associated with lower complication rates, especially vesical dysfunction. Pretreatment evaluation and intraoperative evaluation of adverse prognostic factors in patients undergoing LACC is feasible and useful to determine if a less radical surgery is applicable and safe.

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**130 Less radical surgery possible in patients with stage IB1 cervical cancer**

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**Objective:** To define which parameters are associated with a low risk for parametrical involvement in patients with stage IB1 cervical cancer to identify a group of patients that can be safely cured by a less radical surgery.

**Methods:** We retrospectively reviewed 211 patients with stage IB1 cervical cancer who had undergone radical hysterectomy (class III) and pelvic lymphadenectomy from 1996 to 2011. To find independent factors associated with parametrical involvement, a stepwise multiple logistic regression analysis (P for removal was set at 0.1 and P for entry was set at 0.05) was conducted. Receiver operating characteristic (ROC) analysis was used to find the optimal cutoff of depth of invasion (DOI) for the prediction of parametrical involvement.

**Results:** Parametrical involvement was found in 20 patients (9.5%). Patients with parametrical involvement were significantly older and had greater DOI and tumor size. Also, the proportion of patients with parametrical involvement was greater in those with positive lymphovascular space involvement (LVSI) and in those with lymph node metastasis. Multiple logistic regression analysis showed that increased age (odds ratio [OR]=1.07, 95% CI: 1.02-1.12, P=0.004), depth of invasion (OR=1.11, 95% CI: 1.04-1.18, P=0.002), and lymph node metastasis (OR=5.25, 95% CI: 1.61-17.19, P=0.006) were associated with increased risk for parametrical involvement. ROC curve analysis showed that the optimal cutoff of DOI for the prediction of parametrical involvement was 13 mm, with sensitivity of 80% and specificity of 74.9%. Women with DOI ≤13 mm had 2.7% odds for parametrical involvement while women with DOI ≤13 mm and negative pelvic lymph nodes had 0.7% risk for parametrical spread. Tumor size ≤2.4 cm represented a less sensitive cutoff for the prediction of parametrical involvement (sensitivity of 75% and specificity of 57.6%).

**Conclusions:** Patients with DOI ≤13 mm and negative lymph nodes represent a subgroup with a very low risk for parametrical spread. These patients could be considered for less radical surgery such as cervical conization or simple hysterectomy with pelvic lymphadenectomy.

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**131 The clinical significance of beta adrenergic receptor expression in cervical cancer tissue**

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**Objective:** Chronic stress and related sustained increases in tissue catecholamines have been shown to promote tumor growth and metastasis via cell signaling mediators such as vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8). However, the clinical significance of beta-adrenergic receptor expression (ADRB) in cervical cancer is not known and was examined here.

**Methods:** Human cervical cancer samples were obtained at the time of diagnosis from 168 women. ADRB1 and ADRB2 expression was examined using immunohistochemical peroxidase staining, and semiquantitative scores were related to patient outcome. In addition, we examined the effects of catecholamines on production of proangiogenic factors (VEGF, IL-8) by cervical cancer cell lines (SiHa and Caski) using qRT-polymerase chain reaction.

**Results:** The median age of patients in this study was 45.3 years (range, 22 – 83 years). Among the 168 tumor samples evaluated, 85% had increased ADRB1 expression and 61% had increased ADRB2 expression. Tumor stage or grade was not related to ADRB expression. ADRB1 expression was not related to overall patient survival (P=0.86), but ADRB2 was significantly related (mean 146 months for those with increased expression vs. 206 months for those with low or absent expression; P=0.038). Upon stimulation with norepinephrine or isoproterenol, the levels of VEGF did not change appreciably, but the levels of IL-8 increased by 3.5 – 6-fold (P<0.001).

**Conclusions:** These data support the hypothesis that ADRB2 might play a pivotal role in cervical cancer growth and progression via stimulation of IL-8 and have potential clinical implications for new therapeutic strategies.

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**132 Distance traveled for treatment of cervix cancer: Who travels the furthest and does it impact outcome?**

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**Objective:** Access to care is crucial with cervix cancer (cxa) because it is a potentially preventable disease via screening. Demographic factors have been linked with further travel for care of endometrial cancer. Within our rural state, we sought to examine the impact of distance traveled on characteristics of cxa and recurrence rates.

**Methods:** A retrospective chart review of patients treated for cxa at a single center during 2006-2011 was performed. Demographic, socioeconomic, oncologic, and therapeutic characteristics were recorded, and distance traveled from zip code of residence to treating hospital was calculated. Recurrence and follow-up data were also extracted. SAS 9.2 was used for statistical analysis.

**Results:** 219 patients were treated for primary cxa during the study period. 75% were Caucasian, 9% Native American, 6% Hispanic, and 5% African American. 49% were ever-users of tobacco with 29 median pack-years. Stage distribution was 51% stage I, 39% stage II/III, and 10% stage IV. Insurance type was 46% private, 25% Medicaid, 20% Medicare, and 9% uninsured. Distance between residence and treating hospital was 29% <15 miles, 21% 15 to 30 miles, 17% 30 to 50 miles, and 33% >50 miles. 24% of patients were treated on a clinical trial. 26% were treated with surgery alone; 74% had chemoradiation. Median length of follow-up was 23 months. Caucasians were more likely to travel >30 miles to the treating hospital (P=0.18). Non-Caucasian patients were less likely to have private insurance (P=0.0005) and more likely to have disease recurrence (P=0.0045). Recurrence was highest (50%) in African American patients. Travel distance >30 miles was not associated with age, stage, histology, tobacco abuse, employment status, clinical trial enrollment, primary chemoradiation.
for stage IB disease, or longer radiation window. Travel distance >30 miles was associated with government insurance (P=0.029) and a trend toward unemployment (P=0.059). 36-month progression-free survival (34% vs 31%, P=0.4785) and overall survival were not significantly different between < or >30 mile travel (41% vs 35%, P=0.76).

Conclusions: 50% of patients in this study lived >30 miles from the treating hospital. Despite the barrier of further travel for care, stage, clinical trial enrollment, treatment type, radiation completion, and recurrence rates were similar in cxc patients at our center. Non-Caucasian patients were less likely to travel >30 miles and had higher recurrence rates.

133
A cost analysis of colposcopy following abnormal cytology in post-treatment surveillance for cervical cancer
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Objective: To determine the cost and outcomes associated with colposcopy (colpo) following an abnormal Papanicolaou test (Pap) for women with a history of invasive cervical cancer.

Methods: Simple decision models were constructed to compare the costs and number of isolated local recurrences detected using 2 strategies for women with a history of cervical cancer and a low-grade squamous intraepithelial lesion (LSIL)/atypical squamous cells of unknown significance (ASCUS)- related papillomavirus (HPV) (low-grade) or an high-grade squamous intraepithelial lesion (HSIL) (high-grade) Pap: 1) colpo or 2) no colpo. Outcomes were modeled based on cohorts of 50 women with low-grade Pap and 78 women with high-grade Pap following a diagnosis of invasive cervical cancer. Costs of colpo and of treatment for high-grade dysplasia were obtained using national reimbursement data.

Results: We identified 556 patients with invasive cervical cancer who collectively underwent 2,900 surveillance Paps. Of the 97 patients with recurrences, 28.9% had either a low- or high-grade surveillance Pap. Among 50 women with low-grade Pap, 27 underwent colpo and 23 did not. Of the 3 recurrences in the colpo group, only 1 was an isolated local recurrence and was diagnosed with colpo. Of the 6 recurrences in the no colpo group, 2 were isolated local recurrences, and both were diagnosed with non-colposcopic diagnostic methods. For low-grade Pap, the colpo strategy cost on average $334 more than no colpo and resulted in a lower rate of diagnosis of isolated pelvic recurrence compared to non-colpo diagnostic methods (3.7% vs 8.6%). Among 78 women with a high-grade Pap, 60 underwent colpo and 18 did not. Of the 15 recurrences in the colpo group, 3 were isolated local recurrences diagnosed with colpo. Of 4 recurrences in the no colpo group, none were isolated local recurrences. For high-grade Pap, colpo cost on average $623 more than the no colpo strategy but resulted in a higher rate of diagnosis of isolated local recurrence than the no colpo strategy (6% vs 0%). Colpo following high-grade Pap was associated with a cost of $7,481 per additional isolated local recurrence detected.

Conclusions: Colposcopy following low-grade Pap adds significant cost and does not appear to increase the probability that cervical cancer recurrence will be detected when salvageable. Colposcopy following a high-grade Pap also adds significant cost but appears to be associated with a higher probability that cervical cancer recurrence will be detected when salvageable. These findings add to the mounting evidence that suggest withholding colposcopy for abnormal Pap tests less than high grade in this population.

134
Outcomes of locally advanced cervical cancer in an underserved indigent US population
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Objective: To report outcomes of locally advanced-stage cervical cancer in an underserved population of the United States outside a research setting.

Methods: We performed a retrospective, single-institution chart review of patients with stages IIB-IVA cervical cancer who presented for treatment between 2003-2011. The stage status of each patient was verified. Toxicities were graded using the CTCAEv4.0 criteria. Progression-free survival (PFS) and overall survival (OS) were calculated using Kaplan Meier curves.

Results: 204 patients were included in the study. The median age was 46 years (range, 20-82 years). Forty-four percent of the patients were Hispanic, 28% were African American, 25% were Caucasian, and 2% were Asian. Ninety seven percent of women were underpriviledged based on total family income and household members. Ninety five percent of women were compliant with radiation therapy. Ninety five percent of patients received concomitant cisplatin chemotherapy with external beam radiation; 3% received external beam radiation alone. Seventy percent of patients had a complete response to treatment. Five percent had persistent disease, 13% had progressive disease, and 11% had recurrence. No grade 3/4 toxicities due to chemotherapy were noted. 11% of the patients had a grade 3/4 toxicities due to radiation complication, which included fistulas (15/204 [7%]), radiation cystitis (1/204), radiation proctitis (7/204), and small bowel obstruction (2/204). There were no deaths due to radiation treatment or its long-term toxicities. Mean PFS and OS were 53 and 53 months respectively. The cumulative disease-specific 5-year survival rate was 34.2%.

Conclusions: The majority of underpriviledged women with locally advanced cervical cancer are compliant with standard of care treatment recommendations. Although treatment related deaths were not observed, 11% of patients had grade 3/4 toxicities.

135
Abdominal radical trachelectomy (ART) for cervical malignancies: Fertility outcomes in 124 Chinese patients
X. Wu, J. Li
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Objective: Abdominal radical trachelectomy (ART) has been accepted as a fertility-sparing procedure for cervical cancer patients. However, worse fertility outcomes in comparison with vaginal radical trachelectomy (VRT) have been questioned. The purpose of this study was to report fertility outcomes of ART in patients with cervical malignancies.

Methods: We conducted a retrospective review of a prospectively maintained database of patients undergoing fertility-sparing ART for cervical malignancies at our institution from 04/2004 to 08/2012. A survey was also conducted 6 months after surgery to investigate reproductive functions and fertility outcomes.

Results: Of the 124 patients who underwent attempted ART, 3 required a conversion to radical hysterectomy. The median age was 28.1 years (range, 11-44 years). Histology included 117 (94.3%) with cervical cancer and 7(5.65%) with botryoid sarcoma. Seventy-eight patients (63%) had stage IB disease, or longer radiation window. Travel distance >30 miles was associated with government insurance (P=0.029) and a trend toward unemployment (P=0.059). 36-month progression-free survival (34% vs 31%, P=0.4785) and overall survival were not significantly different between < or >30 mile travel (41% vs 35%, P=0.76).

Conclusions: 50% of patients in this study lived >30 miles from the treating hospital. Despite the barrier of further travel for care, stage, clinical trial enrollment, treatment type, radiation completion, and recurrence rates were similar in cxc patients at our center. Non-Caucasian patients were less likely to travel >30 miles and had higher recurrence rates.

133
A cost analysis of colposcopy following abnormal cytology in post-treatment surveillance for cervical cancer
A. Tergas1, L. Havrilesky2, S. Guntupalli1, W. Huh1, L. Massad3, A. Nickles Fader1, B. Rimel1
1Johns Hopkins University Hospital, Baltimore, MD, 2Duke University Medical Center, Durham, NC, 3Washington University, St. Louis, MO, 4UAB Comprehensive Cancer Center, Birmingham, AL, 5Cedars Sinai Medical Center, Los Angeles, CA

Objective: To determine the cost and outcomes associated with colposcopy (colpo) following an abnormal Papanicolaou test (Pap) for women with a history of invasive cervical cancer.

Methods: Simple decision models were constructed to compare the costs and number of isolated local recurrences detected using 2 strategies for women with a history of cervical cancer and a low-grade squamous intraepithelial lesion (LSIL)/atypical squamous cells of unknown significance (ASCUS)-related papillomavirus (HPV) (low-grade) or a high-grade squamous intraepithelial lesion (HSIL) (high-grade) Pap: 1) colpo or 2) no colpo. Outcomes were modeled based on cohorts of 50 women with low-grade Pap and 78 women with high-grade Pap following a diagnosis of invasive cervical cancer. Costs of colpo and of treatment for high-grade dysplasia were obtained using national reimbursement data.

Results: We identified 556 patients with invasive cervical cancer who collectively underwent 2,900 surveillance Paps. Of the 97 patients with recurrences, 28.9% had either a low- or high-grade surveillance Pap. Among 50 women with low-grade Pap, 27 underwent colpo and 23 did not. Of the 3 recurrences in the colpo group, only 1 was an isolated local recurrence and was diagnosed with colpo. Of the 6 recurrences in the no colpo group, 2 were isolated local recurrences, and both were diagnosed with non-colposcopic diagnostic methods. For low-grade Pap, the colpo strategy cost on average $334 more than no colpo and resulted in a lower rate of diagnosis of isolated pelvic recurrence compared to non-colpo diagnostic methods (3.7% vs 8.6%). Among 78 women with a high-grade Pap, 60 underwent colpo and 18 did not. Of the 15 recurrences in the colpo group, 3 were isolated local recurrences diagnosed with colpo. Of 4 recurrences in the no colpo group, none were isolated local recurrences. For high-grade Pap, colpo cost on average $623 more than the no colpo strategy but resulted in a higher rate of diagnosis of isolated local recurrence than the no colpo strategy (6% vs 0%). Colpo following high-grade Pap was associated with a cost of $7,481 per additional isolated local recurrence detected.

Conclusions: Colposcopy following low-grade Pap adds significant cost and does not appear to increase the probability that cervical cancer recurrence will be detected when salvageable. Colposcopy following a high-grade Pap also adds significant cost but appears to be associated with a higher probability that cervical cancer recurrence will be detected when salvageable. These findings add to the mounting evidence that suggest withholding colposcopy for abnormal Pap tests less than high grade in this population.
of them had restored menstruation. Forty-eight completed the survey aimed at determining what factors influenced patients’ reproductive outcomes (Table). Only 15 (12.1%) patients attempted to conceive and (26.7%) of them succeeded (one employed assisted reproductive techniques). All of them delivered by cesarean section between 37-39 weeks’ gestation.

**Conclusions:** We observed a 26.7% pregnancy rate, with all of these pregnancies resulting in deliveries of >37 weeks. Influenced by social, familial, and physical factors, only a small fraction of patients attempted to conceive after ART. This could be the most important reason that our series had unfavorable obstetric outcomes. Cervical stenosis, which could be effectively prevented by installation of a tailed T-IUD, is the unique and major complication after ART. Clinicians should be aware of the late occurrence of cervical stenosis for which neocervix dilation would be helpful. Larger study is needed to confirm our findings.

<table>
<thead>
<tr>
<th>Table. Issues Influencing the Reproductive Outcomes</th>
</tr>
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<tbody>
<tr>
<td><strong>Issues</strong></td>
</tr>
<tr>
<td>Physical and sexual problems</td>
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<tr>
<td>Reproductive schedule (When will you attempt to conceive?)</td>
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<tr>
<td>Do you have any adverse social/familial sequelae of cancer or cancer-related treatment?</td>
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</tbody>
</table>

* Patient responses may contain more than one problem; percentages will not equal 100%.

**Clinical Practice Issues**

**136**

**Predictive model of venous thromboembolism in endometrial cancer**

K. Matsuo, E. Wu, A. Yessaian, Y. Lin, H. Pham, L. Muderspach, H. Liebman, C. Morrow, L. Roman

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**Objective:** To profile the characteristics and survival of endometrial cancer patients who develop venous thromboembolism (VTE) and to establish a predictive model of VTE in endometrial cancer.

**Methods:** Cases were identified using an institutional database between January 2000 and March 2011. VTE was correlated to clinicopathologic information and survival outcomes. Frequency and odds ratio (OR) of VTE were examined in a predictive model based on the combination patterns of independent risk factors for VTE.

**Results:** VTE was seen in 42 (8.1%, 95% CI 5.8-10.5) of 516 cases. Multivariate logistic regression analysis identified 4 independent risk factors for VTE: elevated CA-125 (OR 5.38, P=0.001), extraterine disease (stage III-IV, OR 3.04, P=0.02), high-risk histology (serous and clear cell, OR 2.73, P=0.023), and thrombocytosis (OR 2.41, P=0.04). In survival analysis, VTE was the strongest variable for decreased progression-free and overall survival in multivariate analysis (hazard ratio 4.12 and 7.68, respectively, P<0.001). In a predictive model of VTE, the presence of multiple risk factors was significantly associated with increased risk of VTE: frequency of VTE 1.4% if no risk factors, 0.9-3.5% (OR 1.0-2.42) if a single risk factor, 11.1%-25.0% (OR 9.0-24.0) if 2 risk factors, and 42.9%-46.2% (OR 54.0-61.7) if ≥3 risk factors (Figure).

**Conclusions:** VTE was the worst prognostic indicator for survival of endometrial cancer patients. Multiple risk factors of VTE in our predictive model demonstrated exceedingly high risk of VTE. The findings suggest a certain population of endometrial cancer patients may benefit from long-term anticoagulant prophylaxis to improve survival outcome.

**137**

**Clinical factors predictive of postoperative pulmonary embolism in gynecologic cancer patients**

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**Objective:** Pulmonary embolism (PE) is a serious event in gynecologic oncology patients. Postoperative diagnosis is imperative, but clinical presentation is nonspecific in this high-risk group. We sought to determine key risk factors and clinical findings that may assist clinicians in the diagnosis of PE in the inpatient setting.

**Methods:** After institutional review board approval, we queried radiology data over a 6-year period to identify gynecologic cancer patients who had a postoperative PE evaluation with computed tomography pulmonary angiography (CT-PA). Demographic data, medical history, surgical and pathological features, and clinical findings at the time of the PE evaluation were then abstracted from the patients’ charts. Univariate and multivariate logistic regression analyses were performed to identify predictors associated with PE.

**Results:** Between 7/15/2002 and 10/31/2008, there were 2,498 major gynecologic oncology surgeries performed at our academic medical center. Within 14 days of surgery, 107 CT-PA studies were performed: 47.3% for low oxygen saturation, 33% dyspnea, 24.5% tachycardia, 9.4% chest pain, 9.4% mental status changes. Of these patients, 26 were PE-positive and 81 were PE-negative, a positive study rate of 24.3%. Statistical significance was not found for age, oxygen saturation, and heart rate between patients with and without PE. Analyses for individual variables after controlling for known confounders such as oxygen saturation and previous history of venous thromboembolism indicated higher plateau count as a significant predictor of PE (P=0.006) and a trend toward presence of PE in patients with ascites (P=0.074). Platelet count (odds ratio [OR]=1.004, 95% CI: 1.001-1.008, P=0.006) and previous history of venous thromboembolism (OR=17.1, 95% CI: 1.77-Inf, P=0.014) were identified as independent predictors of PE in the multivariate model.

**Conclusions:** Aside from broad risk factors for PE, there are few data on inpatient clinical findings predictive of PE in our high-risk population. While traditionally tachycardia and low oxygen saturations have prompted PE imaging studies, these are nonspecific signs. We were not able to find multiple key factors that would allow for the creation of a scoring system to identify patients with a high likelihood of PE, but we can conclude that the positive predictive value of CT-PA in patients with high plateau counts or history of VTE is increased, and the threshold for ordering CT-PA in these patients could be lowered.
138

Defining practice patterns: What is "standard" postoperative care? A survey of the SGO membership

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Objective: To determine practice patterns of the SGO membership regarding "standard" postoperative management.

Methods: A survey was sent to SGO members with multiple-choice questions regarding feeding after laparotomy and laparoscopy, and nasogastric tube (NGT) use after bowel resection. Statistical analysis included frequency distributions and nonparametric tests (Friedman, Wilcoxon Signed Ranks, Kruskal-Wallis, and Mann-Whitney where appropriate).

Results: Three hundred one members of SGO started and 294 completed the survey from 1,345 eligible members with a response rate of 22.4%. There was a statistically significant difference in advancing diet before laparotomy based on extent of surgery \( (\chi^2=105.8066, P<0.001) \). Compared to an uncomplicated total abdominal hysterectomy (TAH)/bilateral salpingo-oophorectomy (BSO), respondents were significantly less likely to advance diet if a lymph node dissection (LND) or if LND/infracolic omentectomy (O) was performed with TAH/BSO \( (P<0.001) \). Additionally, respondents were significantly less likely to advance diet in the case of a TAH/BSO/LND/O when compared to a TAH/BSO/LND \( (P<0.001) \) (Figure 1A). After laparoscopy, respondents were significantly more likely to immediately feed a laparoscopic hysterectomy (LH) alone when compared to a LH/LND \( (P<0.001) \) (Figure 1B). Respondents were more likely to feed a higher-order diet to LH on postoperative day 0 than TAH/BSO on postoperative day 1 \( (P<0.001) \) as well as to LH/LND rather than TAH/BSO/LND \( (P<0.001) \). 50.8% of respondents did not keep an NGT in after a small bowel (SB) resection, while 71.5% of respondents did not keep an NGT in after a large bowel (LB) resection \( (P<0.001) \). Most respondents (41.3% SB, 41.7% LB) await passage of flatus before discontinuing the NGT. There was no statistically significant difference with regard to postoperative feeding or NGT use based on membership category (fellow in training, candidate member, or full member, \( P=0.082-0.848 \)) or practice setting (private, academic university, or academic community, \( P=0.060-0.940 \)). Similarly, there was no difference in management styles when stratifying by years in practice for the above categories \( (P=0.209-0.791) \).

Conclusions: Despite randomized, controlled trials in gynecologic oncology showing the safety of regular diet after laparotomy, most gynecologic oncologists do not give regular diet as the first meal, especially with more extensive surgery. There was no difference in feeding patterns based on membership category, years in practice, or practice setting.

A

Laparotomy Management: Advancing Diet on POD01

B

Laparoscopy Management: Advancing Diet on POD00

Abstract withdrawn

139

Effectiveness of cyanoacrylate microbial sealant (CMS) in the reduction of surgical site infection in gynecologic oncology procedures: A single-center randomized study: interim analysis


University of Oklahoma, Oklahoma City, OK

Objective: Despite continued advances in aseptic technique, surgical site infections/disruptions occur in ~20% of patients (pts) undergoing surgery for gynecologic malignancy. Consequences of wound infections include escalating cost, delayed adjuvant treatment, and increases in morbidity/mortality. The purpose of this study was to evaluate the effectiveness of CMS in reducing hospital-acquired infections.

Methods: Randomized study: interim analysis


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bacterial contamination and subsequent wound infection after exploratory laparotomy for gynecologic oncology procedure.

**Methods:** Pts were randomized using a 1:1 allocation to receive a standard skin preparation vs standard preparation +CMS stratified by body mass index (BMI) > or <30. Pts were prospectively followed for 6 weeks for wound complications and adverse surgical outcomes. Data on clinicopathologic factors, surgical procedures, and postoperative care were collected through the in- and outpatient medical records. Associations between wound infections/disruptions, use of CMS, and multiple factors were explored using descriptive statistics and chi-square analysis. Per protocol, an interim analysis evaluating incidence of surgical site infections/disruptions was specified after 75 pts were randomized.

**Results:** Of 80 pts enrolled, median age was 58 years (range, 20-81 years), and mean BMI was 38.8 in pt cohort with BMI >30, and 26.3 for pt cohort with BMI <30. Presence of significant medical comorbidities included: 45% cardiovascular disease, 25% diabetes mellitus, 15% pulmonary disease, 45% current/history of tobacco use, and they were comparable between CMS and non-CMS groups. All pts received preoperative antibiotics, 54% had malignancy, 84% of procedures were classified as clean-contaminated or contaminated, 20% of pts underwent bowel surgery, 26% received transfusion, and mean estimated blood loss was ~500 mL. Overall wound infection rate was 13.3%, with a wound disruption rate of 29.5%. The CMS cohort underwent significantly more bowel surgery ($P=0.029$), but no difference in wound separation or infection rates was noted ($P=0.27$, $P=0.58$, respectively). Univariate analysis demonstrated that clean procedures showed a trend toward reduced wound infection ($P=0.08$).

**Conclusions:** Pts undergoing open abdominal surgery with gynecologic oncologists have frequent wound complications secondary tomodifiable and non-modifiable risk factors. Adding CMS to preoperative skin preparation in patients undergoing surgery for known or suspected gynecologic malignancy may contribute to the reduction of surgical site infection. Study enrollment continues with 90/300 pts and study likely completed in 12-18 months.

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**Is it reasonable to administer pegfilgrastim on day 1 of a myelosuppressive chemotherapy regimen? A cost-utility analysis**

C. Billingsey1, D. Cohn1, A. Crim1, D. O'Malley1, L. Havrilesky2

1The Ohio State University, Columbus, OH, 2Duke University Medical Center, Durham, NC

**Objective:** There is evidence to support the efficacy and safety of day 1 (versus United States Food and Drug Administration-approved day 2) administration of pegfilgrastim in patients undergoing myelosuppressive chemotherapy for gynecologic malignancies, but with possible increased risk of prolonged neutropenia. We sought to determine the comparative effectiveness of pegfilgrastim on day 1 compared to day 2 for primary prevention of neutropenia in women receiving chemotherapy with an intermediate risk for febrile neutropenia.

**Methods:** A cost-utility decision model was designed to compare standard day 2 (D2) versus experimental day 1 (D1) administration of pegfilgrastim for prevention of neutropenia in stage III/IV ovarian cancer patients undergoing chemotherapy. We assumed per American Society of Clinical Oncology guidelines that the regimen carried an a priori risk of febrile neutropenia (FN) of 20% (justifying primary prevention with granulocyte cell-stimulating factor). Rates of FN despite prophylaxis were modeled as 11% for D1 and 10% for D2 pegfilgrastim. Societal costs associated with D2 injection (travel, facility fee, and loss of patient/caregiver wages: total $127) were incorporated using nationally available data. The quality of life (QOL) associated with modeled health conditions in newly diagnosed ovarian cancer (utility for active treatment 0.67, FN 0.5) were from published data; we assumed an additional decrement in QOL on chemotherapy administration or injection days (utility 0.6). Sensitivity analysis was performed to gauge the impact of pertinent uncertainties.

**Results:** D1 administration of pegfilgrastim was less costly ($1,253 vs. $1,266) and resulted in greater QOL (0.2298 quality adjusted life years [QALYs] versus 0.2287 QALYs) than D2. D1, therefore, dominated D2 (Figure). These results were highly sensitive to the risk of FN in each arm. If the FN rate with D1 is assumed between 11% and 12%, D1 remains cost-effective, with an incremental cost-effectiveness ratio (ICER) less than $100,000/QALY compared to D2. If the FN rate with D1 is greater than 12%, D1 is not cost-effective compared to D2, with an ICER greater than $100,000/QALY. Model findings are stable and insensitive to changes in the modeled cost of treating FN, the additional cost of D2 injection, and in the QOL associated with treatment visits.

**Conclusions:** Administration of D1 pegfilgrastim is potentially cost-effective in women with ovarian cancer treated with regimens with an intermediate risk of FN. Assumptions about the rate of FN affect the cost-effectiveness of strategies.

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**Revolver of obstruction – An Analysis of gynecologic oncology readmission**


Memorial Sloan-Kettering Cancer Center, New York, NY

**Objective:** Patients readmitted to the hospital lead to additional stress and utilization of resources on an already overburdened health care system. Proactive measures to avoid readmission would be of great benefit. We sought to analyze the readmission diagnoses and clinical characteristics of gynecologic oncology (GO) patients (pts).

**Methods:** Using our institutional database, we identified all GO readmissions at our institution from 1/07-6/12. Days to readmission from initial discharge were calculated and divided into 61-90 days, 31-60 days, and ≤30 days. Exclusion criteria included readmission >90 days and complications relating to recent (<30 days) surgery. Site of cancer diagnosis, stage of disease, and the diagnosis associated with readmission were recorded. ICD9 codes were used to assign diagnoses and categorize readmissions. Readmissions that occurred in ≤30 days were further evaluated to assess the leading cause.

**Results:** During the study period, 1,196 GO pts were readmitted with a median time from initial discharge of 18 (1–90) days. Of those 1,196 pts, 665 (56%) were diagnosed with ovarian/fallopian tube/primary peritoneal (OC/FT/PP) carcinoma, 324 (27%) with uterine cancer, 114 (10%) with cervical cancer, and 28 (2%) with vaginal/vulvar cancer. Six hundred thirty-three (53%) pts readmitted were originally diagnosed with advanced stage disease. Of 1,196 pts, 657 (55%) had readmissions within 30 days. Of these patients, the top 5 reasons for readmission were categorized as gastrointestinal, fluid/ electrolyte/ nutrition, infectious, pulmonary, and renal. The most common reason for readmission in 30 days was gastrointestinal, which accounted for 47% of readmissions. Bowel obstruction accounted for 45% of the gastrointestinal readmissions and 21% of all readmissions within 30 days.

**Conclusions:** The majority of GO readmissions are in those diagnosed with OC/FT/PP cancer and those with advanced disease. The most common readmission diagnosis is categorized as gastrointestinal. In patients readmitted within 30 days of discharge, bowel obstruction is the leading cause.
Objective: The primary objective was to determine the difference in postoperative (PO) pain outcomes for the staging (hysterectomy and lymphadenectomy) of endometrial cancer (EC) by hysterectomy performed as robotic surgery (RS) or laparotomy (LAP). Secondary objectives included analysis of differences in length of stay (LOS), quality of recovery (QoR), and quality of life (QoL).

Methods: A prospective, single-center, observational study was conducted on 109 women with clinical stage I or II EC undergoing surgical staging by RS or LAP. Patients were treated with a standardized regimen of either intravenous opioids via patient-controlled analgesia or oral opioids for PO pain. Visual analog scale (VAS) scores at rest and after leg extension were obtained at baseline and 24 hours after surgery to assess pain. Mean opioid consumption was calculated until hospital discharge by converting all medications to oral morphine equivalent. QoR was assessed using the QoR-40 survey at PO day 1 and day 10, and QoL was assessed using the SF-36 scoring tool.

Results: Of the 109 study subjects, 75 underwent RS and 34 LAP for the staging of EC. There were no significant differences observed with regard to demographic information. The mean difference between baseline and day 1 VAS at rest was 27.4±25.9 mm (RS group) vs. 33.9±22.5 mm (LAP group) (Table). The mean difference between baseline and day 1 VAS leg extension was 26.7±32.0 mm (RS group) vs. 31.2±23.7 mm (LAP group). Analysis of mean opioid consumption from the first 24 hours after surgery resulted in a statistically significant difference (RS: 81.3±54.9 mg vs. LAP: 126.2±97.6 mg, P<0.0001). The mean length of stay was 1.24±0.60 and 3.47±1.43 days for RS and LAP, respectively (P<0.0001). Statistical significance was observed at QoR day 10, but not QoL.

Conclusions: In this prospective study, opioid consumption was significantly less in the RS compared to LAP group without a statistically significant reduction in VAS scores. Furthermore, RS is associated with an improved recovery compared with LAP. Continued prospective comparison of RS vs. LAP or laparoscopy is needed to comprehensively evaluate these surgical approaches.

145 Routine cystoscopy after robotic gynecologic oncology surgery: Are we increasing urinary injury detection or simply achieving medical-legal benefit?
M. Nguyen1, C. LaFargue1, M. Karsy1, E. Stevens2, S. McKernan1, T. Pua1, C. Gorelick1, S. Tedjarati1, T. Pradhan1
1New York Methodist Hospital/Cornell Medical College Affiliate, Brooklyn, NY

Objective: To determine whether the use of routine cystoscopy increases the detection rate of urinary injury (bladder and/or ureteral) after robotic surgery performed by gynecologic oncologists.

Methods: A retrospective chart review of patients who presented to gynecologic oncology for robotic surgery from 2009-2012 was performed at 2 separate teaching institutions (one institution performed routine cystoscopy and the other did not). Patient demographics such as age, body mass index (BMI), primary surgical indication, surgical procedures, hysterectomy specimen size, blood loss, operative time, and urinary complications were analyzed. Conversions from robotic surgery to laparotomy, cystoscopy performed in the non-cystoscopy group, and the absence of cystoscopy in the routine cystoscopy group were excluded. Statistical analysis was performed using T-tests and chi-squared tests. The primary outcome was urinary injury detection rate by cystoscopy.

Results: One hundred forty cases of nonroutine and 109 routine cystoscopy cases were identified. There were no intra- or postoperative urinary injuries detected. There were no significant differences in age (59.4±12.3 vs. 57.0±11.9 years), BMI (33±8 vs. 33±8), and estimated blood loss (68.3±44.1 vs. 101.6±124.4 mL) between the non-cystoscopy group and routine cystoscopy group. Greater specimen size was seen in the nonroutine cystoscopy group (132.6±86.2 vs. 218.6±239.5 g, P=0.001). There were no differences in surgical indications except that more patients underwent hysterectomy for ovarian cancer (including borderline tumors) in the routine cystoscopy group (2 vs. 11, P=0.0192). For procedures performed, there were significantly more hysterectomies in the non-cystoscopy group (85 vs. 40) and a higher number of hysterectomies with lymphadenectomy in the cystoscopy group (47 vs. 57, P=0.0007). There were no differences in other primary and secondary procedures, including bilateral salpingo-oophorectomy, radical hysterectomies, ureterolysis, and pelvic organ prolapse-related procedures. Mean operative time for the routine group was 180 minutes (range, 51 to 340 minutes) vs. 360 minutes (range, 120 to 730 minutes) for the non-cystoscopy group, P<0.0001.

Conclusions: There were no urinary injuries diagnosed in either group. The routine use of cystoscopy after robotic surgery did not appear to increase the detection rate of intraoperative urinary injury. Under the care of a gynecologic oncologist, routine cystoscopy may only provide medical-legal benefit should an injury be detected postoperatively.

Table. Primary and Secondary Objective Outcomes RS vs. LAP*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Robotic Surgery (n=75)</th>
<th>Laparotomy (n=34)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Day 1 VAS change - at rest (mm)</td>
<td>27.4 (25.9)</td>
<td>32.9 (22.2)</td>
<td>0.2997</td>
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<tr>
<td>Day 1 VAS change - leg extension (mm)</td>
<td>32.7 (32.0)</td>
<td>31.2 (23.7)</td>
<td>0.4651</td>
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<tr>
<td>Intraoperative opioid consumption (mg)</td>
<td>110.9 (97.4)</td>
<td>106.5 (50.2)</td>
<td>0.8043</td>
</tr>
<tr>
<td>Mean opioid consumption 24 hr PO (mg)</td>
<td>81.3 (54.9)</td>
<td>162.2 (97.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hospital LOS</td>
<td>1.24 (0.60)</td>
<td>3.47 (1.43)</td>
<td>&lt;0.0001</td>
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<tr>
<td>QoR-40 Day 10 mean score</td>
<td>182.1 (12.2)</td>
<td>171.6 (20.1)</td>
<td>0.0036</td>
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</tbody>
</table>

1Data are presented as mean (SD).

146 Postoperative wound separation among obese women
T. Bass, R. Miller, S. Slone, F. Ueland, L. Baldwin, J. Hoff, J. Elder, C. DeSimone
University of Kentucky Medical Center, Lexington, KY

Objective: The number of gynecologic surgeries performed upon obese women increases each year in the United States. Minimally invasive surgery is preferred for this population but often in unachievable due to medical comorbidities. The objective of this study was to compare the rate of wound separation among obese women versus overweight/normal-weight women following a laparotomy.

Methods: A retrospective chart review was conducted at the University of Kentucky from 2005-2010 to assess postoperative wound complications following an abdominal surgery performed through a vertical, midline incision. The incision was closed in 3 layers: fascial suture; interrupted, deep dermal sutures; and a running, subcuticular suture. Patients with a body mass index (BMI) >30 utilized an abdominal binder. Patient demographics, medical comorbidities, and postoperative complications were recorded and analyzed using SAS version 9.3. Comparisons between groups were calculated using the chi-square test and a logistic covariate model adjusting for significant risk factors (P value < 0.05).

Results: Seven hundred thirty-two patients were identified for analysis. The median age was 50 years (range, 22-90 years), weight was 192 lb (range, 78-425 lb), and BMI 32.3 (range, 13.3-73.3). Medical comorbidities were recorded: hypertension (49%), malignancy (44%), smoking (26.8%), diabetes (22.3%), hypothyroidism (17.4%), coronary artery disease (9.7%), chronic obstructive pulmonary disease (4%), synchronous hernia repair (3.3%),
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

147 A silent threat: The prevalence of undiagnosed obstructive sleep apnea among gynecologic oncology patients

M. Courtney-Brooks1, M. Barrett2, L. Cantrell3
1University of Virginia, Charlottesville, VA, 2University of Virginia Health System, Charlottesville, VA

Objective: Patients with obstructive sleep apnea (OSA) are at increased risk for life-threatening breathing irregularities, perioperative complications, and postoperative mortality. Due to the high prevalence of undiagnosed OSA, an institutional screening initiative was enacted for all patients preparing to undergo surgery. All preoperative patients are screened using a Modified STOP BANG Questionnaire. For those patients scoring ≥3 points, providers consider completion of a sleep study before surgery. The objective of this study was to estimate the prevalence of undiagnosed OSA among gynecologic oncology patients.

Methods: All gynecologic oncology surgical patients initially seen as outpatients between January 31 and August 31, 2012, were included. Data abstracted from the electronic medical record included demographic data, past medical history, documentation of either known OSA or a completed Modified STOP BANG Questionnaire for those without a known diagnosis of OSA, and results of sleep studies.

Results: A total of 316 women met inclusion criteria. Nineteen (6%) women had the diagnosis of OSA at time of presentation. Of the 297 women with no diagnosis of OSA, 278 (93%) were screened using the Modified STOP BANG Questionnaire and 57 (20%) scored ≥3 points. Of these, 21 completed a sleep study and 20 were diagnosed with OSA. The prevalence of undiagnosed OSA was at least 7.2% among gynecologic oncology patients. Sixty women had a BMI ≥40, and 11 (18%) of these women with class III obesity had the diagnosis of OSA before presentation. Of the 49 women with class III obesity who had no diagnosis of OSA, 47 were screened using the Modified STOP BANG Questionnaire and 28 (60%) had a score ≥3 points. Eleven women completed a sleep study and 10 were diagnosed with OSA. The prevalence of undiagnosed OSA among gynecologic oncology patients with class III obesity was at least 20%.

Conclusions: Screening for undiagnosed OSA is accepted and feasible in a busy surgical clinic setting. The rates of undiagnosed OSA are high among gynecologic oncology patients, particularly in the super obese category. This is likely an underestimate because fewer than half the patients with scores ≥3 actually completed a sleep study and the vast majority of patients who had a sleep study were diagnosed with OSA. Due to the increased perioperative morbidity and mortality associated with undiagnosed OSA, universal screening among gynecologic oncology patients should be considered.

148 Postoperative pain control in the gynecologic laparotomy patient: A prospective, randomized comparison of acetaminophen with narcotics vs. ketorolac with narcotics

J. Rakowski, C. Jeppson, J. James, S. Ahmad, G. Bigsby IV, G. Ghurani, R. Holloway, J. Kendrick IV
Florida Hospital Cancer Institute, Orlando, FL

Objective: To determine which non-narcotic analgesics, acetaminophen or ketorolac, provides better postoperative pain control when combined with an opioid patient-controlled analgesic (PCA) pump, with attention to clinically important differences in ileus, narcotic requirement, length of hospitalization, and postoperative blood loss.

Methods: A prospective, randomized comparison trial of 2 different postoperative pain regimens for patients undergoing laparotomy for benign or cancerous gynecologic conditions. In addition to a standard opioid PCA, patients received either acetaminophen 1 g every 6 hours or ketorolac 15 mg every 6 hours from postoperative day 1 to 3. A hydromorphone hydrochloride PCA was used for those with allergies or adverse reactions to morphine sulfate. Patients were excluded for renal insufficiency, active peptic ulcer disease, recent gastrointestinal hemorrhage, allergy to acetaminophen or ketorolac, asthma, warfarin or therapeutic enoxaparin use, liver disease/impaired function, or significant postoperative bleeding. Abstracted data included quantification of pain via visual analog pain scales (VAS), volume of narcotic PCA used, liver enzymes, daily hemoglobin (HB), urine output, blood transfusions, return of flatus, and length of hospitalization.

Results: Fifty-nine patients have been studied to date, with 29 in the ketorolac (K) group and 30 in the acetaminophen (A) group. The groups were equally matched for gynecologic cancer staging procedures (33% K vs. 34% A). VAS pain levels (3.6 K, 3.7 A) and morphine PCA use (85.86 mg K vs. 92.91 mg A) showed no difference statistically. Hydromorphone hydrochloride PCA use was less by ketorolac patients than their acetaminophen counterparts (18.37 mg K vs. 43.75 mg A, P=0.026). Postoperative blood loss revealed a significant difference in HB drop between the 2 groups (2.96 g K vs. 2.04 g A, P=0.008), but this did not translate into an increased rate of blood transfusion (30% K vs. 31% A). Daily urine output was similar between the groups (1,998 mL K vs. 2,450 mL A). Return of flatus (2.79 days K vs. 3.87 days A, P=0.002) and length of hospitalization (4.48 days K vs. 5.53 days A, P=0.059) were both improved in the ketorolac group.

Conclusions: Ketorolac and acetaminophen provide similar postoperative analgesia through VAS pain scales. Adding ketorolac to the standard opioid regimen leads to less dependence on PCA narcotics, faster return of bowel function, and a shorter hospital stay. Ketorolac patients did not show any clinically significant postoperative bleeding.

149 A single institution review of continuous epidural anesthesia and analgesia in gynecologic oncology patients

M. Courtney-Brooks, C. Tanner Kurtz, E. Pelkofski, J. Nakayama, L. Duska
University of Virginia Health System, Charlottesville, VA

Objective: Epidural analgesia is an effective therapy for the management of pain after laparotomy among general surgery patients. Studies performed among gynecologic oncology (GO) patients are less clear. The majority of these studies examined the use of patient-controlled epidural analgesia (PCEA), but it has been suggested that continuous epidural infusion (CEI) may provide superior analgesia. Our objective was to compare the use of CEI to the use of patient-controlled analgesia with intravenous opioids (PCA) in GO patients undergoing laparotomy.

Methods: GO patients undergoing laparotomy from July 1, 2011 through July 31, 2012 were identified. Patient demographic data, perioperative details, and postoperative pain scores were abstracted from the medical record. The primary outcome was mean patient visual analog pain score on each postoperative day.
Secondary outcomes included length of hospital stay, duration of urinary catheterization, and rates of postoperative urinary tract infection (UTI) and venous thromboembolic (VTE) events.

**Results:** There were 237 laparotomies during the study time period. Fifty-six women had CEI for postoperative pain management and 181 had PCA. There was no difference in age, body mass index, prevalence of medical comorbidities, or proportion of patients with a cancer diagnosis between groups. Patients with CEI had lower mean visual analog pain scores on postoperative days 0 (3.8 vs. 5.3, P < 0.01), 1 (2.6 vs. 4.0, P < 0.01), and 2 (2.5 vs. 3.5, P < 0.01) compared to women with PCA. There was no difference in the length of stay between those with CEI and those with PCA (103 vs. 94 hours, P = 0.32). Women with CEI did have a longer length of urinary catheterization (56 vs. 26 hours, P = 0.01) but not an increased rate of UTI (5.5% vs. 1.8%, P = 0.24). There was a trend toward urinary retention necessitating replacement of a catheter (18.9% vs. 7.7%, P = 0.06), but this did not reach statistical significance. There was a higher rate of postoperative VTE among women with CEI (8.9% vs. 1.7%, P = 0.02).

**Conclusions:** In this small series, GO patients undergoing laparotomy had improved postoperative pain control when their analgesia regimen included CEI. In this patient cohort, the use of CEI did not result in a longer hospital stay or increase rates of UTI. The use of CEI should be considered in GO patients undergoing laparotomy. Further analysis is planned to examine the rate of VTE in this population as patients with CEI may have low-molecular weight heparin withheld due to concerns of epidural hematoma.

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**Table. Hospital Costs: A. Anastomotic Leak (AL) vs. Controls**

<table>
<thead>
<tr>
<th></th>
<th>AL cases (n=42)</th>
<th>Controls (no AL) (n=84)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost 30 Days</strong></td>
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<tr>
<td>Median (IQR)</td>
<td>$72,760.4</td>
<td>$53,453.7</td>
<td>&lt;0.0001</td>
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<tr>
<td>(52858.9-104449.2)</td>
<td>(27891.0, 41743.0)</td>
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<tr>
<td><strong>Cost 3 Months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>$77,421.3</td>
<td>$54,017.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(69866.2, 126174.5)</td>
<td>(27891.0, 46488.5)</td>
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<td></td>
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<tr>
<td><strong>Cost 6 Months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>$81,591.7</td>
<td>$54,017.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>(64968.8, 126228.6)</td>
<td>(27891.0, 49351.8)</td>
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</tr>
<tr>
<td><strong>Cost 1 Year</strong></td>
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<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>$92,241.3</td>
<td>$58,072.7</td>
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</tr>
<tr>
<td>(69195.5, 128026.0)</td>
<td>(28307.1, 52371.4)</td>
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</table>

**B. AL vs. PPS**

<table>
<thead>
<tr>
<th></th>
<th>AL cases (n=42)</th>
<th>PPS (n=27)</th>
<th>P value*</th>
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</thead>
<tbody>
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<tr>
<td>Median (IQR)</td>
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<td>$41,101.3</td>
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</tr>
<tr>
<td>(52858.9, 104449.2)</td>
<td>(32216.9, 55120.4)</td>
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<tr>
<td><strong>Cost 3 Months</strong></td>
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<tr>
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<td>$77,421.3</td>
<td>$49,523.5</td>
<td>&lt;0.0001</td>
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<tr>
<td>(69866.2, 126174.5)</td>
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<tr>
<td><strong>Cost 6 Months</strong></td>
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<td>0.0002</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>$81,591.7</td>
<td>$52,029.0</td>
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<tr>
<td>(64968.8, 126228.6)</td>
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<td><strong>Cost 1 Year</strong></td>
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<td>(69195.5, 128026.0)</td>
<td>(48283.2, 104197.9)</td>
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</table>

*Wilcoxon rank sum test

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**150**

**A cost-analysis of anastomotic leak vs. prophylactic bowel diversion at the time of large bowel resection for primary ovarian cancer**

E. Kalogera, L. Haas, B. Borah, S. Dowdy, W. Cliby
Mayo Clinic, Rochester, MN

**Objective:** To compare 1-year hospital costs between cases developing anastomotic leak (AL) after large bowel resection (LBR) for ovarian cancer (OC) vs. cases undergoing prophylactic protective stoma (PPS) at LBR.

**Methods:** All cases of AL following LBR for OC between 1994 and 2011 were identified and matched (1:2) with controls (LBR without AL) on age (±5 years), substage (IIA/IIIB; IIIC; IV), and date of surgery (±4 years). Additionally, all cases with PPS at time of LBR for OC during the same time period were identified and matched to cases as a third cohort. Total hospital cost data standardized to Medicare-reimbursable rates through 30 days, 3 months, 6 months, and 1 year were compared between groups using the Wilcoxon rank sum test. Outpatient cost data were excluded to minimize the impact of uncaptured costs due to delivery of chemotherapy at referring facilities. In contrast, nearly all surgical complications and reoperations occurred at our institution and hence, costs were capturable.

**Results:** We identified 42 AL cases (mean age, 63.9±12.3 years) and matched with 84 no-leak controls. AL was associated with more than double the median costs at 30 days, 3 months, 6 months and 1 year (Table, Panel A). We compared cost of AL to those cases where PPS was used to prevent AL after LBS. A total of 27 cases were identified (70.4% stage IIIC, 29.6% stage IV). 16/27 (59%) of AL cases underwent reoperation to restore bowel continuity following AL. Despite this low fraction of cases ultimately underwent reoperation for AL. In a disease where the rate of AL exceeds the rate of PPS, these data should compel surgeons to reexamine the decision to forego diversion for intermediate- and high-risk patients.
blinded review by institutional radiologists and final results will be analyzed. There was 1 false-positive MRI result for the diaphragm, 4 false-positives for liver surface involvement, and 1 false-positive for mesenteric disease. **Conclusions:** In this small study of patients, which is currently ongoing, DW-MRI appears to be effective in detecting peritoneal dissemination involving the diaphragm, cul de sac, and bowel mesentry.

### Table. Detection of Sites of Disease-CT and DW-MRI

<table>
<thead>
<tr>
<th>Sites of Disease</th>
<th>CT (%)</th>
<th>MRI (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omentum</td>
<td>9/13 (69)</td>
<td>11/13 (85)</td>
<td>NS</td>
</tr>
<tr>
<td>Liver surface</td>
<td>1/6 (17)</td>
<td>3/6 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Liver parenchyma</td>
<td>1/2 (50)</td>
<td>1/2 (50)</td>
<td>NS</td>
</tr>
<tr>
<td>Spleen</td>
<td>0/3 (0)</td>
<td>0/3 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>0/11 (0)</td>
<td>0/11 (0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pelvic/para-aortic nodes</td>
<td>8/4 (75)</td>
<td>1/4 (25)</td>
<td>NS</td>
</tr>
<tr>
<td>Bowel mesentery</td>
<td>3/12 (25)</td>
<td>9/12 (75)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cul de sac</td>
<td>0/9 (0)</td>
<td>0/9 (0)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

152

**Lower extremity edema after primary radiotherapy versus radiotherapy after pretreatment laparoscopic surgical staging in locally advanced cervical cancer**

M. Lim, J. Lee, H. Yoo, S. Seo, S. Kang, J. Kim, S. Park  
National Cancer Center, Goyang-si, Republic of Korea

**Objective:** To investigate clinical manifestation of lower extremity edema (LEE) after primary radiotherapy vs. radiotherapy after pretreatment laparoscopic surgical staging in locally advanced cervical cancer using a gynecologic cancer lymphedema questionnaire (GCLQ).

**Methods:** Medical records were reviewed in 222 patients with locally advanced cervical cancer. One hundred thirty-seven patients were excluded due to death (n=28), invalid phone number (n=50), no responding to the phone (n=43), and refusing to take the GCLQ (n=16). Of 85 evaluable patients with locally advanced cervical cancer, 42 underwent pretreatment laparoscopic surgical staging followed by radiotherapy and 43 received primary radiotherapy.

**Results:** The median age of the patients was 54.4 years (range, 22.1-80.5 years). Squamous cell carcinoma was the main histology (n=130 [90.3%]). The incidence of LEE was statistically high in the pretreatment laparoscopic surgical staging followed by radiotherapy group compared to the primary radiotherapy group (69% vs. 11.6%). Of 42 patients, 29 patients (69%) in the pretreatment laparoscopic surgical staging followed by radiotherapy group had past and/or current patient-reported LEE: past and current LEE in 13 (18.3%) and 23(56.8%) patients, respectively. The frequency of GCLQ responses >10% was: swelling (59.5%), numbness (54.8%), heaviness (45.2%), firmness/tightness (33.3%), stiffness (21.4%), leg or foot weakness (19.0%), aching (16.7%), groin swelling (16.7%), swelling with pitting (14.3%), limited movement of ankle (11.9%), and increased temperature in the leg (11.9%) in the pretreatment laparoscopic surgical staging followed by radiotherapy group. Chronic lymphedema-related angiosarcoma developed at the pelvis in 1 patient who had complex and unresolved lymphedema 7 years 10 months after pretreatment laparoscopic surgical staging and radiotherapy (Figure). Of 43 patients in the primary radiotherapy group, 5 patients (11.6%) had past and/or current patient-reported LEE: past and current LEE in 2 (40%) and 3 (60%) patients, respectively. In the primary radiotherapy group, numbness (40.5%), limited movement of knee (26.2%), leg or foot weakness (26.2%), heaviness (23.8%), aching (23.8%), and limited movement of ankle (19.0%) were reported in the GCLQ.

**Conclusions:** LEE is significantly high in patients receiving radiotherapy after pretreatment laparoscopic surgical staging compared to those receiving primary radiotherapy. Prospective clinical trials are needed to determine the clinical significance, impact on quality of life, and preventive measures.

153

**Excess risk of Clostridium difficile enterocolitis in ovarian cancer is related to exposure to broad-spectrum antibiotics**

J. Kim, K. Ward, N. Shah, C. Saenz, M. McHale, S. Plaxe  
UCSD- The Moores Cancer Center, La Jolla, CA

**Objective:** To determine if a diagnosis of ovarian cancer (OC) is independently associated with an increased risk of Clostridium difficile enterocolitis (CDE).

**Methods:** University HealthSystems Consortium (UHC) maintains an administrative database with information contributed by 116 academic medical centers and 276 affiliate hospitals, representing over 90% of United States nonprofit academic medical centers. All female inpatients (pts) having total hysterectomy, with and without a diagnosis of OC, registered in the UHC database from October 1, 2008 through June 30, 2012 were studied. Only admissions during which total hysterectomy (all ICD-9 codes) was performed were included to avoid overrepresentation of OC pts. OC patients were compared to non-OC pts to evaluate relative risk (RR) of CDE. To assess whether a diagnosis of OC was independently associated with an increased risk of CDE, adjustment was made for known or suspected risk factors for CDE. The study was powered to detect a doubling of the risk of CDE (RR ≥2) for OC pts compared to non-OC pts with 95% certainty.

**Results:** One hundred fifteen thousand, two hundred three patients were included; 402 (0.35%) were diagnosed with CDE. Of the 9,074 OC pts, 73 (0.80%) had CDE. OC pts were diagnosed with CDE 2.5 times as frequently as non-OC pts (RR=2.5; 95% CI=2.0 to 3.4). Stratification by age, presence of other comorbidities, or administration of antineoplastic drugs did not significantly modify the elevated risk associated with OC. Controlling for administration of broad-spectrum antibiotics (BSAbx) (cephalosporins, fluoroquinolones, lincosamides, extended-spectrum penicillins, carbapenem) reduced the RR associated with a diagnosis of OC to a level not significantly different from 1 (RR=1.3, 95% CI=0.3 to 4.3). Compared to non-OC pts, OC pts were more frequently treated with BSAbx (86% vs. 80%; RR=1.07, 95% CI=1.06 to 1.08), had a 39% longer median duration of BSAbx therapy (2.5 days vs. 1.8 days), and had 2.5 times greater mean total exposure to BSAbx (43.9 vs. 17.5 resource units/case).

**Conclusions:** After adjustment for antibiotic exposure, OC pts were not at excess risk of CDE. Additional studies are needed to understand the indications for and benefits of the dose, duration, and frequency of BSAbx prescription for OC pts leading to higher total exposure. Reduction of exposure to BSAbx may offer an opportunity for lowering morbidity and expense in OC pts.
154 Surgical “Apgar” score identifies a population of women with gynecologic malignancy at high risk for surgical morbidity
R. Clark1, M. Lee1, L. Bradford1, D. Boruta1, D. Del Carmen1, J. Schorge1, A. Goodman1, W. Growdon1
1Massachusetts General Hospital, Boston, MA, 2Massachusetts General Hospital/ Harvard University, Boston, MA

Objective: Surgical Apgar scoring has been proposed in general surgery literature as a quality improvement metric that correlates with morbidity. The objective of this investigation was to validate this described surgical Apgar as a possible predictor of surgical morbidity in patients undergoing hysterectomy for cervical, endometrial, and ovarian cancer.

Methods: This retrospective cohort study identified all hysterectomies performed for a gynecologic cancer at a single academic institution between 2008 and 2010. The surgical Apgar score was derived from estimated blood loss (EBL), lowest mean arterial pressure, and lowest heart rate from anesthesia records. In addition, other pertinent clinical data were extracted. Univariate and multivariate logistic regression were used to identify specific surgical complications associated with a described surgical Apgar score.

Results: During the study period, 638 women underwent laparoscopic (35%) and open (65%) hysterectomy for a spectrum of gynecologic malignancies, including endometrial (58%), ovarian (32%), and cervical (10%). Mean patient age was 60 years. Out of this cohort, 102 women (16%) experienced a major complication, defined as an unplanned intensive care admission (ICU) or return to the operating room (OR), EBL >2 L, transfusion >4 units, vascular, nerve, or visceral injury, sepsis, anastomotic leak, bowel obstruction, or death. The most common complications observed were >4 units transfused intraoperatively (9%), EBL >2 L (7%), and unplanned ICU admission (6%). Median surgical Apgar score was 7. An Apgar score of ≥8 was associated with a 6-fold decrease in the odds of these major complication events on univariate analysis (P<0.01) (Figure). Age-adjusted multivariate logistic regression controlling for surgical approach, OR time, and American Society of Anesthesiologists class identified that a surgical Apgar of ≤7 was an independent factor associated with major complications (odds ratio 3.2, 95% CI 1.7 – 6.3). Patients with an Apgar score of ≤5 had a 40%-70% complication rate, as opposed to those patients with an Apgar of 10, who had a 0% complication rate (P<0.01).

Conclusions: These data suggest that a surgical Apgar score is associated with potential morbidities facing patients who undergo hysterectomy for gynecologic. This metric is straightforward, inexpensive, and easily reproducible. It serves to identify those at a heightened risk of perioperative morbidity and may aid in the optimization of quality care delivery.

155 Comparison of outcomes in patients undergoing rectosigmoid resection: End colostomy versus reanastomosis
M. Quimper, J. Lesnock, S. Beriwal, T. Krivak, A. Olawaiye, J. Lin, P. Sukumvanich
Magee-Women’s Hospital of UPMC, Pittsburgh, PA

Objective: Patients who undergo rectosigmoid resection at the time of initial debulking have an increased risk for bowel leak following primary reanastomosis, which may delay the start of chemotherapy. The aim of this study was to compare outcomes and time to chemotherapy in patients undergoing a cytoreductive surgery that included a rectosigmoid resection with reanastomosis vs. end colostomy.

Methods: Following institutional review board approval, a retrospective chart review was made of consecutive patients who underwent a rectosigmoid resection as part of a cytoreductive surgery for a gynecologic malignancy between 2002 and 2012 at a single institution. Perioperative and follow-up data were collected. Chi-square, Fisher’s exact test, and Mann-Whitney U test were used for univariate analysis where applicable. Binary logistic regression was used for multivariate analysis.

Results: Of the 144 patients who underwent a rectosigmoid resection, 61 (42%) had creation of an end colostomy (EC), and 83 (58%) had primary reanastomosis (RA). The median time to chemotherapy for the EC group was 41 days compared to 43 days for the RA group (P=0.43). In the RA group, 8 (9.9%) patients experienced a bowel leak compared to 0 in the EC group (P<0.05). Postoperative infection rates were 27.9% and 30.1% for the EC and RA groups, respectively (P=0.72). Fistula formation occurred in 5 (6%) patients in the RA group compared with 0 patients in the EC group (P=0.07).

Risk of any surgical complication was 59.3% and 40.5% in patients who had a hemostatic products (such as fibrin sealant) was and was not used, respectively (P<0.05). Median estimated blood loss for the RA group was 600 mL compared to 1,000 mL in the EC group (P<0.005). No factor was independently predictive of infectious/leak complications. Age at surgery (hazard ratio 1.102, 95% CI 1.003-1.212 per year, P<0.05) and use of hemostatic products (hazard ratio 7.988, 95% CI 1.186-53.819, P<0.05) were independently associated with experiencing a surgical complication on multivariate analysis.

Conclusions: There was no significant difference in time to chemotherapy following cytoreductive surgery with rectosigmoid resection for gynecologic malignancy with either reanastomosis or end colostomy. The degree of tumor burden is difficult to assess and may be a significant confounder in this study. Increasing age and use of hemostatic products were associated with surgical complications, which may warrant future studies.

156 Burdens of the gynecologic literature
E. Pavlik, M. Schwartz
University of Kentucky Medical Center/Markey Cancer Center, Lexington, KY

Objective: Fifty-eight journals reporting findings relevant to gynecologic oncology (2010-2012) were assessed for relative impact and cost.

Methods: The journals considered were evaluated in terms of current impact factor (IF), change in IF, Eigen factors (EF), and article influence scores (AI). Subscription costs were obtained from publisher information.

Results: CA-Cancer J Clin had the highest IF (94.3) and AI (100) and second highest EF (99). Nature Review Cancer, the Journal of Clinical Oncology, and Lancet Oncology were cancer-specific journals with IFs >15; while the top EF journals were The Journal of Clinical Oncology, Cancer Research, and Clinical Cancer Research. Rankings for Gynecologic Oncology were IF=45 out of 58, EF=33 out of 58, and AI=49 out of 58. Rankings for The International Journal of Gynecologic Cancer were IF=56 out of 58, EF=NA, AI=NA. The current IF improved from the 5-year IF in 31 journals (including Gynecologic Oncology, 16/31) and decreased in 18 (including The International Journal of Gynecologic Cancer, 13/18). Subscription costs were $60-1,350 (members), $162-4,600 (nonmembers), and $60 for CA otherwise $650-7,610 (institutions/library).
Clinical Trial Design

158 Phase 0 studies in gynecologic malignancies are feasible and acceptable to patients

L. Duska, H. Lothamer, W. Faust, G. Petroni, P. Fracasso, S. Parsons
University of Virginia, Charlottesville, VA

Objective: In 2006 the United States Food and Drug Administration released an exploratory investigational new drug guidance to support the clinical evaluation of novel biologic drugs. The resulting phase 0 mechanism has different goals than traditional clinical trials, one of which is to evaluate an agent's biologic mechanism of action in humans. Phase 0 trials have no therapeutic intent but are instead designed with scientific endpoints to better direct the appropriate development of new cancer drugs. We undertook a study of dasatinib in endometrial cancer utilizing this mechanism. We hypothesized that significant inhibition of Src activity after treatment with dasatinib would be observed in a majority (≥80%) of patients in the endometrial tumor tissue and in the blood in at least 1 dose level.

Methods: There were 2 primary endpoints of our study: 1) to determine whether there are significant changes in levels of Src family of kinases (SKF) protein activity in endometrial tumor tissue and blood induced within 2 different doses of dasatinib treatment, and 2) to determine if the changes in levels of SKF protein activity in blood correlated with changes in levels in endometrial tumor tissue. Eligible participants were patients with endometrioid adenocarcinoma undergoing planned surgical therapy. Patients had to agree to have: a repeat endometrial biopsy before surgery for fresh tissue, pre-dasatinib blood collection, and multiple blood draws post-dasatinib for pharmacokinetic studies. Patients were aware that there was no personal benefit from their participation in the study.

Results: To date, approximately 50% of the patients approached for participation have agreed to the study, with 7 patients signing consent after eligibility review. The primary reason cited for willingness to participate in the study was to help future patients. Five patients have undergone dasatinib treatment and tissue and blood collection. There have been no serious adverse events from dasatinib treatment.

Conclusions: The phase 0 study mechanism is feasible and acceptable to patients. This mechanism allows better understanding of the biology of the response to drugs at the blood and tissue levels. Once the current study has been completed, other biologic drugs can be substituted in this model to gain more knowledge about their biologic mechanisms in blood, tumor tissue, and normal tissue.
and endpoint was described as pathologic complete response (pCR) on D&C. Patients without pCR or with progression continued on megestrol for an additional 12 weeks, after which they were similarly reassessed. There were no dose escalations or modifications. Treatment could continue if necessary for as long as 24 months. After pCR, patients were instructed to pursue fertility or start a lower-dose progestin-based maintenance agent. Under this 1-stage design, a sample size of 30 patients achieved 80% power to detect a difference of 0.25 between the H0 of 0.4 and the H1 of 0.65 using a 2-sided Z test.

Results: Among 31 patients enrolled in the study, 30 underwent protocol-defined treatment. Ages ranged from 27 to 49 years, with a median age of 37.5 years. 42% of patients were not Caucasian. Median time on study was 210 days (range, 50–768 days). To date, 13/30 (43%) experienced pCR, 3/30 (10%) a partial response, 5/30 (17%) an unconfirmed complete response, 7/30 (23%) stable disease with 3 still undergoing treatment, and 2 (7%) progressing. In 14 instances, EMB did not correlate with D&C. One third of patients experienced adverse effects; grade 1. There were 3 grade 3 adverse effects: thrombosis and headache leading to treatment discontinuation and additional headache resolving.

Conclusions: In a prospective evaluation using a consistent, well-tolerated protocol, conservative management of EN with megestrol yielded a 70% response rate, with 43% achieving pCR. Assessment of response by EMB did not reflect accurate diagnosis in more than one third of cases.

160 Characteristics and outcomes of platinum-resistant patients treated in a phase I clinic
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Objective: Patients with platinum-resistant ovarian/peritoneal cancer have limited therapeutic options. Historically, no single agent or combination therapy has been shown to be beneficial. Novel molecular agents may hold promise for this difficult-to-treat population.

Methods: After institutional review board approval was obtained, we reviewed the characteristics and clinical outcomes of platinum-resistant patients with ovarian, peritoneal, or fallopian tube cancer enrolled in phase I clinical trials from 1999 through 2012 at a single institution.

Results: Ninety-six platinum-resistant patients, enrolled in 19 different phase Ia and Ib trials, were identified. The median age was 55.2 years (range, 20–75 years). The median number of prior treatment regimens was 4 (range, 1–14). Histology was predominately high-grade serous (69%), followed by low-grade serous (9.4%), germ cell (7.3%), mucinous (4.2%), and endometrioid (5.2%). Phase I therapeutic agents included novel cytotoxics (n=2), novel cytotoxic delivery methods (n=2), combination cytotoxics and novel agents (n=4), antibody drug conjugates (n=2), tyrosine kinase inhibitors (n=3), PI3K/MTOR inhibitors (n=2), BRAF/MEK inhibitors (n=2), and other novel agents (n=2). Twenty-two patients received treatment with a targeted agent requiring tissue selection. Seventy-eight patients were evaluable for response using RECIST criteria. There were 2 complete responses (2.6%), 5 partial responses (6.4%), 39 stable disease (50%), and 32 progressive disease (41%). The overall clinical benefit rate was 59%. The 1-year survival rate was 57.7%. The median progression-free survival (PFS) was 3.5 months. Patients with prior antiangiogenic exposure had comparable median PFS to those who had not been previously treated with an antiangiogenic agent (3.5 months vs. 4.0 months). However, patients with previous exposure to an antiangiogenic agent and subsequent treatment with another antiangiogenic on a phase I trial had a 48% response rate compared to an 80% response rate for patients without prior exposure.

Conclusions: Phase I trials provide comparable results to previously reported response rates for platinum-resistant patients treated on phase II trials, and thus, may be a reasonable alternative for management. Prior antiangiogenic exposure does not affect PFS on phase I trials. However, repeated exposure to antiangiogenic agents may predict less favorable response rates when subsequent antiangiogenic agents are used.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

2009 through 2010. Costs included direct institutional costs for all aspects of care during the initial surgery and immediate postoperative stay and all costs incurred after discharge up to 6 months postoperatively. The amortized cost (AC) included the capital cost of 3 dual-console DaVinci Si platforms and 5 years of service contracts for each of the 3 platforms amortized over 5 years assessed to each case based on the number of total robotic cases performed monthly. Nonamortized costs (NAC), which excluded these capital equipment costs, were also calculated. An intent-to-treat analysis was used in that costs were assessed based on the planned surgical approach. Modeling was then done to estimate the mean cost of surgical care for patients presenting with endometrial cancer from 2007-2010 based on previously published rates of surgical approach at our institution.

Results: Direct costs were assessed for 436 cases (132 laparoscopic [LRS], 262 robotic [RBT], and 42 laparotomy [LAP]). The median age was similar for all 3 groups. The median BMI was higher in the RBT and LAP groups compared to the LRS group (P=0.007). Stage distribution was similar for all 3 groups. The total mean AC per case was $20,489 (LRS), $23,646 (RBT), and $24,642 (LAP) (P<0.05; RBT vs. LRS, and P=0.6; RBT vs. LAP). The total NAC per case was $20,289 (LRS), $20,467 (RBT), and $24,433 (LAP) (P=0.9; RBT vs. LRS, and P=0.03; RBT vs. LAP). The planned surgical approach distribution in 2007 was 68% LRS, 8% RBT, and 24% LAP compared to 26%, 64%, and 9%, respectively, in 2010 (P<0.001). The modeled mean AC of each case was $21,738 in 2007 and $20,573 in 2010 (-$725).

Conclusions: LRS is less costly compared to LAP and RBT when including the capital acquisition costs of 3 robotic platforms. LRS and RBT are comparable if these upfront capital costs are excluded, and both are less costly than LAP. Cost neutralization of RBT appears to occur if incorporation of the platform affects the overall decrease in the rate of LAP over time. A potential cost benefit is possible for these cases.

163 Prospective lifestyle modification in patients with good prognosis endometrioid adenocarcinoma of the uterus


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Objective: Seventy-five percent of patients diagnosed with endometrioid adenocarcinoma (EC) are treated at an early stage, which results in excellent long-term disease-specific survival. Obesity and metabolic syndrome represent important uniting mechanisms for the development of EC. Many of the commonly found medical comorbidities are the cause of death in ~50% of patients. The goal of this study was to use EC diagnosis as an opportunity to improve overall health by identifying and proactively treating medical comorbidities associated with metabolic syndrome.

Methods: A prospective, patient-selected behavioral modification pilot study, initiated February 2011, was offered to women following surgery for EC stage I and II, grade 1 and 2. Patients elected standard surveillance with their primary care practitioner vs. initial evaluation with indicated treatment of medical comorbidities using dietary/exercise therapy and medical management. Serial surveys assessed recruitment, dropout, and compliance with lifestyle intervention, social well-being, and quality of life.

Results: Study participation was offered to 89 consecutive women through July 2012. Forty-three of 89 declined participation, with 34/46 selecting standard follow up and 12/46 selecting the intervention. Median age was 60 years (range, 30-81 years), mean body mass index was 39.9, 57% had grade 1, and 84% had stage IA EC. Medical comorbidities were: 73% cardiovascular disease, 39% diabetes, 17% hypothyroidism, 22% depression, and 34% screened and/or had sleep apnea diagnosed. 27 women were screened for every 1 patient enrolling. 7 were screened for every 1 agreeing to actively participate in prevention counseling. The dropout rate among active participants was 41%, the majority of which occurred before active intervention initiation. Seventy-five percent of the active intervention group was diagnosed as having metabolic syndrome. Through the intervention, minimal weight reduction was achieved (-3.7%), blood pressure and lipid profiles improved in 16%, and 1 patient initiated continuous positive airway pressure.

Conclusions: A majority of patients with good-prognosis EC have multiple medical comorbidities potentially amenable to optimization. EC patients should be screened for metabolic syndrome, depression, and sleep apnea. Key methodologic issues for a large-scale trial of lifestyle intervention in EC should include identifying methods for motivating participation in lifestyle interventions and minimizing early dropout. Our study suggests that interventions immediately following diagnosis of EC may not be the opportune motivational time.

164 Lymphadenectomy in women with early-stage intermediate-to-high risk endometrial cancer (HIR-EC) decreases local recurrence but not overall recurrence or survival: A retrospective cohort study

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Objective: There is reasonably strong data to suggest that lymphadenectomy may be safely omitted in women with apparent early-stage endometrioid endometrial cancer (EC) and low-risk uterine specimen features. However, among patients with uterine specimen features that suggest HIR-EC, such as lymphovascular space invasion (LVSi), FIGO grade 2 or 3 histology (G2/3), or outer half myometrial invasion (OI), there is no consensus on the utility of performing lymphadenectomy. Our aim was to review our experience and outcomes among a focused subset of women with HIR-EC who did and did not have lymphadenectomy.

Methods: We performed a retrospective cohort study of women with surgically treated stage I or II EC. Patients from 1994 to 2010 were included if they had LVSi, G2/3 histology, or OI. We performed multivariate logistic regression analyses to identify the relationship of lymphadenectomy to overall, local, and distant recurrences and Kaplan-Meier survival curves of progression-free survival (PFS), disease-specific survival (DSS), and overall survival (OS) among patients with and without lymphadenectomy as well as Cox proportional hazard ratios to adjust for other confounding factors and adjuvant treatments affecting PFS, DSS, and OS.

Results: Three hundred thirty-seven patients met histologic criteria. They had a median follow-up of 60 months (range, 6–194 months). Two hundred forty-five patients (73%) underwent lymphadenectomy while 159 patients (47%) underwent adequate lymphadenectomy (at least 10 lymph nodes removed). Pelvic radiotherapy was administered to 29% of patients in each group (NS). 6.9% of patients died of disease in the lymphadenectomy group and 8.8% in the no lymphadenectomy group. After controlling for uterine factors and adjuvant therapies, lymphadenectomy is associated with a decrease in local recurrences (odds ratio 0.44; 95% CI, 0.20-1.00), but not overall or distant recurrences. Lymphadenectomy was not significantly associated with PFS or OS. However, in a Cox proportional hazards model, lymphadenectomy was associated with a nonsignificant trend toward decrease in DSS (hazard ratio 0.39; 95% CI, 0.13-1.11; P=0.08).

Conclusions: Lymphadenectomy, regardless of the number of nodes removed, is only associated with a decrease in local recurrence and a trend toward a decrease in DSS in patients with early stage HIR-EC.
Fertility-sparing treatment of complex atypical hyperplasia and low-grade endometrial cancer using oral progestin

Objective: Oral progestin is an alternative to hysterectomy for women with complex atypical hyperplasia (CAH) or grade 1 endometrial cancer (G1EMCA) who wish fertility preservation. The aim of our study was to evaluate oncologic and fertility outcomes in women treated with oral progestin for CAH/G1EMCA.

Methods: Women with CAH or G1EMCA who were <45 years old, wished to preserve fertility, and were treated with oral progestin were identified from databases from two cancer centers between 2000 and 2011. Clinical and demographic data were obtained from medical records and phone questionnaires. Time intervals from progesterin start until complete response (CR) and from CR until recurrence were censored for patients without events and analyzed for associations with patient and treatment characteristics using Cox models; cumulative incidence functions were used to estimate the probability of an event over time.

Results: Forty-four patients were identified: 19 (43%) with CAH and 25 (57%) with G1EMCA. Median age was 36.5 years (range, 26-44 years) and median body mass index was 30 (range, 21-66). CR was achieved by 24 (55%), with a median follow-up of 39 months (range, 5-128 months). Probability of CR is represented in a cumulative incidence function (Figure). The median time to CR was 11 months. Older age at diagnosis was the only variable associated with a lower likelihood of CR (hazard ratio 0.84, 95% CI, 0.8-0.9, P=0.0003). Among those with CR, 13 (54%) recurred; the median time to recurrence was 3.5 years. Overall, 24 patients (55%: CAH n=11; G1EMCA n=13) underwent hysterectomy. 6 (66%) with CAH had histology upgraded to G1/G2 EMCA and 3 (13%) were upstaged (2 stage II; 1 stage III) on final pathology after hysterectomy. Thirty (68%) patients saw a fertility specialist, and 11 (37%) underwent fertility treatment with the following outcomes: 6 (55%) no pregnancy, 2 (18%) at least 1 live infant (4 live births in total), and 3 (27%) spontaneous abortion. Of the 33 patients who did not receive fertility treatment, 1 (3%) had a live birth.

Conclusions: Oral progestin is an effective temporizing treatment for women with CAH/G1EMCA who wish to preserve fertility, with more than half achieving CR. Women who wish to pursue progestin treatment should have a fertility specialist involved due to the low live birth rate without intervention. Completion hysterectomy should be considered at 1 year in those women who do not respond to a low probability of further response and in women with CR after childbearing due to a high rate of late recurrence.

The significance of positive peritoneal cytology in stage III endometrial cancer

Objective: According to the revised FIGO staging system for endometrial cancer, positive cytology is reported without affecting the stage. This change may lead to a decline in obtaining peritoneal cytology. While such a decline may have little impact in early-stage disease, the implications for stage III patients are unclear. The aim of this study was to determine the prognostic significance of positive peritoneal cytology in patients with FIGO (2009) stage III endometrial cancer.

Methods: Patients were identified who had stage III endometrial cancer and were treated at a tertiary cancer center between 04/1995 and 12/2009. All patients had peritoneal cytology. Those with positive cytology as their only extrauterine disease extension were excluded.

Results: Of the 196 patients in this cohort, 114 (58%) were ≥60 years old, 94 (48%) had deep myometrial invasion, 139 (71%) had lymphovascular invasion, and 49 (25%) had cervical stromal invasion. Aggressive histology (serous, clear cell, undifferentiated, or grade 3 endometrioid) was present in 90 patients (46%), adnexal involvement in 73 (37%), and nodal involvement in 154 (79%). Pelvic lymph node dissection was performed in 174 cases (89%). Positive peritoneal cytology was present in 45 patients (23%) and was significantly (P ≤0.03) associated with cervical stromal invasion, adnexal involvement, and aggressive histology. Regarding adjuvant therapy, positive cytology patients were more likely to receive chemotherapy (80% vs. 68%, P<0.01) but less likely to radiation (60% vs. 74%, P=0.08). With a median follow-up of 47 months, the 5-year rate of relapse was 58% for positive cytology vs 31% for negative (P <0.001). The corresponding rates for death from endometrial cancer were 66% vs. 28% (P <0.001). Positive cytology retained its independence on multivariate analysis (Table). Patients with positive cytology had significantly higher rates of recurrence in the para-aortic nodes and peritoneum (30% vs. 9% and 23% vs. 4%, respectively; P ≤0.008) but similar rates of relapse in the pelvis and other distant sites compared to those with negative cytology.

Conclusions: Positive peritoneal cytology is highly predictive of poor outcome in stage III endometrial cancer, independent of other adverse features, and is associated with distinct patterns of relapse. Therefore, the status of peritoneal cytology not only provides important prognostic information, but also may have treatment implications.

Table. Hazard Ratios (HR) for Specific Factors in Stage III Endometrial Cancer

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard for Relapse</th>
<th>Hazard for Death from Endometrial Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positve peritoneal cytology</td>
<td>2.3 (1.3-3.9)</td>
<td>2.9 (1.6-5.1)</td>
</tr>
<tr>
<td>Myometrial invasion ≥50%</td>
<td>2.2 (1.3-3.7)</td>
<td>2.0 (1.1-3.6)</td>
</tr>
<tr>
<td>Aggressive histology</td>
<td>4.1 (2.3-7.3)</td>
<td>3.7 (2.0-6.9)</td>
</tr>
<tr>
<td>Omission of radiation</td>
<td>1.9 (1.1-3.2)</td>
<td>0.014</td>
</tr>
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Risk of uterine malignancy (UM) increases proportionally with increasing body mass index (BMI)

Objective: To quantify the relationship of UM with BMI.

Methods: University HealthSystems Consortium (UHC) maintains an administrative database with information contributed by 116 academic medical centers and 276 affiliate hospitals, representing more than 90% of United States nonprofit academic medical centers. The UHC database was queried to identify all women undergoing hysterectomy (all ICD-9 68x.x) with a recorded BMI in
the overweight and obese categories (BMI 25 to 39.9; ICD-9 v6521-39). The admission for total hysterectomy was chosen to avoid biasing the sample with multiple admissions for the same patient. Least squares regression was applied to evaluate the association between increasing BMI and the proportion of women with a diagnosis of UM (all ICD-9 182.x and 179). Multivariate binary logistic regression was then performed to adjust for other known risk factors for endometrial cancer (EC) in addition to BMI, including age, race (white, black, or other), and presence of any of 23 other comorbidities.

**Results:** Six thousand, nine hundred five (4.6%) of women having hysterectomy had recorded BMI within the study range. One thousand, eight hundred ninety-five (27.4%) of these had UM. In the overweight and obese cohorts separately, and when combined into a single-study population, least squares fit of the probability of UM vs. BMI demonstrated a linear relationship (Figure). For the entire population, the line was described by the equation: \( y = 0.015x - 0.23 \), \( R^2 = 0.92 \) where risk of EC is the ordinate and BMI is the abscissa. After adjusting for other risk factors, we found that each 1-unit increase in BMI was independently associated with an 11% increase in the proportion of patients diagnosed with uterine malignancy (odd ratio 1.11, 95% CI 1.09-1.13, \( P < 0.001 \)). Increasing age and white race were also independently associated with uterine cancer. The presence of other comorbidities was not found to be independently related to the risk of UM.

**Conclusions:** In a population of women undergoing hysterectomy, risk of UM increased linearly with increasing BMI. Since the majority of United States women have a BMI between 25 and 40, these results can be regarded as applicable to the general population’s risk. Our findings further support the importance of weight management as a component of general health maintenance and cancer risk reduction.

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**Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology**

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**169**

Tumor diameter and preoperative CA-125 level evaluation for high-risk endometrial cancer patients

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**Objective:** The systematic lymphadenectomy is commonly performed to improve tailored adjuvant treatment for high-risk (HR) endometrial cancer. Recognizing those cases by frozen section can be challenging. Tumor diameter and preoperative CA-125 level were analyzed to predict tumor spread. We propose the correlation of those parameters with HR.

**Methods:** All patients operated upon for endometrial cancer between September 2011 and August 2012 were included. Cases with definitive pathology consistent with grade 3 or nonendometrioid histology or myometrial invasion >50% were classified as HR. Cases that did not match 1 of those criteria were classified as low-risk (LR) endometrial cancer. Cases with simple polyps or hyperplasia lesions were considered benign lesions. Means of tumor diameter (cm) and preoperative CA-125 levels were compared between groups using Kruskall-Wallis test and Mann-Whitney test to determine differences between each group. \( P \) value of <0.05 was considered significant.

**Results:** A total of 42 patients were included (19 HR, 16 LR, and 7 benign lesions). Means of tumor diameter in each group were, respectively, 5.00 cm (standard deviation [sd]: 2.56), 3.52 cm (sd: 1.87), and 2.21 cm (sd: 1.57) (\( P = 0.02 \)). The differences were not significant between HR vs. LR groups (\( P = 0.09 \)), and LR vs. benign lesion (\( P = 0.12 \)), but it was significant considering HR vs. benign lesion (\( P = 0.01 \)). Mean of CA-125 preoperative levels in each group was, respectively, 24.56 U/dL (sd: 12.51), 23.42 U/dL (sd: 23.66), and 14.38 U/dL (sd: 10.17) (\( P = 0.34 \)).

**Conclusions:** In this initial sample, tumor diameter and preoperative CA-125 value were not able to differentiate HR from LR group, and, therefore, were not considered adequate parameters to decide if the patient should undergo systematic lymphadenectomy.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

March 1991 to July 2009. Patients with ovarian involvement, peritoneal disease, and distant metastasis were excluded.

**Results:** Mean age was 64.3 years (range, 29-94 years). One hundred seventy-nine (75.2%) patients underwent complete staging that included lymphadenectomy with a median of 12 pelvic (range, 1-90) and 6 para-aortic (range, 1-38) nodes removed. Median follow-up was 64.4 months (range, 1.6-208.7 months). One hundred sixty-eight patients had peritoneal washings analyzed and in 13 (7.7%) the cytology was positive. Five patients with positive cytology (41.7%) succumbed and all had distant metastasis. Positive cytology did not correlate with depth of invasion (>50%), lymph node metastasis, and lymphovascular invasion. Positive cytology had a negative impact on progression-free survival (P=0.006) and overall survival (P=0.001). Nevertheless, the presence of positive cytology also increased the risk of recurrence (HR 6.65; 95% CI 2.2-20.0; P=0.001) and death (HR 5.99; 95% CI 1.9-18.6; P=0.002) in multivariate analysis when adjusted for lymph node metastasis, grade, and depth of invasion.

**Conclusions:** Our findings suggest that positive cytology is an independent prognostic factor in endometrial cancer. The presence of positive cytology increases the risk of recurrence and death.

171 Endometrial cancer lesion size is predictive of disease recurrence and long-term survival

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**Objective:** Intraoperative endometrial cancer treatment algorithms use preoperative grade, depth of myometrial invasion, visible extent of disease, and endometrial tumor size to direct the surgical staging procedure. Our study objective was to correlate primary tumor size (<2 cm vs. >2 cm) with disease outcome, including recurrence and long-term survival.

**Methods:** All eligible patients were surgically treated for endometrial cancer at a single institution between 2004 and 2011. Tumor size was recorded as the largest of 3 dimensions after fixation. Patient demographics, clinical and pathological characteristics, and disease status were analyzed using SAS version 9.3. Comparisons between groups were calculated using the chi-square test and a logistic covariate model adjusting for significant risk factors (P<0.05).

**Results:** Of the 387 eligible patients, 147 (38%) had an endometrial tumor <2 cm and 240 (62%) had a tumor >2 cm. Mean age, parity, and body mass index did not vary between groups. Tumors <2 cm were significantly more common in premenopausal women (P=0.02), early-stage (IA-IB) cancers (P<0.0001), grade 1 tumors (P=0.0001), and tumors without lymphovascular space involvement (LVSI) (P=0.0001). Only 6% of patients with tumors <2 cm had disease extending beyond the corpus (stage II-IV), and 3% had stage III-IV disease. Women with tumors <2 cm were less likely to have recurrent disease (P<0.0001) and die from their disease (P=0.0001). Disease recurrence was noted in 3/147 patients (2%) with tumor size <2 cm, and all were salvaged with additional therapy. A logistic covariate model was created for recurrence, which incorporated age, grade, LVSI, tumor size, and percentage depth of myometrial invasion (<30% vs. ≥30%). Grade, tumor size, and percentage of myometrial invasion were independent risk factors for recurrence using a stepwise selection model. Using these factors, a second model evaluating tumor size ≥2 cm revealed a relative risk of 3.7 (95% CI, 1.05-13; P=0.04) for disease recurrence. Myometrial invasion ≥30% had a relative risk of 4.6 (95% CI, 2-10.6; P=0.003) for recurrent disease.

**Conclusions:** Endometrial cancer tumor size is an important predictor of disease recurrence and patient survival. Lesion size <2 cm correlates with early-stage disease, low-grade cancers, and the absence of both LVSI and lymph node metastases. Small tumor size appears to be a useful marker for low-risk disease and should remain part of an intraoperative assessment to determine extent of surgical staging.

172 Uterine washing biomarkers as a novel screening tool for high-grade serous carcinoma

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**Objective:** High-grade serous carcinoma (HGSC) of the pelvis is an aggressive gynecologic malignancy often detected at advanced stage. Clinically proven screening tests are lacking. Recent data suggest that a precursor lesion – serous tubal intraepithelial carcinoma – arises from the distal fallopian tube. We hypothesize that given HGSC’s tubal origin, biomarkers previously studied in the serum may also be elevated in washings from the uterine cavity, representing a novel approach to early detection.

**Methods:** Women undergoing primary cytoreduction for stage IIIIC or IV, high-grade serous carcinoma and those undergoing bilateral salpingo-oophorectomy for benign indications were enrolled from May 2011 to June 2012. Patients with concurrent malignancy, prior malignancy requiring pelvic radiation, and previous hysterectomy were excluded. Serum, uterine washings, and peritoneal washings were collected from each patient and analyzed for CA-125, YKL-40, HE4, and mesothelin (MSLN).

**Results:** Of 25 women studied, 11 had high-grade serous carcinoma and 14 were noncancer controls. Age and BRCA status were similar in the 2 groups (P>0.05). CA-125, YKL-40, HE4, and MSLN levels in serum, peritoneal washings, and uterine washings were all significantly higher in HGSC patients than controls. In uterine washing specimens, median CA-125 values were 4.4-fold greater in carcinoma patients than in controls (8,520 U/mL vs. 1,955 U/mL, P=0.008). Median YKL-40, HE4, and MSLN uterine washing levels were 6- to 12-fold greater in carcinoma patients than in controls (P<0.004 for all) (Figure). Furthermore, median values for CA-125 and HE4 in cancer patients were 38- and 23-fold higher in the uterine washings than serum, respectively. YKL-40 levels in cancer patients were ~50% lower in uterine washings than serum, and MSLN levels were similar. Receiver operating characteristic curves were constructed for each biomarker, and the AUC for both serum and uterine washings was >0.8 for all markers, suggesting that elevation is highly associated with disease status.

**Conclusions:** Common ovarian biomarkers were elevated in the uterine washings from HGSC patients in this pilot study. Although this study was restricted to advanced-stage patients, it provides a foundation to explore a new approach to ovarian cancer screening that considers a putative precursor lesion within the distal fallopian tube. Further testing is warranted to determine if uterine washing biomarkers are more sensitive than current serum measurements.
Regional variation in postoperative radiation therapy (PORT) for early endometrial cancer (EC)

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Objective: To describe geographic patterns of care in use of PORT for localized EC.

Methods: A retrospective cohort study was performed that included all patients with clinical stage I high-grade (36%) and clinical stage II endometrial carcinoma (24%) who participated in the participating institutions. Of these, 34 patients (1.8%) with a diagnosis of ECC were identified as controls. A total of 1,898 patients diagnosed with early-stage (stage IA vs. IB vs. II) endometrial carcinoma (MEC) and were treated at the participating institutions. Of these, 34 patients (1.8%) with a diagnosis of ECC were identified as controls. Sixty-eight cases of ECC were identified as controls. The criteria for which the groups had been matched of age, substage, and of radiotherapy treatment (20.6% vs. 10.2%; P= 0.05) and HRs were determined using Cox proportional hazards modeling.

Results: The study included 121 patients (mean age, 68±10 years) with clinical stage I high-grade endometrial cancer. The median follow-up duration was 26 months and median time to recurrence was 11 months. Twelve percent of patients (28 of 76 who underwent lymphadenectomy) had lymph node metastases. Forty-five percent of patients received pelvic with or without vaginal vault radiotherapy, 11% of patients received chemotherapy, and 16% of patients received both radiotherapy and chemotherapy. Twenty-eight percent (34/121) of patients recurred. In univariate analyses, recurrence was only significantly associated with age (P=0.05) and treatment received (P=0.004). On multivariate analysis, age older than 60 years was significantly associated with increased risk of recurrence (HR 4.0, P=0.03), while histologic subtype may influence risk (P=0.08), namely carcinosarcoma (HR 4.8, P=0.003) and serous types (HR 1.8, P=0.30). Treatment with radiotherapy (HR 0.43, P=0.07) or combined chemotherapy with radiotherapy (HR 0.50, P=0.27) may be associated with decreased risk.

Conclusions: Risk of recurrence is significantly associated with patient age and histologic subtype. Risk may be modified by adjuvant treatment received, which, at our center, is based on a predetermined common treatment policy.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

176
Pathologic ultrastaging improves micrometastasis detection in sentinel lymph nodes during endometrial cancer staging
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Objective: To describe the incidence of low-volume metastases in sentinel lymph nodes (SLN) identified at surgical staging for endometrial carcinoma (EC) and to correlate it with depth of myoinvasion (DMI) and tumor grade.

Methods: We reviewed all patients who underwent primary surgery for EC with successful mapping of at least 1 SLN at our institution from 9/2005 through 12/2011. SLN ultrastaging protocol involved cutting an additional 2 adjacent 5-mcm sections at each of 2 levels, 50-mcm apart, from each paraffin block lacking metastatic carcinoma on routine hematoxylin and eosin (H&E). At each level, 1 slide was stained with H&E and with immunohistochemistry (IHC) using anticytokeratin AE1:AE3.

Results: Of the 1,920 patients meeting inclusion criteria, 1,205 (63%) were in the DMI group on univariate analysis (37.4% vs. 64.0% 5-year OS, \(P=0.006\)). The removal of PA LNs demonstrated an improved OS (death occurred in 205 of 1,920 (10.8%) patients; median OS was 13 (range, 1-53). Among the patients with PA LNs assessed, the median number of PA LNs excised was 5 (range, 1-67). On univariate analysis, age, stage, histology, and grade were significantly associated with OS (\(P=0.001\)). The removal of PA LNs was not associated with OS (\(P=0.450\) (Figure)). On subset analysis by stage, the assessment of PA LNs remained insignificant. When evaluated by histology, the removal of PA LNs demonstrated an improved OS in the papillary serous group on univariate analysis (37.4% vs. 64.0% 5-year OS, \(P=0.006\)), but after controlling for stage on multivariate analysis, there was no significant association of PA LN assessment with OS in papillary serous patients (\(P=0.132\)).

Conclusions: SLN mapping with pathologic ultrastaging in EC detects additional low-volume metastasis (4.5% of all cases), which would otherwise go undetected with routine pathologic nodal evaluation. The oncologic clinical significance of this finding requires long-term follow-up. These data strongly support the incorporation of pathologic ultrastaging and SLN mapping algorithm in EC staging surgery.

Table. Incidence of Sentinel Node MM and ITC As Detected During Ultrastaging by Depth of Myometrial Invasion (DMI) and Final Grade

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No Invasion</th>
<th>(&lt;50% \text{ invasion})</th>
<th>(\geq 50% \text{ invasion})</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM</td>
<td>MM 0 ITC 0</td>
<td>MM 0 ITC 0</td>
<td>MM 0 ITC 0</td>
<td>2/244=0.8%</td>
</tr>
<tr>
<td>ITC</td>
<td>ITC 1</td>
<td>ITC 4</td>
<td>ITC 4</td>
<td>16/202=7.9%</td>
</tr>
<tr>
<td>n=166</td>
<td>n=41</td>
<td>n=64</td>
<td>n=57</td>
<td></td>
</tr>
<tr>
<td>n=81</td>
<td>n=44</td>
<td>n=64</td>
<td>n=57</td>
<td></td>
</tr>
<tr>
<td>n=38</td>
<td>n=41</td>
<td>n=64</td>
<td>n=57</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10/262=3.8%</td>
<td>4/121=3.3%</td>
<td>10/131=7.5%</td>
<td>23/516=4.5%</td>
</tr>
</tbody>
</table>

MM: micrometastasis; ITC: isolated tumor cells
An additional 12/351 (3.4%) of nodal disease was found in “low-risk” tumors (highlighted in dark box).

177
Does para-aortic lymph node assessment during endometrial cancer staging impact overall survival?
Memorial Sloan-Kettering Cancer Center, New York, NY

Objective: The effect of lymphadenectomy in endometrial cancer on overall survival (OS) remains controversial. The 2 randomized clinical trials performed on this topic addressed pelvic but not para-aortic (PA) lymphadenectomy and found no impact on survival. We sought to determine if the surgical effort to assess PA lymph nodes (LNs) at initial staging surgery affected OS.

Methods: All patients diagnosed with endometrial cancer from 1/1993 through 12/2011 who had LNs excised were included. The following histologic groups were evaluated: adenocarcinoma, carcinosarcoma, clear cell, papillary serous, and other. Patients were divided into 2 groups based on whether PA LNs were assessed, as defined by the identification of 1 or more PA LNs on final pathology. A subset analysis of the effect of PA LN assessment by stage or histology was performed. Standard statistical survival analyses were utilized.

Results: Of the 1,920 patients meeting inclusion criteria, 1,205 (63%) were in the PA LN assessment group and 715 (37%) were in the no PA LN assessment group. The median number of pelvic LNs removed was 13 (range, 1-53). Among the patients with PA LN assessed, the median number of PA LNs excised was 5 (range, 1-67). On univariate analysis, age, stage, histology, and grade were significantly associated with OS (\(P<0.001\)). The removal of PA LNs was not associated with OS (\(P=0.450\) (Figure)). On subset analysis by stage, the assessment of PA LNs remained insignificant. When evaluated by histology, the removal of PA LNs demonstrated an improved OS in the papillary serous group on univariate analysis (37.4% vs. 64.0% 5-year OS, \(P=0.006\)), but after controlling for stage on multivariate analysis, there was no significant association of PA LN assessment with OS in papillary serous patients (\(P=0.132\)).

Conclusions: The additional effort of assessing PA LNs in endometrial cancer at the time of initial surgical staging was not shown to affect OS, though the removal of PA LNs may be more important in the setting of papillary serous histology. Until prospective research demonstrates the importance of PA LNs in this setting, the additional effort involved in assessing PA LNs should be utilized sparingly.
of PA lymphadenectomy on the survival of women with endometrial cancer, the benefit of performing a routine PA LN dissection for staging remains controversial.

178
Redefining stage I endometrial cancer: Incorporating histology, grade, myoinvasion, and whether or not lymph nodes were removed
Memorial Sloan-Kettering Cancer Center, New York, NY

Objective: The current FIGO staging system does not include histology, grade, or nodal assessment in its stage I classification. The purpose of this study was to propose a new staging system for stage I endometrial cancer that takes into consideration histology, grade, myoinvasion, and whether or not lymph nodes were examined and to compare its performance to the 2009 FIGO staging system.

Methods: All patients diagnosed with FIGO stage I endometrial cancer from 1/1993 through 8/2011 were analyzed, with the exception of sarcomas and undifferentiated carcinomas. The proposed staging system was as follows: IA. Endometrioid carcinoma (grades 1 and 2) with <50% myometrial invasion; IA1. Negative nodes; IA2. No nodes removed; IB. Endometrioid carcinoma (grade 3) or nonendometrioid carcinoma with no myometrial invasion; IB1. Negative nodes; IB2. No nodes removed; IC. Endometrioid carcinoma (grades 1 and 2) with ≥50% myometrial invasion; IC1. Negative nodes; IC2. No nodes removed; ID. Endometrioid carcinoma (grade 3) or nonendometrioid carcinoma with any myometrial invasion; ID1. Negative nodes; ID2. No nodes removed.

Results: Data from 1,843 patients were analyzed. The 5-year overall survival (OS) for the 2009 stage IA was 91.5% compared to 81.1% for stage IB (P<0.001). When patients were restaged with our proposed system for stage I disease, the 5-year OS significantly differed (P<0.001) as follows: IA1 96.7%, IA2 92.2%, IB1 92.2%, IB2 76.4%, IC1 83.9%, IC2 78.6%, ID1 81.1%, and ID2 68.8% (Figure). The bootstrap-corrected concordance probability estimate (CPE) for the CPE of 0.530 (95% CI 0.516-0.544) for the 2009 FIGO staging system.

Conclusions: By incorporating the well-known important variables of histology, grade, myoinvasion, and whether or not lymph nodes were removed (a measure of surgical staging), our proposed staging system for stage I endometrial cancer provides additional relevant clinical information and has a superior predictive ability over the 2009 FIGO staging system. Adopting this new staging system would provide more accurate prognostic information and may assist in treatment planning.

179
Use of metformin is associated with improved endometrial cancer survival
N. Nevadunsky, A. Van Arsdale, G. Kaur, M. Frimer, E. Conroy, M. Einstein, G. Goldberg
Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

Objective: Impaired glucose tolerance and diabetes are known risk factors for endometrial cancer. Through unknown mechanisms, recent data suggest improved progression-free survival in patients with ovarian cancer who take metformin. The goal of our study was to evaluate the association between metformin use and overall survival in women with uterine cancer.

Methods: A retrospective cohort study was performed at a high-volume single institution of all patients with a diagnosis of uterine cancer from January 1999 through December 2009. Sociodemographic and survival data were abstracted from the medical record and national death registry using social security numbers. Demographic data included age, body mass index (BMI), race/ethnicity, histologic subtype, stage, grade, diabetes status, metformin use, and hyperlipidemia. A Cox proportional hazards model was used to determine the effect of metformin use on overall survival.

Results: Of 987 patients with endometrial cancer, 115 (12%) were diabetic and treated with metformin, 136 (14%) were diabetic and were not using metformin, and 736 (74%) were not diabetic. For patients of all histologic subtypes, the overall survival was improved in diabetics with uterine cancer who were taking metformin (log rank test P=0.016) (Figure). For patients with endometrial histology (n=595), there was no difference in overall survival among the 3 groups. For patients with nonendometrioid histology, there was a significant survival advantage in the diabetics taking metformin vs. diabetics not taking metformin and endometrial cancer patients who were not diabetic (stratified log rank test P=0.01). The hazard of death in those with metformin use was estimated to be 60% (odds ratio 0.60; 95% CI 0.36, 1.01) of that of nondiabetics after controlling for age, BMI, histologic type, clinical stage, grade, race, and presence of hyperlipidemia (Table). There was no difference in hazard of death between diabetics not using metformin and nondiabetics (HR 0.83; 95% CI 0.55, 1.24). Increasing age, stage, grade, and type 2 histologic type all were strongly associated with increased hazard of death.

Conclusions: These data suggest a survival advantage for diabetic women with uterine cancer who use metformin. The pathway for this is presently unknown, but insulinlike growth factor pathways have known implications in endometrial cancer survival, and insulinlike growth factor is also a metformin target.
Further study of the efficacy benefits of metformin in prospective studies, with appropriate translational markers, are warranted.

### Table. Univariate and Multivariate Cox Proportional Hazard Regression

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate HR</th>
<th>95% CI</th>
<th>P Value</th>
<th>Multivariate HR</th>
<th>95% CI</th>
<th>P Value</th>
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</thead>
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<tr>
<td>Age (years)</td>
<td>1.04</td>
<td>(1.03, 1.06)</td>
<td>&lt;0.001</td>
<td>1.03</td>
<td>(1.01, 1.04)</td>
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<td>BMI</td>
<td>0.96</td>
<td>(0.94, 0.98)</td>
<td>&lt;0.001</td>
<td>1.00</td>
<td>(0.98, 1.02)</td>
<td>0.89</td>
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<td>Race</td>
<td></td>
<td></td>
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<tr>
<td>White</td>
<td>1.00 (ref.)</td>
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<td></td>
<td>1.00 (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1.96</td>
<td>(1.49, 2.56)</td>
<td>&lt;0.001</td>
<td>1.14</td>
<td>(0.83, 1.57)</td>
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<td>Hispanic</td>
<td>1.18</td>
<td>(0.85, 1.64)</td>
<td>0.32</td>
<td>0.98</td>
<td>(0.68, 1.42)</td>
<td>0.93</td>
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<tr>
<td>Other</td>
<td>0.49</td>
<td>(0.24, 1.02)</td>
<td>0.06</td>
<td>0.66</td>
<td>(0.28, 1.52)</td>
<td>0.53</td>
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<td>Endometrioid</td>
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<td>1.00 (ref.)</td>
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<tr>
<td>Nonendometrioid</td>
<td>5.76</td>
<td>(4.43, 7.49)</td>
<td>&lt;0.001</td>
<td>2.32</td>
<td>(1.47, 3.67)</td>
<td>&lt;0.001</td>
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<td>Clinical Stage</td>
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<tr>
<td>Stage I</td>
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<td>1.00 (ref.)</td>
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<tr>
<td>Stage II</td>
<td>1.80</td>
<td>(1.13, 2.86)</td>
<td>0.014</td>
<td>1.39</td>
<td>(0.86, 2.26)</td>
<td>0.18</td>
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<td>Stage III</td>
<td>4.05</td>
<td>(2.92, 5.61)</td>
<td>&lt;0.001</td>
<td>2.66</td>
<td>(1.85, 3.83)</td>
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<td>Stage IV</td>
<td>11.72</td>
<td>(8.68, 15.82)</td>
<td>&lt;0.001</td>
<td>5.84</td>
<td>(4.14, 8.24)</td>
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<td></td>
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<td></td>
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<tr>
<td>2</td>
<td>2.24</td>
<td>(1.38, 3.64)</td>
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<td>(0.96, 2.88)</td>
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<td>3</td>
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<td>(5.03, 10.1)</td>
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<td>2.03</td>
<td>(1.18, 3.49)</td>
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<td>1.00 (ref.)</td>
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</tr>
<tr>
<td>Yes</td>
<td>0.68</td>
<td>(0.51, 0.92)</td>
<td>0.013</td>
<td>Coxinear with metformin</td>
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<td>Metformin</td>
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<tr>
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<td>1.00 (ref.)</td>
<td></td>
<td></td>
<td>1.00 (ref.)</td>
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</tr>
<tr>
<td>Yes</td>
<td>0.51</td>
<td>(0.32, 0.82)</td>
<td>0.006</td>
<td>0.60</td>
<td>(0.36, 1.01)</td>
<td>0.053</td>
</tr>
<tr>
<td>No but diabetic</td>
<td>0.84</td>
<td>(0.58, 1.20)</td>
<td>0.32</td>
<td>0.83</td>
<td>(0.55, 1.24)</td>
<td>0.37</td>
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<td>Hyperlipidemia</td>
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<td></td>
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<tr>
<td>No</td>
<td>1.00 (ref.)</td>
<td></td>
<td></td>
<td>1.00 (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.45</td>
<td>(0.33, 0.63)</td>
<td>&lt;0.001</td>
<td>0.04</td>
<td>(0.29, 0.57)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Objective: Previous studies suggest that clear cell carcinoma (CCC) of the ovary is associated with a worse prognosis compared to other histologic types. There remains a paucity of data examining the prognostic significance of uterine CCC vs. uterine serous carcinoma (USC). This study was conducted to determine the prognostic effect of histologic subtypes using propensity score model (PSM). PSM is used to reduce the impact of treatment selection bias. It involves generating a propensity score for each subject, then equating the different groups based on selected variables.

Methods: In this institutional review board-approved study, our prospectively maintained database of 1,540 patients with endometrial cancer was reviewed. One hundred twenty-five patients with uterine CCC and USC were identified. PSM was used to match patients with CCC and USC as 1:1 based on an algorithm using hierarchical sequence that included these variables in order: positive lymph node involvement, 2009 FIGO stage, lymphovascular space involvement, age, adjuvant platinum-based chemotherapy, adjuvant radiation therapy, and lower uterine segment involvement. This resulted in a study cohort of 60 patients (30 patients with CCC and 30 with USC). All patients underwent surgical staging between 1991 and 2010. The impact of histologic type on disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS) was calculated.

Results: Median follow-up for the study cohort was 45 months. Median age was 63 years. All patients underwent surgical staging, with a median of 13 lymph nodes removed (range, 8–54). Thirty-two patients had 2009 FIGO stage I, 12 had stage II, and 16 had stage III. Adjuvant chemotherapy was 3–6 cycles of platinum-based regimens. Adjuvant radiation treatment included vaginal cuff brachytherapy, external beam, or a combination of both. Comparing uterine CCC patients to patients with USC showed no statistically significant difference between the 2 groups in regard to 5-year DFS, DSS, and OS. 5-year DFS was 67% vs. 56% (P=0.848), DSS was 77% vs. 68% (P=0.520), and OS was 52% vs. 48% (P=0.698), respectively.

Conclusions: Using a matched analysis, there appears to be no significant prognostic difference for surgically staged patients with CCC and USC. Due to the rarity of these histologies, these data need validation with a larger pool of data.

180 Application of propensity score model to examine the prognostic significance of uterine clear cell versus uterine serous carcinoma

O. Gayar1, S. Patel, C. Cogan, T. Buekers, A. Munkarah, M. Elshaikh

Henry Ford Health System, Detroit, MI

Objective: Previous studies suggest that clear cell carcinoma (CCC) of the ovary is associated with a worse prognosis compared to other histologic types. There remains a paucity of data examining the prognostic significance of uterine CCC vs. uterine serous carcinoma (USC). This study was conducted to determine the prognostic impact of histologic subtypes using propensity score model (PSM). PSM is used to reduce the impact of treatment selection bias. It involves generating a propensity score for each subject, then equating the different groups based on selected variables.

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Results: Median follow-up for the study cohort was 45 months. Median age was 63 years. All patients underwent surgical staging, with a median of 13 lymph nodes removed (range, 8–54). Thirty-two patients had 2009 FIGO stage I, 12 had stage II, and 16 had stage III. Adjuvant chemotherapy was 3–6 cycles of platinum-based regimens. Adjuvant radiation treatment included vaginal cuff brachytherapy, external beam, or a combination of both. Comparing uterine CCC patients to patients with USC showed no statistically significant difference between the 2 groups in regard to 5-year DFS, DSS, and OS. 5-year DFS was 67% vs. 56% (P=0.520), DSS was 77% vs. 68% (P=0.848), and OS was 52% vs. 48% (P=0.698), respectively.

Conclusions: Using a matched analysis, there appears to be no significant prognostic difference for surgically staged patients with CCC and USC. Due to the rarity of these histologies, these data need validation with a larger pool of data.

181 The impact of tumor size and location in high-grade endometrial cancer patients undergoing minimally invasive surgery

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Objective: Tumor size has previously been shown to be an independent risk factor for lymph node metastasis and recurrence in patients with endometrial cancer, while tumor location has shown mixed results with regard to outcomes. Neither has been studied specifically in patients with clinical stage I high-grade endometrial cancer. The goal of this study was to determine if tumor location, in addition to size, conferred an increased risk of lymph node metastasis and recurrence in patients undergoing minimally invasive surgery (MIS).

Methods: This is a multi-institutional cohort study of patients with apparent early-stage, high-grade endometrial cancer (grade 3 or nonendometrioid histology) who received comprehensive surgical staging by MIS. Medical records were reviewed under an institutional review board-approved protocol and demographics, pathologic variables, recurrence, and survival as a function of tumor size and location (lower uterine segment [LUS], mid-corpus, and fundus) were analyzed using logistic regression and exact tests for significance.
Results: One hundred twenty-four patients were identified from January 2005 to January 2012. Median age was 65 years (range, 55–76 years) and median BMI was 29 (range, 25–36). There were 50 endometrioid (40.3%), 22 serous (17.7%), 6 clear cell (4.8%), 10 carcinosarcoma (8.0%), and 36 (29%) undifferentiated or mixed histologies. There were 18 tumors ≤2 cm (14.7%), 104 tumors >2 cm (85.2%), and 2 with no size reported. 22 (17.7%) patients had LUS tumors, 88 (70%) had mid-corpus ± fundal tumor, and 14 (10.3%) had tumor spanning the endometrium. In multivariate analysis, patients with LUS tumors were more likely to have advanced-stage disease (odds ratio [OR] 3.61, 95% CI 1.29–10.08, P=0.01) than those who had mid-corpus/fundal tumors, and patients with tumor size ≥2 cm were more likely to have positive pelvic nodes (OR 6.73, P=0.04) with resultant higher stage (P=0.04). With a median follow-up time of 19.6 months, there were 23 recurrences: 7/22 (31.8%) of the LUS and 16/88 (18.1%) of the mid-corpus/fundal group (P=0.16).

Conclusions: Tumor size and LUS tumor location were significantly associated with lymph node metastasis and advanced-stage disease in women with clinical stage I high-grade endometrial cancers. There was an increased incidence of recurrence in the LUS tumors, but with a small number of recurrences, this did not reach significance. For high-grade endometrial cancer, larger studies may further implicate tumor location, in addition to other variables, as a prognostic indicator for recurrence.

182 Treatment-related outcomes in patients with stage III-IV endometrial cancer treated with chemotherapy with or without the addition of radiation therapy
S. Munns1, A. Semaan1, S. Seward1, A. Munkarah2, P. Paximadis1, S. Miller1, R. Ali1, R. Morris3
1Wayne State University, Detroit, MI, 2Henry Ford Health System, Detroit, MI

Objective: To study the effects of adding radiation to chemotherapy on progression-free survival (PFS) and overall survival (OS) in patients with FIGO stage III-IV endometrial cancer.

Methods: All patients with FIGO stage III-IV endometrial cancer who underwent surgery followed by adjuvant therapy at the Karmanos Cancer Center from 2000-2011 were included. Demographic and clinicopathologic outcomes were compared between groups using chi-square and Fisher’s exact test. Kaplan-Meier survival curves with a log-rank test were used to compare PFS and OS between treatment groups. Regression analysis was performed to identify predictors of recurrence and death.

Results: Seventy patients met the inclusion criteria. Their mean age was 58.6 years. Endometrioid and serous histology comprised 43% and 37% of cases, respectively. Seventy percent of patients had FIGO stage III disease and 30% had FIGO stage IV disease. Adjuvant chemotherapy alone was administered in 60% of cases and chemotherapy with radiation was given in 40% (24 with pelvic radiation ± brachytherapy and 4 with brachytherapy alone). Twenty-eight (40%) patients experienced recurrence and an additional 8 (11%) progressed on primary treatment. Median PFS was 14 months in patients treated with chemotherapy alone and 52 months with the addition of external beam radiation therapy (P=0.023). OS was longer in those treated with chemotherapy and radiation (P=0.037) but median OS was not reached. On multivariate analysis, stage and radiation use were independent predictors of OS and PFS.

Conclusions: Both PFS and OS were improved with the addition of radiation to chemotherapy in patients with advanced stage endometrial cancer.

183 Is body mass index a prognostic factor in patients with early-stage type II endometrial cancer?
R. Jalloul1, Z. Al-Wahab2, M. Alshaikh1, T. Buekers1, M. Mahan1, R. Hanna1
1Henry Ford Health System, Detroit, MI, 2Wayne State University, Detroit, MI

Objective: The effect of body mass index (BMI) on disease outcomes in patients with type II endometrial cancer is unclear. The aim of this study was to assess the impact of BMI on disease recurrence and overall survival of patients with early-stage serous or clear cell carcinoma of the uterus.

Methods: Patients who underwent surgical staging for FIGO stage I and II uterine papillary serous carcinoma (UPSC) and clear cell carcinoma of the uterus were reviewed from a prospectively maintained database of patients with endometrial cancer in 2 large academic centers from 1985 to 2009. The medical records were reviewed and clinical and histopathologic data were collected. All patients were assigned stages based on the 2008 FIGO staging system. The patients were categorized into two BMI groups: <30 and ≥30. The impact of known prognostic factors, including age, myometrial invasion, angiolympathic invasion (ALI), adjuvant therapy, histology type, and the BMI category, was analyzed in a multivariate survival model. Kaplan-Meier and proportional hazard models were used to assess the impact of BMI on overall survival, disease-specific survival, and progression-free survival.

Results: One hundred nineteen patients with stage I and II UPSC and clear cell uterine carcinoma met the inclusion criteria. Forty-seven patients (39.4%) had BMIs <30 and 72 patients (60.6%) had BMIs ≥30. Serous histology was seen in 87 (73%) compared to 32 patients (27%) with the clear cell histology type. Median BMI was 31.75 (range, 19-64.11), median age was 67.5 years (range, 38-91 years), and median overall survival was 52.96 months (range, 2-251.5 months). In multivariate analysis, and when controlling for histology, BMI was a significant predictor for overall survival (HR 2.37, 95% CI 1.17, 4.83, P=0.017) (Figure). However, there was no significant difference in disease-specific survival or progression-free survival based on the BMI (log-rank P=0.636 and 0.274), respectively.

Conclusions: BMI had significant prognostic implications on overall survival but not disease-specific survival or progression-free survival in patients with early-stage type II uterine carcinoma in this small cohort. This emphasizes further the importance of comorbidities on outcomes. Further studies with larger cohort numbers are needed to confirm these findings.
Occult uterine cancer in patients undergoing laparoscopic hysterectomy with morcellation: Implications for surveillance for disease recurrence and outcomes

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Objective: To characterize the treatment, follow-up, and outcomes of patients diagnosed with occult uterine cancer after laparoscopic hysterectomy (LH) with morcellation for benign indications.

Methods: Using our institutional, institutional review board-approved multisite pathology database, patients were identified who had LH with a morcellated specimen and uterine cancer. Inpatient and outpatient records, including operative notes and pathology reports, were reviewed to identify the surgical indication, cancer stage and histology, treatment plan, subsequent staging surgery, and outcomes. Follow-up screening plans were evaluated for each patient.

Results: A total of 1,115 patients underwent LH with morcellation of the uterus. Ten patients had identified uterine cancer (0.9%). Five (50%) of the patients had uterine sarcoma (3 leiomyosarcoma, 2 endometrial stromal sarcoma) and 5 (50%) had endometrial cancer (Table). Five patients underwent a complete staging procedure, with 1 surgery resulting in a higher stage. All patients who underwent staging surgery had negative cytology from their second surgery. All patients had stage 1 disease except for 1 patient with a mixed (clear cell and endometrioid) endometrial cancer (IIIC) and 1 leiomyosarcoma (IIIa). Treatment patterns included observation only for patients with stage 1 endometrioid endometrial cancer and gemcitabine/docetaxel for leiomyosarcoma. The patient with advanced endometrial cancer was treated with carboplatin/paclitaxel with no evidence of disease at 31 months. The mean follow-up time was 26 months (range, 7–59 months), with 1 recurrence identified in a patient with stage IA leiomyosarcoma. All follow-up recommendations were similar to standard care for associated diagnoses without morcellation.

Conclusions: The number of patients undergoing uterine morcellation is increasing due to the increasing use of minimally invasive surgery. Morcellation poses a unique staging, management, and follow-up question, even for presumed early-stage disease. In our series, of patients who were completely staged, 1 of 5 was upstaged based on findings of second surgery. There was 1 recurrence observed during the follow-up period, but it was a leiomyosarcoma, a particularly aggressive cancer. To date, patients in this series have had similar prognoses and treatment plans to patients without morcellation. Larger multi-institutional series and longer follow-up may further elucidate the need for alterations in prognosis, treatment, and follow-up for these patients.

Table. Patient Characteristics

<table>
<thead>
<tr>
<th>Surgery Type</th>
<th>Cancer Type</th>
<th>Staging Surgery</th>
<th>Indication</th>
<th>Stage</th>
<th>Treatment</th>
<th>Follow-up (months)</th>
<th>Disease Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Supracervical hysterectomy</td>
<td>Endometrioid</td>
<td>Yes</td>
<td>Bleeding</td>
<td>IB</td>
<td>Surgery only</td>
<td>28</td>
<td>NED</td>
</tr>
<tr>
<td>2 Total laparoscopic hysterectomy</td>
<td>Endometrioid</td>
<td>No</td>
<td>Fibroids</td>
<td>IA</td>
<td>Surgery only</td>
<td>31</td>
<td>NED</td>
</tr>
<tr>
<td>3 Supracervical hysterectomy</td>
<td>Endometrioid</td>
<td>Yes</td>
<td>Prolapse</td>
<td>IB</td>
<td>Surgery only</td>
<td>12</td>
<td>NED</td>
</tr>
<tr>
<td>4 Supracervical hysterectomy</td>
<td>Endometrioid</td>
<td>Trachelectomy</td>
<td>only</td>
<td>IA</td>
<td>Surgery only</td>
<td>35</td>
<td>NED</td>
</tr>
<tr>
<td>5 Supracervical hysterectomy</td>
<td>Endometrial stromal</td>
<td>No</td>
<td>Bleeding</td>
<td>IA</td>
<td>Surgery only</td>
<td>59</td>
<td>NED</td>
</tr>
<tr>
<td>6 Total laparoscopic hysterectomy</td>
<td>Endometrial stromal</td>
<td>Yes</td>
<td>Fibroids, bleeding</td>
<td>IA</td>
<td>Medroxyprogesterone</td>
<td>7</td>
<td>NED</td>
</tr>
<tr>
<td>7 Total laparoscopic hysterectomy</td>
<td>Mixed (clear cell, endometrioid)</td>
<td>Yes</td>
<td>Fibroids, Bleeding</td>
<td>IIIC</td>
<td>Carboplatin/paclitaxel</td>
<td>31</td>
<td>NED</td>
</tr>
<tr>
<td>8 Supracervical hysterectomy</td>
<td>Leiomyosarcoma</td>
<td>No</td>
<td>Fibroids, Bleeding</td>
<td>IB</td>
<td>Gemcitabine/docetaxel</td>
<td>7</td>
<td>NED</td>
</tr>
<tr>
<td>9 Supracervical hysterectomy</td>
<td>Leiomyosarcoma</td>
<td>Yes</td>
<td>Bleeding</td>
<td>IA</td>
<td>Gemcitabine/docetaxel</td>
<td>28</td>
<td>Recurrence @ 27 months</td>
</tr>
<tr>
<td>10 Supracervical hysterectomy</td>
<td>Leiomyosarcoma</td>
<td>No</td>
<td>Bleeding</td>
<td>IIIA</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

NED=no evidence of disease

Preoperative tumor grade and intraoperative tumor size identifies patients at intermediate risk for lymph node involvement but not necessarily those at increased risk of recurrence

The Ohio State University, Columbus, OH

Objective: Risk stratification for surgical staging of endometrial cancer (EMCA) is an area of continued research and debate. Previous investigators reported that preoperative grade 1 or 2 endometrioid histology and intraoperative (IO) tumor size >2 cm falls into the intermediate-risk (IR) category for lymph node metastasis and requires surgical staging. The goal of this study was to validate those results.

Methods: This was a single-center retrospective review used a database of surgically staged patients with EMCA between 2003 and 2010. Eligibility criteria included those who had IR tumors and absence of peritoneal disease. We analyzed frequency of lymphadenectomy (LND), lymph node (LN) metastases, recurrence rate, progression-free survival (PFS), and overall survival (OS).

Results: There were 262 patients who met IR criteria. Of these, 250 (95%) had pelvic (P) LND and 210 (80%) had para-aortic (Pa) LND. LN metastasis was identified in 24 (9.1%) patients: 22 (8.3%) had positive PLN and 14 (5.3%) had positive PaL.N. Of those with positive PLN, 10 (45%) also had positive PaL.N. Patients who had positive nodes had a median tumor size of 4 cm as compared to 4.5 cm in those with negative nodes. Recurrence was diagnosed in 25 patients (8.7%); only 3 had positive LN at initial staging. Adjuvant therapy was administered to 28% of patients and was not affected by surgical staging. There was no difference in recurrence rate between staged and unstaged patients (8.5% and 7%, respectively, P=0.8588). Twenty-four (9%) patients had high-risk (HR) histology on final pathology, and 6 (25%) of these patients experienced recurrence. Risk of recurrence was not predicted by positive LN (relative risk [RR] 1.48, 95% CI 0.49–4.6, P=0.45), but was predicted by HR histology (RR 3.5, 95% CI 1.5–8.1, P=0.003). Median PFS was not reached in either group (P=0.9314) and median OS was 100 and 96 months, respectively (P=0.3827).
Conclusions: The risk of LN metastasis is high enough to warrant surgical staging in patients who meet IR criteria. However, LN metastasis by itself is not predictive of recurrence in this group. We found that HR pathology on final pathology in this group of patients is associated with recurrence. This may be helpful in postoperative patient counseling.

186 Clinical nomogram to predict for para-aortic lymph node metastasis in advanced-stage endometrial cancer patients
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Objective: To identify clinical risk factors for para-aortic lymph node (PALN) metastasis in advanced-stage endometrial cancer patients and to develop a nomogram model to predict for PALN metastasis.

Methods: Data from endometrial cancer patients between 1991 and 2009 were reviewed. Patients with pelvic lymph node (LN) metastasis alone were compared to those with both pelvic and PALN metastasis. Clinicopathologic risk factors for PALN metastasis were identified by univariate analysis. Multivariate analysis of the identified risk factors was performed using logistic regression, and a prediction model was developed into a nomogram. Discrimination of the model was determined with the AUC. Model calibration was evaluated by comparing the predicted and observed probabilities.

Results: Of 94 eligible patients with both pelvic LNs and PALNs resected, 70 women (74%) with complete information were included. The median age was 65 years (range, 30-86 years). The median number of LNs sampled was 25, the median number of positive LNs (para-aortic and/or pelvic) was 2, and the median number of positive pelvic LNs was 1. Forty-seven patients (67%) had positive pelvic LNs only and 23 (33%) had both positive pelvic LNs and PALNs. Based on uterine pathology, 53% of tumors had endometrioid histology; the remaining 47% had nonendometrioid. Grade 1/2 disease characterized 49% of tumors and grade 3 disease characterized 51%. Lymphovascular space invasion (LVSI) was present in 69% of patients, as was deep myometrial invasion (MI) >50%. 43% of patients had >1 positive pelvic LN. Univariate analysis showed LVSI (P=0.07), nonendometrioid histology (P=0.01), and >1 positive pelvic LN (P<0.01) were associated with PALN metastasis. The multivariate logistic regression model that included these 3 variables (+pelvic LN: odds ratio [OR]=10.74, 95% CI 2.79-41.37, P<0.01; histology: OR=3.83, 95% CI 1.28-11.44, P=0.02; LVSI: OR=2.95, 95% CI 0.01-10.07, P=0.08) had an AUC of 0.82 (95% CI 0.72-0.92, P<0.01). The model was well calibrated (P=0.84).

Conclusions: Further validation of this nomogram can enable individualized care for advanced-stage endometrial cancer patients. This nomogram may serve as a useful clinical tool to aid physicians in assessing a patient’s risk of PALN metastasis. Results can then inform the need for further surgical and postoperative treatment.

187 Are postmenopausal women with body mass indices <30 with grade 1 endometrial cancer more likely than their obese counterparts to have advanced or recurrent disease?
The Ohio State University, Columbus, OH

Objective: To determine if postmenopausal women with a body mass index (BMI) <30 are more likely than their obese counterparts (BMI >30) to have advanced or recurrent disease.

Methods: We obtained institutional review board approval to access an endometrial cancer patient database that exists at our institution. We accessed patients diagnosed from 1/1/2003-12/31/2010 and performed a retrospective cohort study. All patients who were age 52 or older were reviewed for postmenopausal status. If postmenopausal status could not be confirmed, patients were still included if age 55 or older. Patients were included if preoperative biopsy was diagnosed as grade 1 endometrioid or mucinous histology. Relative risk (RR) and 95% CI were calculated for >50% myometrial invasion, presence of lymphovascular space invasion (LVSI), any positive lymph node, stage >1, grade >1 on final pathology, and recurrence rates.

Results: We identified 226 postmenopausal patients with grade 1 tumors. Of those, 66 had a BMI <30 and 160 had a BMI >30. In the <30 BMI group, median BMI was 25.7 (range, 19.1-29.9), while in the >30 group, median BMI was 40.1 (range, 30.1-98.2). Median age at the time of diagnosis in the <30 BMI group was 63.5 years (range, 53-87 years) and 63 years (range, 52-91 years) in the obese group. A family history of Lynch syndrome cancers was present in 12 patients (18%) in the <30 BMI group and in 22 patients (14%) in the >30 BMI group. RR for myometrial invasion, LVSI, and positive lymph nodes were 1.5 (95% CI 0.9-2.6, P=0.07), 1.5 (95% CI 0.8-2.8, P=0.08), and 2.3 (95% CI 0.8-6.9, P=0.06). Twelve patients (18%) in the <30 BMI cohort had >stage I disease on final pathology, while 27 (17%) patients in the >30 BMI cohort had >stage I disease on final pathology. Twenty-three percent vs. 20% had >grade 1 on final pathology. After a median follow-up of 107.3 months (range, 4.0-257.1 months), 8 patients (12%) in the <30 BMI cohort recurred compared with 8 patients (5%) in the >30 BMI cohort. RR for recurrence was 2.5 (95% CI 0.9-6.3, P=0.05). 1 patient in the <30 BMI cohort died of disease (2%), while 3 patients died of disease in the obese group (2%).

Conclusions: Postmenopausal patients with grade 1 endometrioid adenocarcinoma and BMIs <30 are not more likely than their obese counterparts to present with advanced disease, but there seems to be a trend towards positive lymph node and recurrent disease.

188 Importance of platinum sensitivity and treatment modality in advanced-stage uterine papillary serous carcinoma
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The University of Texas, MD Anderson Cancer Center, Houston, TX

Objective: Platinum-sensitivity is a well-known prognostic factor for high-grade serous ovarian cancer. The objective of this study was to analyze the impact of prognostic factors, including platinum sensitivity and treatment modality, on outcome in patients (pts) with advanced-stage uterine papillary serous carcinoma (UPSC).

Methods: A retrospective review of pts diagnosed with stage III or IV UPSC between 1993 and 2012 was performed. Summary statistics were used to describe demographic and clinical characteristics. Overall response rate to each treatment modality was calculated. Overall survival (OS) and recurrence-free survival (RFS) were estimated with the Kaplan-Meier estimator. Cox proportional hazards regression was used to model the association of potential prognostic factors with OS and RFS.
Results: The study included 168 pts with median follow-up of 2.3 years (range, 0.2-13.3 years). Median age was 63 years (range, 38-88 years) and 64% were white. In all, 58.9% were treated with surgery followed by chemotheraphy, 15.5% received surgery + chemotheraphy + radiotherapy, 13.7% had neoadjuvants chemotheraphy (NAC) +/- surgery, and 8.9% had surgery + radiotherapy. The overall complete response (CR) rate was 68.5%, and the overall recurrence rate (RR) was 70.8%. Table 1 depicts CR, RR, median RFS, and median OS by treatment group. Optimal tumor reductive surgery (HR 0.5, P=0.042), platinum sensitivity (HR 0.2, P=0.0001), stage IV (HR 2.19, P=0.0001), and treatment type were associated with RFS. Only platinum sensitivity (HR 0.2, P=0.0001) was prognostic of RFS on multivariate analysis. For OS, pure historyology (HR 1.5, P=0.0439), platinum sensitivity (HR 0.43, P=0.0003), stage IV (HR 2.3, P=0.0001), and treatment type were prognostic in univariate analysis, with platinum sensitivity (HR 0.48, P=0.0024) and stage IV (HR 1.66, P=0.0341) were predictive of OS on multivariate analysis.

Conclusions: Pts with advance- stage UPSC treated with combination therapy, including surgery, chemotheraphy, and radiotherapy, had significant CR rates and lower recurrence rates. Platinum-sensitivity is the most significant predictor of survival in this group of patients.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>CR (n)</th>
<th>RR (n)</th>
<th>Median RFS (years)</th>
<th>Median OS (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAC +/- Surgery</td>
<td>36.4% (7)</td>
<td>78.3% (18)</td>
<td>0.9</td>
<td>1.8</td>
</tr>
<tr>
<td>Surgery + Chemotherapy</td>
<td>72.7% (72)</td>
<td>77.8% (77)</td>
<td>1.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Surgery + Radiation</td>
<td>93.3% (14)</td>
<td>66.7% (10)</td>
<td>1.5</td>
<td>3.7</td>
</tr>
<tr>
<td>Surgery + Radiation + Chemotherapy</td>
<td>73.1% (19)</td>
<td>85.5% (10)</td>
<td>1.8</td>
<td>4.4</td>
</tr>
</tbody>
</table>

190 Can preoperative factors predict the need for postoperative radiation in patients with endometrioid adenocarcinoma of the uterus?

C. Nagel, B. Davidson, K. Elwell, C. Bevan, D. Richardson, S. Kehoe, J. Lea, D. Miller
University of Texas Southwestern Medical Center, Dallas, TX

Objective: The criteria established by the Gynecologic Oncology Group (GOG) in Protocol 99 and the Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial are used to determine if adjuvant radiation is required after surgical staging for endometrial cancer. Our objective was to determine if these criteria could be used preoperatively to predict the need for postoperative radiation.

Methods: This was a retrospective review of patients treated for endometrioid adenocarcinoma of the uterus at our institution between 2002 and 2012. Inclusion criteria were: a preoperative endometrial biopsy that included both histology and grade definitive surgical management with an intraoperative frozen section that included an estimate of myometrial invasion (MI). Patients were determined to have met GOG 99 criteria if they were >70 years old and had a moderately to poorly differentiated tumor along with outer 1/3 MI or >70 years old with either of these criteria. Since lymphvascular space invasion is difficult to determine on preoperative endometrial biopsy and frozen section, this was omitted. PORTEC-2 criteria were met if patients were >60 years old and had >50% MI with a grade 1 or grade 2 tumor or <50% MI with a grade 3 tumor. The same criteria were used to determine qualification based on final pathology. Descriptive statistics were performed using Microsoft Excel 2011 and Instat was used to perform chi-square analyses.

Results: One hundred fifty-seven patients met the inclusion criteria. The mean age was 57 years (range, 27-89 years), and all patients had endometrioid histology. The majority of patients (67%), had a grade 1 tumor, followed by grade 2 (27%) and grade 3 (6%) on preoperative endometrial sampling. Twenty-nine percent (n=46) of patients had no MI, 59% (n=92) had <50% MI, and 12% (n=19) had >50% MI on frozen section. Forty-six percent (n=11) of patients who met GOG 99 criteria on evaluation of final pathology could be correctly identified based on preoperative information. PORTEC-2 criteria revealed a slightly higher sensitivity for preoperative analysis (57%). The specificity and negative predictive value of both sets of criteria were significantly higher (GOG 99: 93% and 91%, respectively; PORTEC-2: 96% and 96%, respectively).

Conclusions: The GOG 99 and PORTEC-2 criteria for determining the need for postoperative radiation can be successfully applied preoperatively to determine those patients who will not need adjuvant therapy.
at high risk for surgical complications. A potential option is hysteroscopic removal of endometrial tumor, but obtaining adequate margins poses a challenge. The objective of this study was to evaluate multimodal optical imaging using a combination of widefield fluorescence imaging (WFI) and high-resolution microendoscopy (HRME) to determine tumor margins in patients with endometrial cancer.

**Methods:** A prospective phase II study of women with newly diagnosed endometrial cancer undergoing hysterectomy was performed. Immediately following hysterectomy, multimodal optical imaging was performed on the endometrium. White light and autofluorescence images at 460 nm excitation were obtained. Topical proflavine (0.01%) was applied to the endometrial surface and widefield fluorescence imaging performed. Based on gross examination of the endometrium, HRME images were obtained of tumor, tumor margins, and normal endometrium. The HRME imaging findings were then correlated with histopathologic results.

**Results:** Twenty patients were enrolled in the study. The median age was 63 years (range, 36–84 years). The most common histologic subtype was endometrioid adenocarcinoma (90%). The majority of patients had stage IA (85%) grade 2 (70%) disease. The median operative time was 210.5 minutes (range, 78–404 minutes). Ninety percent of patients underwent hysterectomy by a minimally invasive approach. The median duration of HRME imaging ex vivo was 20 minutes (range, 13–26 minutes). The sensitivity and specificity of HRME in detecting any abnormal tissue (complex hyperplasia and/or carcinoma) was 73% and 86%, respectively. Overall, there was a concordance rate of 74% (95% CI, 62%–83%) between HRME and final histopathologic results. In comparison, the concordance rate between gross evaluation and final histopathologic results was only 59% (95% CI, 47%–71%).

**Conclusions:** Multimodal optical imaging methods using HRME demonstrated good sensitivity and specificity in distinguishing tumor from normal endometrium in patients with endometrial cancer. Our results suggest that this good sensitivity and specificity in distinguishing tumor from normal endometrium in patients with endometrial cancer. Ninety percent of patients underwent hysterectomy by hysterectomy via hysteroscopy in women with endometrial cancer undergoing conservative uterine-sparing surgery via hysteroscopy

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**Table.** Epidemiologic and Pathologic Characteristics and Univariate and Multivariate OS by Factor

<table>
<thead>
<tr>
<th>Factor</th>
<th>NHW</th>
<th>HISPANIC</th>
<th>AI</th>
<th>BLACK</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEC of cases (%)</td>
<td>102 (49.5)</td>
<td>73 (35.4)</td>
<td>28 (13.6)</td>
<td>3 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age SD</td>
<td>60.8±14.4*</td>
<td>57.3±14.03*</td>
<td>49.3±14.08*</td>
<td>64.08±4.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BM±SD</td>
<td>33.98±11.77</td>
<td>35.67±11.64</td>
<td>36.64±10.08</td>
<td>40.84±11.92</td>
<td>0.45</td>
</tr>
<tr>
<td>Pneumocytes SD</td>
<td>2.25±2.25*</td>
<td>3.94±3.70*</td>
<td>2.04±2.46*</td>
<td>4.00±1.0</td>
<td>0.0003</td>
</tr>
<tr>
<td>Birth±SD</td>
<td>1.79±1.94*</td>
<td>3.17±3.18*</td>
<td>1.75±2.30*</td>
<td>4.00±1.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Menarche</td>
<td>12.96±2.11</td>
<td>12.57±1.60</td>
<td>12.77±1.35</td>
<td>11.35±1.15</td>
<td>0.49</td>
</tr>
<tr>
<td>Menopause (%)</td>
<td>27 (75.5)</td>
<td>49 (70.7)</td>
<td>10 (33.3)</td>
<td>3 (100)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OC Use (%)</td>
<td>26 (33.3)</td>
<td>16 (21.9)</td>
<td>11 (44.4)</td>
<td>0 (0%)</td>
<td>0.559</td>
</tr>
<tr>
<td>HPT (%)</td>
<td>54 (52.9)</td>
<td>37 (50.7)</td>
<td>9 (32.1)</td>
<td>3 (100)</td>
<td>0.14</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>26 (25.3)</td>
<td>13 (17.8)</td>
<td>2 (10.7)</td>
<td>3 (100)</td>
<td>0.20</td>
</tr>
<tr>
<td>ERT use (%)</td>
<td>19 (18.6)</td>
<td>7 (9.6)</td>
<td>1 (3.6)</td>
<td>1 (33.3)</td>
<td>0.076</td>
</tr>
<tr>
<td>Alcohol use (%)</td>
<td>44 (43.1%)</td>
<td>16 (21.9%)</td>
<td>10 (35.7%)</td>
<td>0 (0%)</td>
<td>0.015</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>49 (71.7)</td>
<td>30 (41.1)</td>
<td>7 (25.9)</td>
<td>2 (66.6)</td>
<td>0.068</td>
</tr>
<tr>
<td>Stage (III/IV vs. I/II, %)</td>
<td>22 (21.6)</td>
<td>27 (37.0)</td>
<td>2 (7.14)</td>
<td>2 (66.6)</td>
<td>0.0036</td>
</tr>
<tr>
<td>Histologic type (2 vs. 1, %)</td>
<td>12 (12.8)</td>
<td>17 (23.3)</td>
<td>3 (10.7)</td>
<td>1/3 (33.3)</td>
<td>0.10</td>
</tr>
<tr>
<td>Myoinvasion ≥50%</td>
<td>32 (31.4)</td>
<td>23 (31.5)</td>
<td>6 (21.4)</td>
<td>1/3 (33.3)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

**Objective:** To determine if multietnic/racial (E/C) differences exist with respect to clinical presentation and survival in patients with endometrial carcinoma (EC).

**Methods:** Between 11/1997 and 7/2007, 206 women with EC were prospectively enrolled into an institutionally approved longitudinal study: Exclusion criteria included coexisting malignancy (not disease-free x 5 years) and severe anemia. All patients underwent hysterectomy, bilateral salpingo-oophorectomy, and peritoneal inspection, but lymph node dissection was not required. Data were abstracted from questionnaires, charts, tumor board review, and the state's tumor registry. The median follow-up (range) 77.7 (1.5–82.5) months. The last reported death from EC was 2/20/2004, and the date for follow-up 12/2012. Because only 3 black women enrolled, they were not included in the statistical comparisons by R/E. Statistical methods included ANOVA and Fisher’s Exact tests for measures of association, and Cox proportional hazards models.

**Results:** By R/E (Table), there were significant differences in prior hormone exposure, use of alcohol/smoking, parity, stage, and grade (all <0.05). Hispanics were more likely to present with advanced stage (P=0.0036), high-grade (P=0.057), and type 2 tumors (NS, P=0.10), but no significant differences in overall survival (OS) by R/E (P=0.67) were found. Therefore, all other comparisons were pooled across R/E. In univariate models, factors predictive of OS included age ≥70 years, prior progesterone use, histology, lymphatic invasion, cervical involvement, cytology, lymph node involvement, metastatic tumor (microscopic vs. ≥ 2 cm), residual disease, cervical involvement, depth of myometrial invasion, use of adjuvant chemotherapy, and stage (all <0.05). OS was reduced stepwise with cervical gland vs. stromal involvement. Pooling significant univariate factors (without stage or lymph node sampling), 3 factors were significant: myoinvasion, cytology, and tumor grade. When added to the model, positive finding on pelvic lymph node sampling was not significant, but positive finding on para-aortic lymph node sampling was highly significant (HR 44.18; 95% CI 7.87, 247.9; P <0.001), along with grade (P=0.009) and cytology (P<0.03).

**Conclusions:** Significant differences by R/E were observed that included age, prior hormonal therapy, use of tobacco/alcohol, and parity. Of these, only age significantly affected OS in univariate models. Despite significant R/E differences by stage and grade at presentation, there were no differences in OS by R/E. In both univariate and multivariate models, para-aortic lymph node status was the factor most predictive of OS.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology were estimated with the Kaplan-Meier method. Between 1993 and 2012. Summary statistics were used to describe demographic and clinical characteristics. Intergroup comparison was performed using the Cox Proportional Hazards Models for Overall Survival.

Neoadjuvant chemotherapy in stage IV uterine papillary serous carcinoma

L. Holman, P. Soliman, N. Fal, H. Mhadgut, A. Klopp, R. Broadus, N. Fleming, M. Munsell, K. Lu, S. Westin
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Objective: The use of neoadjuvant chemotherapy in advanced high-grade serous ovarian cancer has been shown to be effective. Little data exist regarding the utility of neoadjuvant chemotherapy (NAC) among patients (pts) with uterine papillary serous carcinoma (UPSC). The objective of this study was to characterize NAC use in stage IV UPSC and describe clinical outcomes.

Methods: We performed a review of all pts diagnosed with stage IV UPSC between 1993 and 2012. Summary statistics were used to describe demographic and clinical characteristics. Intergroup comparison was performed using the Fisher's exact test. Overall survival (OS) and recurrence-free survival (RFS) were estimated with the Kaplan-Meier method.

Results: Of the 90 pts with stage IV UPSC, 23 received NAC. The median age was 66 years (range, 47–81 years) and 47.8% were African-American. Reasons for receiving NAC included disease site (n=13), medical comorbidities (n=4), both disease site and medical comorbidities (n=3), and unknown (n=3). Women completed 1-12 cycles of either carboplatin, paclitaxel, or both for NAC. There were no clinical predictors of CR, including age (P=0.999), median number of NAC cycles (P=0.942), and optimal tumor reduction surgery (P=0.999). To date, 18 pts (78.3%) have recurred with a median RFS of 0.9 years. Median OS was 1.8 years.

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Conclusions: While NAC has been shown to be an effective alternative to upfront cytoreductive surgery in ovarian cancer, our study demonstrates that
NAC may only have modest activity in patients with stage IV UPSC. This treatment should be limited to patients for whom primary cytoreductive surgery is not a safe option.

194

Identifying a subgroup of endometrial cancer patients who may potentially forego para-aortic lymphadenectomy

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Objective: Para-aortic lymph node (PA) dissemination in endometrial cancer (EC) is uncommon, and a systematic infrarenal PA dissection carries morbidity. The objective of this study was to identify a subgroup of EC patients who may potentially forego PA lymphadenectomy (LND).

Methods: All EC patients at a single institution (1999-2008) undergoing staging according to a prespecified, published, and validated surgical protocol. Patients with nonendometrioid histology, stage IV disease, synchronous cancers, and neoadjuvant chemotherapy or chemoradiation were excluded. For the patients who had adequate PA lymphadenectomy (≥5 nodes), the study end point was detection of metastasis to PA nodes. For patients who did not have PA LND or had inadequate PA LND, the study end point was PA recurrence within 2 years. The outcome of interest was, hence, labelled as PAMR (PA metastasis or recurrence).

Multivariable logistic regression analysis identified predictors of PAMR.

Results: Nine hundred fifty-six patients met inclusion criteria, of whom 62% had pelvic LND and 47% had PA LND. Mean age was 64 years and mean BMI was 34. FIGO histologic grade distribution was 59%, 31%, and 9% for grade I, II, and III, respectively. Distribution of myometrial invasion (MI) was 21%, 62%, and 16% for no MI, ≤50%, and >50%, respectively. PAMR was observed in 4% (38/956). Multivariable analysis identified positive pelvic nodes (odds ratio [OR] 26, 95% CI 11-62, P<0.001), >50% MI (OR 5, 95% CI 2-14, P<0.001), and lymphovascular space invasion (LVSI) (OR 4, 95% CI 1-9, P=0.005) as the only 3 independent predictors of PAMR. When all 3 factors were absent (77% of study cohort), the predicted probability of PAMR was 0.6%. When all 3 factors were present (1.7% of study cohort), the predicted probability of PAMR was 76%. When intraoperative frozen section was not available on pelvic lymph nodes and LVSI, omitting PA LND in all patients with ≤50% MI would affect 84% (798/956) of total study cohort with PAMR of 1.1%.

Conclusions: The majority of patients with endometrioid EC may potentially forego PA LND with expected reductions in surgical morbidity and cost of care. This cohort may be identified by a combined presence of 3 factors: negative pelvic nodes, absence of MI or ≤50% MI, and absence of LVSI. At institutions where only MI can be reliably diagnosed on frozen section, omission of PA LND in patients with ≤50% MI would carry a 1.1% risk of PAMR.

195

Redefining obesity, diabetes, and race in type I and type II endometrial cancers

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1University of North Carolina at Chapel Hill, Chapel Hill, NC, 2Duke University Medical Center, Durham, NC

Objective: Type I endometrial cancers (EC) classically occur in obese, Caucasian women and arise in a hyperestrogenic milieu. In contrast, type II EC (i.e., serous and clear cell) behave more aggressively and occur more frequently in African-American (AA) women. Obesity has not been considered a risk factor for type II EC, but recent studies are lacking. Given the obesity and diabetes (DM) epidemic and the poorer outcomes in AA with EC, we sought to assess the relationship of obesity, DM, and race between type I and type II EC.

Methods: A multi-institutional institutional review board-approved cross-sectional analysis of all type I and type II EC cases diagnosed at 2 academic institutions from January 2005 through December 2012 was performed to assess the distribution of obesity, race, and DM. Clinical and pathologic data were collected from electronic medical records. Statistical analyses using student t-test, and χ2 tests were performed in SAS 9.3. Two-sided statistical significance was set at P=0.05.

Results: Of 1,462 (1,187 type I and 275 type II) EC cases, 15% of type I and 32% of type II were AA. Comparison of type I and type II EC showed 85% vs. 78% were overweight-obese (OvOb) and 65% vs. 50% were obese (P<0.001). By race, 75.3% of AA and 58.7% of Caucasian (Cau) were obese. Within type I EC, AA had greater mean BMI than Cau (27.6 vs. 34.9, P=0.0008). Within type II EC, AA also had greater mean BMI than Cau (35 vs. 29.9, P<0.0001). By race, AA were 3.3 times as likely as Cau to have having type II EC, even after controlling for obesity. Overall, 25% of EC patients had DM, and the proportion of DM did not differ between type I and type II EC (25 vs. 23%, P=0.42). AA were more likely to have DM than Cau (38 vs. 21%, P<0.0001). Within type II EC, AA were 3.7 (95% CI 2.1-6.7, P<0.0001) times as likely as Cau to have DM.

Conclusions: Despite traditional dogma, the great majority of both types I and II EC patients are obese and DM is equally prevalent in types I and II EC. Thus, strategies to affect obesity may just be as critical for women faced with type II as type I disease.

196

Metformin reduces recurrence and improves survival in endometrial cancers

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1University of North Carolina School of Medicine, Chapel Hill, NC, 2Duke University Medical Center, Durham, NC, 3University of North Carolina at Chapel Hill, Chapel Hill, NC

Objective: Obesity and diabetes (DM) are associated with increased recurrence rates and worse survival in endometrial cancer (EC). Metformin, classically used as first-line treatment for type 2 diabetes, has been shown to decrease cancer risk and reduce cancer-related mortality in several epidemiologic studies. Preliminary data presented at American Society of Clinical Oncology 2012 suggests that metformin may improve EC outcomes. We sought to evaluate the impact of metformin on EC recurrence and survival in this multi-institutional study.

Methods: One thousand, five hundred sixty-one EC patients were identified, of whom 577 were diabetic. Of these, 54% used metformin. Mean age was 63.0 years (standard deviation [SD] 11.6 years), and mean body mass index (BMI) was 39.1 (SD 11.3). 252 (64%) were Caucasian and 120 (30.7%) were African-American. 310 (82%) were obese. 297 (75%) had endometrioid histology. Stage distribution included the following: 308 (78%) stage I, 16 (4%) stage II, 52 (13%) stage III, and 181 (44%) stage IV. Median follow-up was 33 months (interquartile range, 19 to 87 months).

Results: Metformin use was significantly associated with improved progression-free survival (HR 0.57, 95% CI 0.391-0.852). Metformin users also had significantly improved overall survival (chi-square P=0.002, HR 0.05, 95% CI 0.33-0.78). After adjusting for BMI, stage, and adjuvant treatment, metformin use was associated with improved progression-free survival (HR 0.56, 95% CI 0.36-0.86) and overall survival (HR 0.47, 95% CI 0.29-0.77).

Conclusions: Metformin use was associated with an improved progression-free survival and overall survival in EC diabetic cases. These findings suggest that metformin may have a role as adjuvant and maintenance therapy for this obesity-driven disease and should be further explored in the setting of a clinical trial.
197

Recurrences patterns following robotic-assisted surgical staging for endometrial carcinoma
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Objective: To report first-site recurrence patterns in women with endometrial carcinoma who were surgically staged using robotic-assisted laparoscopy.

Methods: Retrospective chart review for all consecutive endometrial cancer patients surgically staged with robotic-assisted laparoscopy at the University of North Carolina Hospital from 2005 to 2010. Demographic data and recurrence patterns were analyzed. Study results were compared to historical data.

Results: Five hundred seventeen patients met inclusion criteria and were included in the analysis. Recurrence was documented in 58 patients (11.2%). Median follow up was 25 months (range, 0-91 months). Median age was 62.5 years (range, 27-90 years) and the median body mass index was 32.4 (range, 17-65). 55% of recurrences occurred in stage I patients (n=32), while 25.9% of recurrences were in stage III patients (n=15). Vaginal cuff recurrence occurred in 14 patients (2.7%). Pulmonary recurrence was detected in 8 patients (1.5%). 30 patients (5.8%) were diagnosed with recurrence in the abdomen and pelvis, with 17 recurrences (3.3%) in the retroperitoneum. Port-site metastases were detected in 5 patients (1.0%), with 1 port-site recurrence documented during the postoperative visit. Fifty-nine percent of recurrences were endometrioid histology. Thirty-eight patients (7.4%) with recurrence received adjuvant radiotherapy, while 19 patients (3.6%) received both adjuvant chemotherapy and radiotherapy following initial surgical staging. Recurrence rates and first-site recurrence patterns were similar to historical data for traditional laparoscopy.

Conclusions: Sites of first recurrence after robotic-assisted surgical staging for endometrial carcinoma are similar to those for traditional laparoscopy and laparotomy. Port-site metastasis is uncommon, with rates similar to laparoscopy.

198

Does comprehensive staging make a difference for recurrence and survival of patients with high-intermediate risk endometrial cancer?
The Ohio State University, Columbus, OH

Objective: To assess recurrence rates and progression-free survival (PFS) for comprehensively staged patients with endometrial cancer.

Methods: We performed a single-institution retrospective chart review of endometrial cancer patients between 2003 and 2009. Patients with serous or clear cell histology and sarcomas were excluded. Clinical and pathologic characteristics and survival data were collected, and patients were assigned to 1 of 4 risk categories. Low risk (LR) was defined as stage IA grade 1, no lymphovascular space invasion (LVI); low-intermediate risk (LIR) as stage I/II that does not meet LR or high-intermediate risk (HIR); HIR as stage I/II with grade 2 or 3, LVI, or >50% myometrial invasion and age >70 years with 1 risk factor, age 50-69 years with 2 factors, or age <50 years with 3 risk factors; and high risk (HR) as stage III/IV. PORTEC-2 HIR was defined as age >60 years and 1C grade 1/2 or 1B grade 3 or stage 2A any age (not >50% grade 3).

Results: Three-hundred ninety-seven patients were identified: 88% stage I, 3% stage II, 8% stage III, and 1% stage IV. 88% of all patients and 95% of HIR patients were comprehensively staged. Twenty-nine (7%) recurred: 5% of patients with FIGO 2009 stage I, 31% with stage II, 15% with stage III, and 75% with stage IV. When patients were divided into risk categories, 22% of HR, 16% of HIR, 7% of LIR, and 2% of LR patients recurred (P<0.001). The majority of the patients in HIR had no adjuvant therapy (NAT). Of those, 5 (11%) recurred (4 vaginal and 1 pelvic) (Table). Two (3%) patients in HIR who received NAT or brachytherapy had a distant recurrence. Thirty-six-month PFS for LR was 99%, LIR was 91%, HIR was 83%, and HR was 75%. Thirty-three of 403 patients met PORTEC-2 HIR criteria. Of these, 9% recurred (Table). Locoregional recurrence rate was 6%.

Conclusions: Locoregional recurrences were low in this group of comprehensively staged patients who met PORTEC-2 HIR criteria and received NAT, and were similar to those who had brachytherapy in PORTEC-2 (3%). Although cross-trial comparisons are of limited value, our distant recurrence rate was favorable (3% vs. 12%, 95% CI 0.53-27.2) compared to PORTEC-2 HIR patients, despite the fact that none of the patients in either study received adjuvant chemotherapy. Similarly, the risk of distant recurrence in HIR patients with no adjuvant therapy was low and may not warrant adjuvant chemotherapy. Therefore, lymphadenectomy may allow patients with HR disease to be appropriately separated from HIR and selected for adjuvant chemotherapy since most distant recurrences are fatal.
with G/T (HR 0.349; 95% CI 0.139, 0.875; P=0.02) were independently associated with OS.

**Conclusions:** Women diagnosed with early-stage, high-grade uterine LMS experience high recurrence rates and poor survival outcomes, irrespective of adjuvant therapy. However, treatment with adjuvant gemcitabine/docetaxel was associated with improved survival. GOO protocol 277, a phase III study of women with early-stage uterine LMS treated with surgery followed by observation vs. adjuvant chemotherapy, is ongoing and will hopefully determine the appropriate management of patients with this disease.

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**Endometrial Cancer**

*(Translational Research/Basic Science)*

**200**

**The effect of loss of mismatch repair gene expression on survival for patients with high risk endometrial cancer**

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**Objective:** It is recognized that endometrial cancer may be associated with the loss of expression of mismatch repair (MMR) genes. This loss of expression may arise from germline mutations (Lynch syndrome) or from acquired epigenetic alterations. Studies indicate that patients with loss of MMR expression display a distinctive phenotype. It remains unclear, however, whether the presence or absence of MMR expression has a significant impact on survival. The current study examines patients with lymphatic invasion (lymphovascular space invasion and/or lymph node metastases) to determine whether the loss of MMR expression affects survival in this high-risk group of patients.

**Methods:** All patients younger than age 70 years with endometrial cancer and lymphatic invasion between 1998-2009 were included. All adenocarcinomas were included. Patients with FIGO stage I-IIIA were included if lymph node metastases were present. Immunohistochemistry (IHC) was performed with antibodies to MLH 1, MSH 2, MSH 6, and PMS 2. A retrospective chart review was performed for pertinent clinical data, and survival data were obtained from the hospital tumor registry. Survival was compared with log-rank statistic and Kaplan-Meier plots.

**Results:** Sixty-six patients were identified for this 12-year time period with endometrial cancer and lymphatic invasion. Forty patients had normal MMR expression by IHC staining. Twenty-six patients were lacking in expression of at least one MMR gene. Ages ranged from 33 to 70 years, with a mean of 53 years. There was no significant difference in mean age, stage distribution (stage I/II vs. stage III/IV), or histology (endometrioid vs. non-endometrioid) between the MMR normal and MMR abnormal groups. MMR abnormal patients demonstrated a significantly improved overall survival (P=0.03) and significantly reduced risk of cancer death (P=0.04) compared to patients with normal MMR expression. Subgroup analysis of only stage IIIC patients also demonstrated a significant improvement in overall survival and reduced risk of cancer death in patients lacking expression of at least one MMR gene.

**Conclusions:** Abnormal MMR expression in patients with high-risk endometrial cancer appears to be associated with significantly improved survival and a lower risk of cancer death. It remains unclear whether this reflects the natural tumor biology or a differential response to therapy.

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**201**

**ER-alpha, PR, EGFR and GPER expression differentially correlate with survival in endometrial carcinoma**

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**Objective:** To evaluate the relationship between GPER (G protein-coupled estrogen receptor), ER-alpha (estrogen), PR (progesterone), and EGFR (epidermal growth factor receptor) and outcome in endometrial carcinoma (EC).

**Methods:** GPER, ER-alpha, PR, and EGFR receptor expression were compared using immunohistochemistry (IHC) in 95 patients with EC diagnosed between 1997 and 2006. Expression was dichotomized as high or low using median H-scores (intensity x percent of epithelial cell staining). IHC results were correlated with clinical and pathologic parameters using Cox proportional hazards models for survival (overall [OS], progression-free [PFS]). Differences in marginal survival analyses were compared using log rank tests.

**Results:** Age (≥70 years), stage (I/II vs. III/IV), histologic subtype, cervical involvement, lymphovascular space invasion (LVI), and depth of invasion (Table, highlighted) were significant predictors of OS, as was prior estrogen (ERT) use. Increased expression or EGFR and GPER correlated with lower OS (EGFR, 50.0% vs. 86.7%, P=0.01; GPER, 45.8% vs. 80.8%, P=0.002), and high ER-alpha expression correlated with improved OS (80.7% vs. 55.3%, P=0.03). The difference in OS by PR (57.6% vs. 71.1%, P=0.10) was not significant. However, EROrPR (increased ER-alpha or PR) was more predictive of OS (82.9% vs. 42.9%, P<0.001) than either ER-alpha or PR alone. High EROrPR expression inversely correlated with cervical involvement, myometrial invasion, LVI, and improved OS irrespective of histologic subtype categorized as either type 1 (endometrioid) or type 2 (non-endometrioid), whereas high EGFR (HR 5.84, 95% CI 1.10-30.87, P=0.038) and GPER (HR 2.83, 95% CI 0.92-8.73, P=0.07) expression correlated with OS only for type 1 tumors. Increased GPER also correlated with age (P=0.021) and cervical involvement (P=0.029). Stratified by stage, GPER correlated with lower OS in stage I/II disease only (HR 1.41-42.25, P=0.0183), whereas EROrPR correlated with improved OS in both early and advanced disease. As biomarkers, either GPER alone or the combination of EROrPR+EGFR were the best predictors of OS.

**Conclusions:** In this study, immunotyping for ER-alpha, PR, EGFR, and GPER differentially correlated with OS. Alone or in combination, the most robust predictor of OS was GPER alone, or EGFR combined with PR. For stage I/II disease, either GPER or EROrPR was predictive of OS (but not EGFR), but only EROrPR conferred a favorable prognosis, irrespective of stage or histologic subtype.

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**Table. Cox Proportional Hazards Models of OS by Clinical Parameters and Receptor Status**

<table>
<thead>
<tr>
<th>Model Number</th>
<th>Clinical Factor</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
<th>Wald P Value</th>
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<tbody>
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<td>Model 1</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Age ≥70 years</td>
<td>2.52</td>
<td>1.16-5.47</td>
<td>0.019</td>
<td>0.019</td>
</tr>
<tr>
<td>1.1</td>
<td>Age ≥70</td>
<td>2.04</td>
<td>0.58-0.27</td>
<td>0.626</td>
<td>0.637</td>
</tr>
<tr>
<td></td>
<td>EGFR</td>
<td>3.74</td>
<td>1.07-13.08</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>Age ≥70</td>
<td>2.80</td>
<td>1.21-6.49</td>
<td>0.016</td>
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</tr>
<tr>
<td></td>
<td>GPER</td>
<td>2.61</td>
<td>1.16-5.87</td>
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<tr>
<td>1.3</td>
<td>Age ≥70</td>
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<td>0.34-0.76</td>
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<td>EROrPR</td>
<td>0.22</td>
<td>0.11-0.46</td>
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<td>ERT use</td>
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<td>0.02-0.86</td>
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<td>EGFR</td>
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<tr>
<td>2.2</td>
<td>ERT use</td>
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<td>0.02-0.86</td>
<td>0.065</td>
<td>0.010</td>
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<tr>
<td></td>
<td>Model 3</td>
<td>Stage (I/II vs III/IV)</td>
<td>5.29</td>
<td>2.49-11.20</td>
<td>&lt; 0.001</td>
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<tr>
<td>3.1</td>
<td>Stage</td>
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<td>1.06-14.07</td>
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<td>Stage</td>
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<td>3.3</td>
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<td>EROePR</td>
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<td>0.08-0.47</td>
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<td>Model 4</td>
<td>Type 1 vs. Type 2</td>
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<td>Type 1 vs. 2</td>
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<td>1.24-14.82</td>
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<td>EGFR</td>
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<td>Type 1 vs. 2</td>
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<td>1.42-7.96</td>
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<td>0.81-4.51</td>
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<td>Type 1 vs. 2</td>
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<td>0.91-5.36</td>
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<td>EROePR</td>
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<td>0.12-0.79</td>
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<tr>
<td>Model 5</td>
<td>Grade (Type 1 only)</td>
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<td>1.60-3.86</td>
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<tr>
<td>5.1</td>
<td>Grade 1+2 vs. 3</td>
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<td>EGFR</td>
<td>5.84</td>
<td>1.10-30.87</td>
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<td>5.2</td>
<td>Grade 1+2 vs. 3</td>
<td>2.50</td>
<td>1.36-4.60</td>
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<td>&lt; 0.001</td>
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<td>2.83</td>
<td>0.92-8.73</td>
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<td>&lt; 0.001</td>
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<td>5.3</td>
<td>Grade 1+2 vs. 3</td>
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<td>1.28-3.95</td>
<td>0.005</td>
<td>&lt; 0.001</td>
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<td>9.27</td>
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<tr>
<td>Model 6</td>
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<td>3.36</td>
<td>1.68-6.76</td>
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<tr>
<td>6.1</td>
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<tr>
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<tr>
<td>6.2</td>
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<td>1.19-6.80</td>
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<tr>
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<tr>
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<td>7E-08-1.02E+16</td>
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<tr>
<td>Model 7</td>
<td>Cervix involved</td>
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<tr>
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<td>Cervix</td>
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<td>Model 8</td>
<td>Myometrial invasion</td>
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<td>2.33-11.61</td>
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<td>8.1</td>
<td>Myoinvasion (≥50%)</td>
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<td>0.81-10.59</td>
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<td>Myoinvasion (≥50%)</td>
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<tr>
<td>8.3</td>
<td>Myoinvasion (≥50%)</td>
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<td>0.11-2.83</td>
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<td>Model 9</td>
<td>Stratified within Stage</td>
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<tr>
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<td>0.50-25.03</td>
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<td>GPER</td>
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<td>1.41-42.25</td>
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<td>0.01-0.69</td>
<td>0.021</td>
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<td>0.53-9.06</td>
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<td>14</td>
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<td>15</td>
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<tr>
<td></td>
<td>GPER</td>
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<td>0.43</td>
<td>0.13-1.37</td>
<td>0.152</td>
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</table>

EGFR, epidermal growth factor receptor; GPER, G-Protein Estrogen Receptor; PReoER, either estrogen receptor (ER) or progesterone receptor (PR) expression; Type 1, endometrioid histology; Type 2, nonendometrioid histology; LVI, lymphovascular space invasion; bold italics used to indicate significant differences; yellow highlights, univariate analyses; Model numbers with decimals indicate bivariate models of a clinical factor and a receptor status; Models with A-F suffixes indicate univariate models within a stratification; missing value structure precluded analysis of models with 3 or more clinical factors.
202 Biomarkers associated with metabolic syndrome, endometrioid adenocar-
cinoma (EC) of the uterus, and disease prognosis
E. Nugent¹, D. Benbrook², A. Long³, K. Moxley³, R. Wild³, D. McMeekin³
¹University of Oklahoma HSC, Oklahoma City, OK, ²University of Oklahoma,
Oklahoma City, OK

Objective: Literature suggests obesity represents a significant risk factor for the
development of EC and other health problems such as diabetes mellitus (DM) and
cardiovascular disease (CVD). Breast cancer literature suggests inflammatory
biomarkers associated with adiposity are associated with cancer and non-cancer
survival outcomes. Our objective was to determine whether inflammatory
biomarkers associated with obesity and metabolic syndrome in patients with
EC are associated with multiple clinicopathologic factors, including disease
recurrence and overall survival.

Methods: Between 2008 and 2010, we identified 84 patients undergoing surgical
therapy for type 1 EC with available banked blood. We tested associated
selected biomarker levels, screened patients for nongynecologic comorbidities,
and examined clinicopathologic factors, including progression-free survival
(PFS) and overall survival (OS). Patients were stratified based on biomarker
levels above or below the median for the cohort. Descriptive statistics, Kaplan-
Meier, and Cox proportional hazard models were used.

Results: Median age was 67 years (range, 31-90 years). Seventy-nine percent
of patients had stage I disease, 12% stage II, 6% stage III, and 1% stage IV.
Medical comorbidities were common: 26% with DM, CVD in 64%, and
40% with elevated cholesterol and/or smoking/alcohol use. 68% underwent
complete surgical staging, 46% underwent adjuvant treatment, and 12%
recurred or progressed. Disease stage, grade, positive cytology, increasing
creatinine, cervical involvement, and lymph node involvement were associated
with recurrent disease. Leptin, adiponectin, tumor necrosis factor-alpha,
adipin, c-peptide, and insulin yielded no associations with recurrent disease.
Recurrence was significantly associated with interleukin-10 on univariate
analysis (P=0.0021). Cox proportional hazard modeling did not reveal any
significant multivariate associations with recurrence.

Conclusions: Our results suggest, unlike recent work done in breast cancer,
that biomarker levels associated with metabolic syndrome including adipin,
leptin, and adiponectin, are not associated with long-term disease prognosis
or overall survival in patients with endometrial cancer. Interleukin-10 is an
immunoregulatory cytokine and may represent a promising target for future
study in predicting EC recurrence and overall survival.

203 The role of ABCG2 and other stem cell markers in tumorigenesis and
chemoresistance - An analysis of fresh uterine tumor specimens
L. Chan¹, A. Sherman¹, J. Shin¹, T. Kiet¹, K. Blansit¹, L. Hu¹
¹UCSF Comprehensive Cancer Center, San Francisco, CA, ²University of California,
San Francisco, San Francisco, CA

Objective: The side-population (SP) of stemlike cancer cells have been
implicated in tumorigenesis and drug resistance. We proposed to determine the
pluripotency of these cells in uterine cancer.

Methods: SP cells were isolated from fresh uterine cancers via flow cytometry
and Hoechst 33342 efflux. Immunocytochemistry was used to characterize
stem cell markers. Genomic data from The Cancer Genome Atlas of uterine
cancers specimens were employed to validate our in vitro findings.

Results: SP cells had a greater proliferation rate compared to non-SP cells
(P >0.01). After exposure to cisplatin, we found that the SP cells were more
resistant to the effects of chemotherapy (P= 0.04). ABCG2 and NANOG
colocalized in SP cells based on immunocytochemistry. Further, OCT4 stained
immunopositive in SP cells. To further validate our initial finding, we used
fresh patient tumors from The Cancer Genome Atlas. Of 52 tumors specimens,
the median age of patients was 62 years (range, 37 to 90 years). Stage I-II vs.
III-IV comprised 42 (81%) and 10 (19%) patients, respectively. Grade 1-2
endometrioid, grade 3 endometrioid, uterine serous, and mixed comprised
48%, 31%, 2%, and 19% of the studied tumors, respectively. We analyzed the
survival of all stem cell markers and found that overexpression of ABCG2 was
associated a survival of 75.4% vs. 88.8%, but was not statistically significant
(P=0.13) in those with lower expression. However, NANOG and OCT4 were
not important in our analysis.

Conclusions: ABCG2/BCRP1, NANOG, and OCT4 are overexpressed
in stemlike uterine cancer cells. These cells are more tumorigenic and
chemoresistant.

204 Stathmin expression in endometrial hyperplasia: A potential marker for
cancer progression
E. Dickson¹, W. Ricketts², A. Jonson¹, P. Judson Lancaster³
¹University of Minnesota, Minneapolis, MN, ²OvarGene Oncology, Irvine,
CA, ³University of South Florida College of Medicine, Tampa, FL

Objective: Stathmin (STMN) expression has been identified as a marker for
PI3KInase activation and poor prognosis in endometrial cancer. PTEN and the
PI3KInase pathway have been associated with endometrial cancer progression.
There continues to be a need to identify prognostic indicators for endometrial
hyperplasia progression to endometrial carcinoma. Our objective was to
identify whether STMN expression could be used as an indicator of aggressive
endometrial hyperplasia.

Methods: In this collaborative project, endometrial tissue samples were
obtained from our institution and sent for outside processing. STMN,
phospho-STMN, and PTEN expression were measured by staining using the
GraphPad program. A Kruskal-Wallis, nonparametric ANOVA was performed
for statistical analysis

Results: Sixty endometrial tissue samples were obtained and analyzed. Of these,
33 were benign tissue, 6 simple hyperplasia, 2 complex hyperplasia without
atypia, 3 simple hyperplasia with atypia, 5 complex hyperplasia with atypia,
and 11 endometrial adenocarcinoma. STMN and pSTMN expression levels
had a statistically significant difference between groups (P=0.0156 and 0.0456,
respectively). When evaluating for PTEN expression, there was no difference
in PTEN copy number between groups when analyzed in comparison to
STMN and pSTMN expression (P >0.05). However, when excluding complex
hyperplasia without atypia and simple hyperplasia with atypia due to low
sample size in these groups, there was a statistical difference between the
remaining 3 groups (P=0.046).

Conclusions: Stathmin (STMN) expression could identify aggressive
endometrial hyperplasia and be used as a marker for physicians to identify
those patients needing increased surveillance. Further studies are warranted
to determine if STMN expression is a marker for progression to endometrial
carcinoma.

205 Estrogen receptor expression as a useful clinical prognosticator in ear-
ly-stage uterine serous carcinoma
Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

Objective: Expression of estrogen receptor (ER) has been described in uterine
serous carcinoma (USC), a biologically aggressive variant of endometrial cancer
that is generally considered to be independent from the mitogenic effects of
estrogen. Understanding the role of ER in the pathogenesis of USC may hold
importance in prognostication. Our objective was to determine the significance
of ER expression on the pathologic and clinical outcomes of patients with USC.

Methods: With institutional review board approval, we retrospectively
identified 99 patients with pure USC from 2002-2012 and extracted relevant
treatment and outcome data. All available tumor blocks were re-evaluated for ER, progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) and scored by a central gynecologic pathologist according to recent American College of Physician guidelines. Student-t test and Fisher’s exact test were used to compare continuous and categorical variables. Log-rank test with Kaplan Meier curves were used to estimate survival proportions.

Results: Clinical-pathologic characteristics for patients are summarized in the Table. Due to similar demographics, stages I and II USC were combined as “early-stage” and stages III and IV were combined as “late-stage” USC. In early-stage USC, ER expression was 64% and was associated with PR (P<0.001), decreased lymphovascular space invasion (P=0.006), platinum sensitivity (P=0.002), and significantly longer progression-free survival (PFS) (67 vs. 34 months, P=0.04). In late stage USC, ER expression was significantly less (49%, P=0.04) and was inversely correlated with HER2 status (P=0.09). While PFS and overall survival (OS) were longer in ER+ late-stage disease, the difference was not statistically significant. HER2 amplification was associated with platinum resistance (P<0.0001) and higher frequency of recurrence (P=0.0001) and significantly associated with worse OS (26 vs. 57 months, P=0.03). Comparing survival in ER+/PR-/HER2+ (triple negative), ER+/PR-, and HER2+ cohorts, HER2 appeared to be the most prognostic of adverse survival outcome (Figure).

Conclusions: While ER expression is present across all stages of USC, it is significantly more common in early-stage disease and has a favorable association with PFS. The concomitant increase in HER2+ USC is correlated with ER loss and may explain why ER loses its prognostic relevance in late-stage disease. The clinical relevance of ER expression warrants future studies of the role of HER2 and ER in mediating platinum sensitivity and survival and may identify a subpopulation of USC patients who may benefit from alternative treatment strategies.

Table. Patient Demographics

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<th>Pathologic Characteristics</th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Stage IV</th>
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<td>Body mass index</td>
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Chemo=chemotherapy, RT=radiation therapy

206 The role of the Yes kinase-associated protein as a proto-oncogene in endometrial cancer
Geisinger Health System, Danville, PA

Objective: The Yes kinase-associated protein (YAP) is a transcriptional coactivator and a potent proto-oncogene. We hypothesized that: 1) Overexpression of YAP is important in the transition from normal endometrium to endometrial cancer (EMCA) and 2) Loss of YAP expression inhibits the growth of Ishikawa EMCA cells.

Methods: A retrospective chart review of patients undergoing a hysterectomy between 2008 and 2011 for benign or malignant conditions was performed at a large medical center. Demographic data were obtained, including age, body mass index, race, grade, stage, lymphovascular space invasion, and lymph node sampling. Cut sections from paraffin-embedded endometrial tumor tissue were stained with YAP markers using standard immunohistochemistry and adequate positive and negative controls. Nuclear and cytoplasmic glandular staining of YAP was analyzed and scored for intensity using a 5-point (0 to 4) scale by a gynecologic pathologist. Continuous and categorical variables were compared among groups using the Wilcoxon rank-sum and chi-square tests. Cell culture experiments were performed by plating Ishikawa EMCA cells transfected with YAP siRNA or scrambled control. Cells were harvested and counted at days 3, 4, and 5 posttransfection.

Results: Two hundred thirty-seven patients were included in the study. The histologic findings were as follows: 12 atrophy, 35 normal endometrium, 14 simple hyperplasia, 144 type 1, and 32 type 2 EMCAs (Table). No difference in nuclear or cytoplasmic YAP expression was noted between proliferative and secretory endometrium. Higher nuclear YAP expression was seen in normal cycling endometrium compared to atrophic endometrium. Similarly, higher YAP nuclear expression was identified in type 1 and type 2 EMCAs compared to normal endometrium. No difference in cytoplasmic YAP expression was identified. No correlation between demographic data and YAP staining was identified. Transfection of YAP siRNA demonstrated a decrease in YAP protein levels between days 3 and 5 posttransfection. Inhibition of YAP decreased proliferation of Ishikawa cells (Figure) compared to the scrambled control.

Conclusions: Since YAP functions as a transcriptional coactivator, its overexpression in the nucleus of cancerous endometrial cells and impact on endometrial cell growth could have important consequences with respect to its role as a proto-oncogene in EMCA. YAP overexpression may be useful in the future as a diagnostic/prognostic indicator or therapeutic target for the treatment of EMCA.
HAND2 expression is increased in endometrial hyperplasia/cancer
J. Franasiak, J. Hubbs, M. Olorvida, S. Young, P. Gehrig, V. Bae-Jump
University of North Carolina School of Medicine, Chapel Hill, NC

Objective: Progestins have an 80% response rate (RR) in the treatment of endometrial hyperplasia (EH) and a 60% RR in treating endometrial cancer (EC). HAND2 is a progesterone-induced transcription factor that suppresses several fibroblast growth factors. Thus, our goal was to explore whether HAND2 expression would predict responsiveness to progestin therapy for EH/EC.

Methods: Women who underwent progestin treatment (oral or intratuterine device) for either EH or EC or cancer were identified. The expression of HAND2 was measured by immunohistochemistry (IHC) in 56 paired formalin-fixed, paraffin-embedded endometrial biopsy specimens before and after progestin treatment. Quantitative analysis of IHC staining was performed. Individual slides were digitized using the Aperio ScanScope (Aperio Technologies, Vista, CA), and digital images were analyzed using Aperio ImageScope software. Statistical analysis was performed using the Student t-test and ANOVA.

Results: Most patients had EH (54/56), but 2 women had grade 1 EC. There were 39 responders to progestin therapy and 17 nonresponders. The body mass index (BMI) between the 2 groups was statistically different at 40.2 for the responders and 49.9 for the nonresponders (P = 0.0007). HAND2 histoscores were lowest for complex hyperplasia/EC (7.7), higher for simple hyperplasia (9.3), and highest for benign endometrium (14.0) (P = 0.0002).

Benign endometrium is representative of women who reverted after progestin treatment. When evaluating the pre- and postprogestin treatment histoscores, the median difference of HAND2 staining scores was -0.41 (95% CI -3.9 to 7.7) for nonresponders and +4.9 (95% CI 0.39 to 10.8) for responders (P = 0.09). When looking at therapy response by patient BMI, there was an approximate 5% increase (odds ratio 1.049) in the odds of not responding to progestin therapy (95% CI 1.006 to 1.095) for every unit increase in BMI score (P = 0.025).

Conclusions: HAND2 expression was not predictive of response to progestin therapy for EH or EC. However, HAND2 expression was decreased in both EH/EC as compared to benign endometrium, and response led to an increased histoscore. Increasing BMI was strongly predictive of lack of response to progestin therapy. Further work is needed to explore the relationship between HAND2, BMI, and other markers to better understand the development and progression of EC and identify opportunities for prevention and therapy.

208 Wnt pathway gene expression and association with clinicopathologic characteristics in endometrial cancer – An analysis of The Cancer Genome Atlas (TCGA)
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Objective: Aberrant activation of the Wnt signaling pathway is an important mechanism of carcinogenesis in endometrial cancer (EC). We evaluated the molecular signature of Wnt pathway genes among EC tumors in TCGA.

Methods: EC samples in TCGA were evaluated using GATHER, a molecular signature tool, to analyze functional enrichment of differentially expressed genes with categories defined by KEGG. Partek software was used to define differentially expressed genes with false discovery rate < 0.05 (based on ANOVA P values) and |fold-change| > 1.5 (for binary variables). Genes with high fold-change were correlated with stage, grade, myometrial invasion, histology, pelvic cytology, residual tumor, menopausal, body mass index (BMI), positive pelvic/para-aortic lymph nodes, and age.

Results: Of 451 downloadable tumor samples, 313 tumors with both clinical and gene expression data were analyzed. Median age of patients was 64 years (range, 31-90 years); 78% were postmenopausal and 7% premenopausal. Thirty-eight percent of patients underwent minimally invasive surgery and 61% open surgery. Stage I, II, III, and IV disease comprised 63%, 9%, 22%, and 6% of patients, respectively. Median BMI was 32.8 (range, 17-68). Histology showed 76% were endometrioid and 19% serous. Grades 1, 2, and 3 comprised 17%, 24%, and 59%, respectively. Median follow-up was 12.6 months. Differentially expressed genes showed enrichment for Wnt pathway genes when associated with age, menopause, and histology. Twelve Wnt pathway genes were downregulated in serous compared to endometrioid tumors: JUN, LEF1, TCF7, SOX17 (transcription factors); AXIN2, CSNK1A, CTNNBIP1 (beta-catenin regulators); FZD10, FZD8, WNT11; and RBX1 and PLCB4 (Wnt signaling modulators). Six genes were downregulated in postmenopausal patients: Wnt antagonists DKK1 and SFRP4 and WNT2, FZD10, CAMK2D, and DAAM2. Stage, peritoneal washings, residual tumor, pelvic/para-aortic lymph node status, and myometrial invasion were not significantly associated with Wnt pathway gene expression. In a subset analysis, SFRP4 was significantly downregulated in high-grade tumors (P = 0.02), low BMI (P = 0.003), and older and postmenopausal patients (P = 0.02, 0.0005, respectively). Overall survival was not associated with Wnt antagonist expression, but only 28 patients died within this cohort and follow-up time.

Conclusions: The Wnt signaling pathway appears to be part of the molecular signature in EC patients who are older, postmenopausal, and have serous tumors. These results may have implications on drug development, as these characteristics comprise more aggressive type II tumors.

209 Iron-modified albumin in cervical-vaginal fluid may lead to a screening test for endometrial cancer
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Objective: Most women with endometrial cancer present with abnormal uterine bleeding, after which a biopsy is performed to confirm the diagnosis. We have developed a novel proteomic-based screening test based on sampling from a site-specific source, specifically the mucus of the cervix and vagina. Our objective was to develop a screening test for endometrial cancer using iron-modified albumin.

Methods: More than 2,000 samples from over 800 patients have been collected under an institutional review board-approved prospective study from February 2008 through July 2010. Endocervical mucus was collected with a cytobrush; vaginal mucus was collected with a Dacron® swab. Specimens were placed in proprietary transport fluid. Cells were removed by centrifuge and the
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

210

A novel marker for the management of women diagnosed with endometrial adenocarcinoma of the uterus

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Objective: Currently there are no accurate biomarkers for the management of women diagnosed with endometrial cancer. Prompt detection of treatment failures may allow for earlier intervention and change in management for women with progressing disease. The biomarker HE4 has been shown to be expressed in the serum of women with endometrial cancers. The objective of this trial was to assess the utility of HE4 as a marker for progressive disease.

Methods: This was an institutional review board-approved retrospective trial using residual serum samples from women diagnosed with endometrial cancer. At least 4 serial samples from women on chemotherapy or in follow-up were obtained. For each blood draw, the medical record was queried for the patient's clinical status (progression vs. no progression) as determined by a combination of physical examination, serum CA-125 levels, and imaging. Two separate analyses were performed to assess changes in HE4 serum levels: 1) A change of 25% over that of the previous value and 2) Velocity of change of HE4. The patient's clinical status at each follow-up visits was cross-tabulated against whether or not HE4 was elevated or changed. The accuracy of HE4 to predict progressive disease was determined along with specificity, sensitivity, and negative predictive value.

Results: A total of 92 patients providing 799 serum samples were identified for analysis. The median age was 64 years (range: 38-92 years) with 31 stage I, 12 stage II, 33 stage III, and 16 stage IV cases. There were 29 (31.5%) endometrioid, 39 (42.4%) serous, 4 (4.4%) clear cell, and 20 (21.7%) mixed or other histologies. Of the 123 serial sample sets, 85 were from patients on chemotherapy and 38 from patients in follow-up. Using a 25% increase of HE4 as an indicator of recurrence/progression in concordance between biomarker and the clinical assessments, HE4 had an accuracy of 83.0% (95% CI 79.8-85.9%) with a specificity of 88.7% (95% CI 85.7-91.2%), a sensitivity of 41.3% (95% CI 30.1-53.3%), and a negative predictive value of 91.7% (95% CI 89.0-93.9%). Measuring the velocity of change of HE4 over each serial sample set provided an accuracy for predicting recurrence/progression of 81.4% (95% CI 73.1-87.9%) with a specificity of 92.4% (95% CI 84.9-96.9%) a sensitivity of 42.3% (95% CI 23.4-63.1%), and a negative predictive value of 85.0% (95% CI 76.5-91.4%).

Conclusions: HE4 has a high accuracy for detecting recurrence/progressive disease in women with endometrial cancer and can be used as clinical biomarker for the management of this disease.

211

Cation-selective transporters are critical to the anticancer efficacy of metformin in endometrial cancer

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Objective: Recent studies show that the antidiabetic drug metformin exhibits anticancer effects against a broad spectrum of cancers, including endometrial cancer. Due to its hydrophilic nature and net positive charge at all physiologic pH values, metformin requires cation-selective transporters to enter cells and interact with intracellular targets. It is reasonable to expect that the expression patterns and levels of these transporters in cancer cells determine the intracellular concentrations of metformin for antiproliferative activity. This study aimed to investigate the expression of metformin transporters in endometrial cancer cell lines and tissues and the role of these transporters in metformin cellular uptake and accumulation.

Methods: Total RNA isolated from 2 human endometrial cancer cell lines, ECC1 and Ishikawa, and from 15 human endometrial tumor tissues and 5 benign specimens was subjected to real-time polymerase chain reaction to determine the expression levels of the common cation transporters. Time-dependent [14C]metformin uptake into endometrial cancer cell lines was measured by quantifying intracellular radioactivity. Metformin uptake in the presence or absence of transporter-selective and general inhibitors of cation transporters can provide information on the contributions of specific transporters to metformin cellular uptake.

Results: MATE1 and MATE2 are the predominant transporters in ECC1 and Ishikawa cell lines. MATE2 expression was 5-fold higher than MATE1 in ECC1 cells and 6-fold higher in Ishikawa cells. The expression of PMAT was 6-fold and 7-fold lower than MATE1 in ECC1 and Ishikawa cells, respectively. OCT1-3 expression in both cell lines was relatively poor. MATE1 was the predominant transporter in endometrial tumor and benign tissues. Cellular uptake studies are in progress and results will be reported.
Conclusions: Based on studies in other cell lines, it is anticipated that the highly expressed MATE1/MATE2 will facilitate metformin intracellular uptake into endometrial tumors and cell lines. ECC1 and Ishikawa cells are relevant in vitro models for investigating metformin treatment in endometrial cancer because expression of metformin transporters in these cell lines is comparable to that in endometrial cancer cells. Chemical inhibition studies in endometrial cancer cell lines should demonstrate an important role for cation-selective transporters in mediating metformin cellular uptake.

212
Phenformin suppresses proliferation and induces apoptosis in endometrial cancer cell lines
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Objective: Obesity and diabetes have been linked to worse outcomes in women with endometrial cancer. Metformin is a biguanide drug that is widely used for the treatment of type 2 diabetes and has been found to have antitumorimogenic effects via AMPK activation and inhibition of the mTOR pathway. Phenformin is another biguanide with antidiabetic activity that was withdrawn from the market due to a small risk of lactic acidosis (64 cases per 100,000 patient-years), which was higher than that seen with metformin. Studies in breast cancer animal models suggest that phenformin may be more potent for inhibiting tumor growth than metformin. Thus, our goal was to assess the effect of phenformin on proliferation and apoptosis in endometrial cancer cell lines.

Methods: Two endometrial cancer cell lines (ECC-1 and Ishikawa) were used in these studies. Cell proliferation was assessed by MTT assay after exposure to phenformin. Cell cycle progression was evaluated by Cellometer. Apoptosis was assessed by Annexin V-FITC assay. Phosphorylated-AMPK, pan-AMPK, phosphorylated-S6, and pan-S6 were assessed by western immunoblot in the endometrial cancer cell lines.

Results: Phenformin significantly inhibited proliferation in a dose-dependent manner in both endometrial cancer cell lines (IC50 for both ECC-1 and Ishikawa was 1 mM at 40 hours; P=0.02 - 0.0004 for ECC-1; P=0.011 - 0.0002 for Ishikawa). Treatment with phenformin resulted in G1 cell cycle arrest and induction of apoptosis. Western immunoblot analysis demonstrated that phenformin induced phosphorylation of AMPK, its immediate downstream mediator, within 18 hours of exposure. In parallel, treatment with phenformin decreased phosphorylation of S6 protein, a key target of the mTOR pathway.

Conclusions: Phenformin potently inhibited endometrial cancer cell growth via G1 arrest and increased apoptosis. Although the risk/benefit ratio clearly favors metformin over phenformin for the treatment of diabetes, this may not hold true for the treatment of cancer if phenformin was found to have superior antitumorimogenic activity. More work needs to be done to explore the benefits of both metformin and phenformin for the treatment of endometrial cancer, a disease strongly associated with obesity and diabetes.

213
The role of estrogen and Wnt signaling in endometrial carcinoma
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Objective: The Wnt pathway has been implicated in the development of endometrial carcinoma, and our laboratory specifically has demonstrated the importance of Lef1 in the development of endometrial glands and carcinoma formation. There are well-defined risk factors for the development of endometrial carcinoma, with obesity being one of the most important. The mechanism is believed to work through excessive estrogen production that stimulates the endometrium to proliferate. We sought to determine the effect of excessive estrogen on Wnt signaling in human endometrial cancer tissue samples. We hypothesized that estrogen stimulates specific genes unique to the Wnt pathway.

Methods: Wnt polymerase chain reaction (PCR) arrays were performed on 27 tissue samples from patients diagnosed with endometrial adenocarcinoma and cell lines specific to types 1 and 2 endometrial cancer. RT-PCR was used to determine Lef1 relative gene expression for a variety of cancerous and noncancerous patient samples (n=154). Retrospective chart review was used to assess patient demographic information, specifically examining body mass index (BMI) as a surrogate for circulating estrogen. Statistical analyses were performed to compare the fold change of Lef-1 and Wnt gene expression in different cell lines (type 1 vs. type 2 vs. normal) and obese vs. nonobese patients.

Results: We identified several genes in which the degree of expression was altered in obese vs. nonobese patients. Multiple Wnts were overexpressed in the obese cohort when compared to the nonobese cohort, specifically Wnt 1, 3, 3A, 5B, 7B, 8A, and 9A, with Wnt 7A being downregulated. The Wnt inhibitor DKK1 was downregulated not only in type 1 cell lines, but also in the obese cohort, specifically the class III group. PITX2, a regulator of Lef-1, was upregulated in all classes of obesity, but not the type 1 cell lines. Lef-1 gene expression increased as BMI increased in all patient samples and was elevated in cancer samples when compared to benign samples.

Conclusions: Specific Wnt genes were altered in obese patients with endometrial cancer when compared to nonobese patients. Multiple Wnts were overexpressed in obese patients, while specific Wnt inhibitors were downregulated. PITX2 was overexpressed in all obesity classes and was known to activate Lef-1, which was elevated in obese patients. Wnt signaling was active in obese patients with endometrial cancer.

214
Comparison of FIGO grade 3 endometrioid endometrial carcinomas with type 2 uterine cancers. Can grade 3 tumors be classified as type 2 cancers? A clinicopathological and immunohistochemical analysis
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Objective: Comparing clinicopathological and immunohistochemical (IHC) features of FIGO grade 3 endometrioid endometrial carcinoma (G3) to type 2 (T2) uterine cancers (papillary serous [UPSC], clear cell [CC], carcinosarcoma [CS], and mixed type 2 [M]) to determine whether G3 can be more accurately classified and treated as a T2 cancer. Methods: Age, body mass index (BMI), uterine factors, lymph node status, and survival data of G3 and T2 patients who had full surgical staging were analyzed. Tissue blocks were constructed and tested for estrogen receptor (ER), progesterone receptor (PR), p53, p16, and human epidermal growth factor receptor-2 (HER2). Percent staining (%), staining intensity (I), and staining index (H= %*I) were calculated. Comparison of means and proportions were evaluated by T-tests and chi-square tests, respectively, with P<0.05 as significant. Receiver operator characteristic (ROC) curves were generated for H.

Results: G3 (n=7) were compared with T2 (n=27) (9 CS, 12 UPSC, 4 CC, and 2 M). Mean age (65 ±10.1 vs. 66 ±9.5 years), BMI (29.3 vs. 28.9), stage, and treatment regimen were not significantly different between G3 and T2. There were no significant differences between groups with respect to tumor size (P=0.23), depth of myometrial invasion (P=0.72), lymphovascular space invasion (P>0.05), or lymph node status (P=0.78). Progression-free survival (8.6±7.3 vs. 9.9±9.8 months) was not significantly different between groups, with mean follow-up of 9.7±8.0 months for G3 and 12.2±10.9 months for T2. G3 and T2 IHC features were compared. No significant difference between G3 and T2 was seen for ER, with % (52 vs. 38, P=0.53), I (P>0.05), and H (155 vs. 106, P=0.56), and PR, with % (50 vs. 29, P=0.29), I (P>0.05), and H (137 vs. 81, P=0.67). For p53, with % (17 vs. 61, P=0.095), I (P>0.05), and H (48 vs. 181, P=0.005), values were not significantly different. P16 % (23 vs. 65, P=0.28) and H (58 vs. 179, P=0.064) were not significant, although I was more strongly staining for T2 (P<0.05). HER2 % (2 vs. 20, P=0.004), I (P>0.05), and H (2
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

Objective: Ovarian versus uterine serous carcinomas: Clinicopathologic and miRNA analysis

Methods: A retrospective chart review was performed on patients (pts) diagnosed with UPSC and OSC from 2001 through 2006 at our institution. Medical records, diagnostic imaging, and pathology reports were reviewed. For miRNA analysis, 47 fresh/frozen and paraffin-embedded samples of UPSC and OSC were collected. MiRNA expression profiles were evaluated by microarray analysis. Statistical analysis was performed.

Results: A total of 50 OSC and 25 UPSC patient charts were reviewed. Median age for pts with UPSC diagnosis was 67 years (range, 49-85 years) and 62.5 years (range, 45-92 years) for OSC. Median follow-up time for UPSC patients was 44 months (range, 0.1-83 months) and 24 months (range, 0.4-110 months) for OSC. Of UPSC patients, 25 (100%) underwent surgical debulking, 20 (83%) received chemotherapy, 44 (92%) received radiation therapy, and 22 had no residual disease. Overall median survival was 25 months (range, 5-79 months), with a 74% 1-year and 26% 5-year survival period. Stages 3 and 4 median survival was 20.5 months (range, 5-79 months), with a 69% 1-year and 19% 5-year survival period. Among OSC pts, 49 (98%) underwent surgical debulking, 44 (92%) received chemotherapy, 3 (6%) received radiation therapy, and 37 had no residual disease. Overall median survival was 20 months (range, 0.4-110 months), with an 88% 1-year and 23% 5-year survival period. Survival stratified by PTEN & PIK3CA dual mutations.

Conclusions: Initial findings suggest that UPSC and OSC have similar clinicopathologic features and a comparable poor 5-year survival rate. Similar to previous studies, this poor 5-year survival rate may likely be due to acquired chemotherapy resistance. MiRNA analysis suggests that these tumors are different biologically, and that although clinical data show similarities between the 2 diseases, their mechanisms of action and susceptibilities may, in fact, differ. More needs to be understood about the biology of these tumors to select better treatment options and, thus, improve overall survival.

216
A uterine-specific PIK3CA and PTEN dual mutation signature is associated with poor prognosis

Objective: To evaluate clinical results from broad-based mutational profiling conducted across all major cancer groups to identify a clinically relevant mutational signature distinct to endometrial cancer.

Methods: Mutational profiles obtained from endometrial cancer patients were compared to those from other cancer disease sites that underwent clinical tumor genotyping at our institution. An additional retrospective cohort consisting of 100 uterine tumors was subsequently evaluated. Statistical analysis was performed with y2 tests. Kaplan-Meier curves were generated to calculate survival estimates.

Results: A total of 4,359 patients undergoing clinical mutational profiling across primary cancer sites were evaluated for disease-specific molecular signatures (lung, n=1299; gastrointestinal, n=888; brain, n=456; breast, n=300; head and neck, n=123; gynecologic, n=201; skin, n=96; other sites, n=996). From this group, we identified 42 patients with endometrial cancer who underwent physician-requisitioned clinical tumor genotyping from 2008 through 2012. This endometrial cohort was composed of recurrent or refractory patients with advanced-stage (53%) and high-grade (78%) disease. A distinct endometrial signature consisting of concurrent mutations in PIK3CA and PTEN was observed in 12% (n=5) of these patients. This signature was observed in only 2 additional cancer samples from other disease sites, leading to a significant overrepresentation in endometrial cancers (P <0.001). While concurrent PIK3CA/PTEN mutations in endometrial cancer were found across grade (grade 1, n=2; grade 2, n=2; grade 3, n=1), this signature was associated with a dramatically decreased overall median survival time of 2 vs. 6 years (logrank P<0.03) (Figure). Genotyping analysis of a retrospective endometrial cancer cohort (n=100) treated in 2006-2011 and representing the spectrum of histologies confirmed a 3% prevalence of this signature that was associated with a decreased progression-free survival (P<0.04).

Conclusions: These data suggest that tumors with activating mutations in PIK3CA in concert with inactivating mutations in PTEN are largely specific to endometrial tumors and are associated with poor prognosis, regardless of tumor grade. Rapid identification of affected patients may expand therapeutic options for this subset by directing them to the most appropriate targeted therapies.
217
Achievable balanced costs in ovarian cancer screening using serial transvaginal ultrasound by preventing progression
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Objective: The prevalence of ovarian cancer, which is about 7 times lower than breast cancer, is considered a limitation to screening. However, the prevalence issue is really a cost issue. This report focused on the cost of screening and the achievable savings from preventing progression using data from the Kentucky Ovarian Cancer Screening Program.

Methods: A total of 39,337 women received 221,576 screens from 1987 through 2012, during which time screening produced 86 true-positives and 472 surgical false-positives. By limiting analyses to 36 early-stage epithelial ovarian cancers and eliminating 6 early-stage cases that might be identified without screening, an analysis was made that considered: 1) The cost of care for these 30 cases if allowed to progress to stage III ovarian cancers in 2011 dollars, 2) unit screen cost, 3) screen equivalents represented by stage III care, and 4) the expenses placed on the healthcare system by the 472 surgical false-positives. These factors were used to determine the net number of screens afforded by preventing progression.

Results: A total of 221,576 screens were performed, and the cost of 85% to 99% of these would be offset by preventing progression to stage III disease at a $40 cost/screen. This offset fell below 10% using a Medicare reimbursement of ~$150. Considering the reported value of life lost due to ovarian cancer ($1.8 million for each of the 15,500 women who will succumb to ovarian cancer in 2012 [J Natl Cancer Inst. 2008;100:1755–1762]), the cost of 46,500 screens would be recovered by preventing a single ovarian cancer death. By itself, the value of life lost more than compensates for the cost of ovarian screening using transvaginal ultrasonography and would provide 1,395,000 screens by avoiding ovarian cancer death in the group of 30 cases considered here, which is ~6 times more than the number of screens used for this analysis.

Conclusions: These analyses indicated that ovarian screening expenses can be in balance with savings from preventing progression.

218
The role of endocervical curettage with colposcopy in HIV-positive (+) patients as compared to HIV-negative (-) patients: A retrospective analysis of 2,591 colposcopic visits from the Women's Interagency HIV study
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Objective: To determine if performing an endocervical curettage (ECC) in HIV-positive patients significantly increases the detection of cervical intraepithelial neoplasia (CIN) II, III, adenocarcinoma in situ, or invasive carcinoma that is otherwise missed by cervical biopsy alone.

Methods: The multisite Women's Interagency HIV Study (WHIS) enrolled 2,625 patients (2,056 HIV+ and 569 HIV-) in 1994 and 1,143 patients (737 HIV+ and 406 HIV-) from 2001 through 2002. Patients were followed at 6-month intervals. Visits were excluded if both ECC and cervix biopsy were not performed or if the antecedent Pap test was >1 year from colposcopy. From study entry until March 2012, ECC and cervical biopsy results from 2,591 colposcopic visits (2,241 HIV+ and 350 HIV-) were extracted from a centralized WHIS database. A positive ECC or cervical biopsy was defined as detection of CIN II or higher. Agreement between cervix biopsy and ECC was determined by Cohen's kappa coefficient. Multiple regression analysis was performed to account for predictors of a positive ECC.

Results: For both HIV+ and HIV- women, the agreement between ECC and cervical biopsy was 88.6%, with a Cohen's kappa coefficient of 0.24 (95% CI 0.18, 0.31) indicating a fair correlation. The mean age of patients was 38 years (range, 18 to 66 years). The mean CD4 count and viral load in the HIV+ group was 357 cells/mm3 (range, 0-1,923 cells/mm3) and 92,907 copies/mL (range, 48 copies-8.3 million copies/mL). The overall rate of detection of CIN II or higher increased from 10.5% to 13.4% based upon ECC findings or a relative increase of 28%. The addition of ECC to cervix biopsy led to a 2.9% absolute increase in detecting CIN II or higher. Based on multiple regression analysis, the estimated probability of a positive ECC from HIV+ visits and HIV- visits was not found to be significantly different (P=0.121). After controlling for HIV status, age, smoking status, and sexual history, the probability of a positive ECC given a negative cervical biopsy was 2.1% (95% CI 0.014, 0.032). A subanalysis of 1,454 satisfactory colposcopies where ECC was performed revealed a 2.0% probability of having a positive ECC given a negative cervix biopsy and 11.9% probability given a positive cervix biopsy (P <0.001).

Conclusions: Based upon WHIS data, ECC yields minimal diagnostic information compared to cervical biopsy alone. A positive ECC did not appear to correlate with HIV status. Clinicians should adhere to general colposcopic guidelines for ECC performance when treating HIV+ patients.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

Pre-operative imaging of granulosa cell tumors in combination with CA-125 as a predictor of malignancy

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Objective: To determine the radiographic characteristics of ovarian granulosa cell tumors (GCT) on preoperative imaging and to evaluate the use of CA-125 levels >35 in combination with imaging as an algorithm for accurate preoperative diagnosis.

Methods: A retrospective analysis of patients diagnosed with ovarian GCT from January 1998 through August 2012 from 2 academic hospitals was conducted. Clinical data included tumor appearance on preoperative imaging (either computed tomography [CT] scan or ultrasound) and CA-125 levels. Demographic data included age, race, and body mass index (BMI). Ovarian cysts were defined as complex if imaging exhibited multicystic areas, hemorrhagic, solid, or cystic and solid components. A CA-125 level >35 was considered abnormal.

Results: A total of 115 patients were diagnosed with GCTs at the time of surgery. Sixty-three were identified with preoperative imaging (CT scan, ultrasound, or both). Median age at surgery was 46 years (range, 12-87 years). The mean BMI was 30.6 (range, 16.2-51.7). Thirty-one patients were African American, 26 Caucasian, 4 Hispanic, and 2 listed as other. Forty-six (63%) patients had preoperative ultrasounds, 42 (66%) had CT scans, and 21 (33%) had both imaging modalities. GCTs were most commonly classified as complex cysts in 57 (90.5%) patients. The most common morphology was solid and cystic (n=44 [70%]). Forty-four (71%) patients had tumors >10 cm. Forty-two patients had a preoperative CA-125 levels for evaluation. Eighty-four (43%) patients had complex masses paired with a CA-125 >35. Twenty patients (48%) had a CA-125 <35 in the presence of a complex mass. The remainder (7%) had simple cysts with a CA-125 <35 or simple cysts with a CA-125 >35 (2%).

Conclusions: In this study, ovarian GCTs were described as large and solid and cystic based on preoperative imaging. There was a near-equal distribution of patients with complex masses and CA-125 levels greater than or less than 35. If complexity and a CA-125 level >35 are used to predict GCTs, we will frequently fail to make the diagnosis preoperatively. Additional studies are needed to generate an algorithm, perhaps including inhibit levels, that can more accurately predict GCTs in these patients before surgery and help guide appropriate preoperative referral to a gynecologic oncologist.

Risk-reducing salpingectomy at the time of benign hysterectomy and permanent sterilization: A survey of obstetricians/gynecologists

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Objective: Recent data from risk-reducing salpingectomy and oophorectomy (RRSO) in patients with BRCA mutations suggest that ovarian cancer may arise in the fallopian tube (FT). This offers a new avenue for preventive strategies in the general population, including salpingectomy at the time of benign hysterectomy or permanent sterilization. The objective was to study the willingness to offer risk-reducing salpingectomy (RRS) among general obstetricians/gynecologists.

Methods: A voluntary and anonymous survey was administered to all attending physicians and residents in obstetrics/gynecology at an urban academic and affiliated community hospital in 2012. The survey instrument assessed provider demographics and knowledge about ovarian cancer prevention. Providers were given a brief summary that included the findings from the RRSO studies and emerging scientific data that FT epithelium is the primary site of serious ovarian cancer. Providers were then surveyed on willingness to offer RRS at the time of hysterectomy or permanent sterilization to patients who would otherwise undergo ovarian conservation. Continuous variables were compared using the Student t test and categorical variables using the χ2 and Fisher’s exact test.

Results: Ninety-one providers completed the survey for a 75% response rate. Seventy percent of surveyed physicians were aware of the literature suggesting that ovarian cancer may arise in the FT. After reading a summary of the available data, significantly more physicians were willing to offer RRS at the time of hysterectomy than at the time of permanent sterilization (80% vs. 55%, P<0.05). Willingness to offer salpingectomy at the time of permanent sterilization was associated with younger provider age (92% 20-30 years, 52% 31-40 years, 43% 41-50 years, 67% 51-60 years, 33% in >60 years, P=0.02) and greater provider surgical experience (43% of providers performing ≥25 hysterecomies per year vs. 91% of those performing >25, P<0.005). Only prior awareness of the mortality impact of ovarian cancer was associated with RRS at the time of hysterectomy (P=0.04).

Conclusions: Our data suggest that obstetricians/gynecologists will offer RRS at the time of benign hysterectomy in those women who elect ovarian conservation. However, providers are less willing to offer RRS at the time of permanent sterilization, and the level of surgical experience affects the likelihood of recommending this intervention.

Retrospective analysis of glandular cells on vaginal cytology smears in women with a previous hysterectomy

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Objective: To determine the clinical significance of glandular cells on vaginal cytology following hysterectomy.

Methods: A retrospective review of women with glandular cells and atypical glandular cells on vaginal cytology after hysterectomy over the last 10 years was performed. Data collected included age; body mass index (BMI); type of hysterectomy; indication for hysterectomy; the use of chemotherapy; radiation therapy; and hormone therapy; and outcome.

Results: A total of 103 patients with 122 vaginal smears were identified with glandular cells and atypical glandular cells after hysterectomy. Of these, 99 (98%) underwent hysterectomy for malignant indications, 66 (54%) received radiation therapy, 49 (40%) received chemotherapy, and 11 (9%) received hormonal therapy for their malignancy. Mean age at diagnosis was 64 years (range, 30–89 years). Mean BMI was 32. Prior to the incident cytology, 65 (53%) women had a normal smear, and afterwards, 49 (40%) had a normal smear. Thirteen (12%) patients had atypical glandular cells on vaginal smear. Of these, 3 underwent hysterecromy for benign indication. Of our cohort, 95 (78%) were managed conservatively with repeat vaginal smear and 14 (13%) patients underwent further evaluation with biopsy, 8 with glandular cells and 6 with atypical glandular cells on vaginal smear. Biopsy results included inflammation 7 (50%), inflammation and radiation effect 1 (7%), other benign condition 4 (29%), and recurrence 2 (14%). Only 3 (3%) patients were diagnosed with recurrent disease and all had clinical evidence of recurrence. One of these developed recurrent disease 10 months after the incident vaginal smear that was diagnosed by physical examination and elevated tumor marker; she had previously been managed with biopsies that were benign. The median time from hysterectomy to vaginal smear in question was 135 months (range, 11–1,365 months). The median follow up was 36 months (range, 0–211 months). Sixty-three (52%) patients had persistent glandular or atypical glandular cells on most current vaginal smear. Twelve (10%) patients did not have follow-up documented.

Conclusions: Patients with glandular cells and atypical glandular cells on vaginal cytology smear after hysterectomy without abnormal physical examination findings can be safely managed conservatively with observation and repeat vaginal cytology smear.

Risk-reducing salpingectomy at the time of benign hysterectomy and permanent sterilization: A survey of obstetricians/gynecologists

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1New York Presbyterian Weill Cornell Medical Center, New York, NY, 2New York Hospital Queens, Fresh Meadows, NY

Objective: To determine the radiographic characteristics of ovarian granulosa cell tumors (GCT) on preoperative imaging and to evaluate the use of CA-125 levels >35 in combination with imaging as an algorithm for accurate preoperative diagnosis.

Methods: A retrospective analysis of patients diagnosed with ovarian GCT from January 1998 through August 2012 from 2 academic hospitals was conducted. Clinical data included tumor appearance on preoperative imaging (either computed tomography [CT] scan or ultrasound) and CA-125 levels. Demographic data included age, race, and body mass index (BMI). Ovarian cysts were defined as complex if imaging exhibited multicystic areas, hemorrhagic, solid, or cystic and solid components. A CA-125 level >35 was considered abnormal.

Results: A total of 115 patients were diagnosed with GCTs at the time of surgery. Sixty-three were identified with preoperative imaging (CT scan, ultrasound, or both). Median age at surgery was 46 years (range, 12-87 years). The mean BMI was 30.6 (range, 16.2-51.7). Thirty-one patients were African American, 26 Caucasian, 4 Hispanic, and 2 listed as other. Forty-six (63%) patients had preoperative ultrasounds, 42 (66%) had CT scans, and 21 (33%) had both imaging modalities. GCTs were most commonly classified as complex cysts in 57 (90.5%) patients. The most common morphology was solid and cystic (n=44 [70%]). Forty-four (71%) patients had tumors >10 cm. Forty-two patients had a preoperative CA-125 levels for evaluation. Eighty-four (43%) patients had complex masses paired with a CA-125 >35. Twenty patients (48%) had a CA-125 <35 in the presence of a complex mass. The remainder (7%) had simple cysts with a CA-125 <35 or simple cysts with a CA-125 >35 (2%).

Conclusions: In this study, ovarian GCTs were described as large and solid and cystic based on preoperative imaging. There was a near-equal distribution of patients with complex masses and CA-125 levels greater than or less than 35. If complexity and a CA-125 level >35 are used to predict GCTs, we will frequently fail to make the diagnosis preoperatively. Additional studies are needed to generate an algorithm, perhaps including inhibit levels, that can more accurately predict GCTs in these patients before surgery and help guide appropriate preoperative referral to a gynecologic oncologist.
223 Routine bilateral salpingectomy at the time of hysterectomy with ovarian preservation
V. Rodriguez-Triana1, S. Park2, M. Amneus3, C. Holschneider4
1UCLA, Los Angeles, CA, 2Olive View-UCLA Medical Center, Sylmar, CA

Objective: A growing body of evidence points to the fallopian tube as the origin of serous ovarian cancer. This study sought to evaluate a department-wide call for surgical practice change to perform routine bilateral salpingectomy at the time of hysterectomy with ovarian preservation, assessing practitioner acceptance and feasibility and impact on morbidity.

Methods: We conducted a retrospective cohort study of all women who underwent an abdominal (TAH), vaginal (TVH), or laparoscopic (TLH) hysterectomy with ovarian preservation at a single institution between January 2009 and June 2012. The proportion of hysterectomies with ovarian preservation where salpingectomy was performed was plotted over time. For morbidity outcomes, a case-control study was conducted, with cases being hysterectomy with ovarian preservation and bilateral salpingectomy. Cases were matched to consecutive hysterectomy without salpingectomy controls using a 1:2 ratio, stratified by type of hysterectomy. Demographic and clinicopathologic data were abstracted as well as the outcome measures of operative (OR) time, estimated blood loss (EBL), intraoperative or postoperative complications (c/o), and length of stay (LOS).

Results: A total of 385 hysterectomies with ovarian preservation were performed during the study period. Bilateral salpingectomy rates in those cases rose from 3.1% in 2009 to 72% in the first 6 months of 2012. Seventy-seven patients were identified as cases and 133 controls. There was no significant difference between cases and controls for patient age, race, body mass index, diabetes, American Society of Anesthesiologists score, presence and severity of endometriosis or adhesions, uterine size (overall and when stratified by type of hysterectomy), or performance of additional procedures. There was no significant difference between cases and control for any of the outcome measures (Table). The 2 intraoperative complications with TVH were a cystotomy and high EBL due to a prolapsing fibroid.

Conclusions: Our data demonstrated rapidly growing provider acceptance and feasibility of routine bilateral salpingectomy at the time of hysterectomy with ovarian preservation with no increase in surgical morbidity. Broad implementation of such practice may deserve further study as a simple means to contribute to a reduction in the development of serous ovarian cancer.

Table. Outcome Measures

<table>
<thead>
<tr>
<th></th>
<th>Abdominal Hysterectomy</th>
<th>Laparoscopic Hysterectomy</th>
<th>Vaginal Hysterectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>With (n=56)</td>
<td>W/out (n=35)</td>
<td>With (n=12)</td>
<td>W/out (n=23)</td>
</tr>
<tr>
<td>Median OR time (min)</td>
<td>178</td>
<td>180</td>
<td>199</td>
</tr>
<tr>
<td>Median EBL (ml)</td>
<td>350</td>
<td>300</td>
<td>225</td>
</tr>
<tr>
<td>Intraop c/o (n,%);</td>
<td>5 (9%)</td>
<td>11 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>Postop c/o (n,%);</td>
<td>10 (18%)</td>
<td>13 (14%)</td>
<td>2 (16%)</td>
</tr>
<tr>
<td>Mean LOS (days)</td>
<td>3.23</td>
<td>2.82</td>
<td>1.63</td>
</tr>
</tbody>
</table>

OR=operating room, EBL=estimate blood loss, c/o=complications, LOS=length of stay

224 Do updated Pap smear screening guidelines prevent the expeditious diagnosis of invasive cervical cancer?
C. Nitschmann, J. Mirkovic, T. May, S. Feldman
Brigham and Women’s Hospital, Boston, MA

Objective: Papanicolaou (Pap) screening has decreased the incidence and mortality of cervical cancer in developed countries. Revised guidelines for the screening of cervical cancer in the United States were published in 2012. Notable changes included delayed screening until age 21, screening every 3 years between 21 and 29 years of age, and the option of extending the screening interval for women ages 30-65 years to every 5 years with cytologic and human papillomavirus (HPV) testing. Increasing Pap screening intervals may increase the risk of invasive cervical cancer. We reviewed the cases of invasive squamous cell carcinoma (ISC) and invasive adenocarcinoma (IAC) of the cervix at our institution to examine how updated screening and management guidelines affected the detection and prevention of invasive cancer.

Methods: Patients diagnosed at Brigham and Women’s Hospital between 2008 and 2012 with ISC or IAC were identified. Diagnosis was confirmed by pathology review. Demographic data, screening history, and modalities utilized for diagnosis and treatment were obtained.

Results: We identified 88 patients, 71 of whom had information on prior screening history. Six patients were age ≤30 years, while 65 were age >30 years. Fifty-three patients (74.64%) had confirmed Pap abnormalities at presentation. Twenty-four patients (33.80%) were diagnosed with IAC. Forty-four patients (61.97%) carried the diagnosis of ISC while three patients (4.23%) carried the diagnosis of other. The mean time from normal Pap to diagnosis of IAC was 18 months in patients >30 years and 13 months in patients ≤30 years. The mean time from normal Pap to diagnosis of ISC was 62 months in patients >30 years and 24 months in patients ≤30 years.

Conclusions: Updated Pap smear screening guidelines may prevent the expeditious diagnosis of invasive cervical cancer. In particular, women age ≤30 years may have a higher risk of developing invasive cancer between recommended screenings.

225 Health Care Reform
Feasibility study of tubal lavage as an early ovarian cancer detection method
M. de Leon, Y. Xu, A. Hassan Hamed, G. Del Priore
Indiana University School of Medicine, Indianapolis, IN

Objective: There are no accurate methods of detecting early ovarian cancer or a premalignant condition. We performed a feasibility study of a new screening method to investigate its efficacy and acceptance by the patients.

Methods: This was a prospective cohort study of all patients diagnosed with a pelvic mass and scheduled for surgery in our institution. Consenting patients were surveyed as to their comfort with, and acceptance of, the new procedure. Pain was assessed both before and within 30 minutes following the procedure using a 10-point visual analog pain scale. Closed- and open-ended survey questions were provided to patients to elicit potential barriers and indicators of acceptance of this procedure. The procedure itself consisted of the infusion of the uterus with 20 mL normal saline through a saline infusion hysterosalpingography catheter under real-time ultrasound (U/S). Fluid passing through the fallopian tubes was then collected from the cul de sac using U/S-guided needle aspiration via posterior fornix. The fluid collected was sent for analysis.

Results: Over a period of 1-4 weeks, 28 patients were scheduled for surgery for a pelvic mass. Twenty-one met all eligibility criteria, and six agreed to participate. Pain was assessed both before and within 30 minutes following the procedure using a 10-point visual analog pain scale. Closed- and open-ended survey questions were provided to patients to elicit potential barriers and indicators of acceptance of this procedure. The procedure itself consisted of the infusion of the uterus with 20 mL normal saline through a saline infusion hysterosalpingography catheter under real-time ultrasound (U/S). Fluid passing through the fallopian tubes was then collected from the cul de sac using U/S-guided needle aspiration via posterior fornix. The fluid collected was sent for analysis.

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226
A new model for provider/insurer relations in gyn oncology
P. Timmins1, K. Panneton2
1Women's Cancer Care Associates, Albany, NY, 2Capital District Physicians Health Plan, Albany, NY

Objective: With the dramatic changes occurring and anticipated in healthcare financing, we endeavored to develop a new relationship model between a private practice gynecologic oncology group and a nonprofit physician-owned health plan.

Methods: Our assumption was that the standard fee-for-service model was becoming obsolete and was inefficient, adversarial, and costly. The hypothesis was that through open consistent communication, a modified capitation payment framework, and a risk-reward structure, we could both enhance the practice's efficiency and revenue and begin to control costs in a meaningful manner that had implications for other specialty practices. The payment model involved examining data from both the health plan and our own electronic data collected over the previous 4 years since introduction of an electronic medical record. We agreed upon an annual per patient cost, which was paid monthly based on historical numbers of patients with a 10% risk window. Above that threshold, further payments would be made. The capitation was for all surgical and office visits and only excluded drug costs. We also agreed upon a survey instrument that the health plan would administer to obtain patient satisfaction data, and we developed a shared savings plan based on identifiable metrics such as emergency department admissions, high-tech imaging, and prevention of short-stay hospital admissions.

Results: After 1 year, both parties felt that the new arrangement was successful enough to renew for another year. It has met the practice's primary goals of improved efficiency, stable revenue structure, and an open two-sided communication strategy with a health insurer. Due to significant increases in patients seen and projections of this trend continuing, the risk window was narrowed to 5%. Practice-wide adjustments, such as increasing patient visits for hydration instead of triaging patients to the emergency department, as well as increased generic drug usage have led to cost savings. Patient satisfaction in terms of quality of care remains very high with this new payment model.

Conclusions: We believe that we have shown through our demonstration project that payment arrangements other than traditional fee-for-service can be implemented in a private practice in such a way to achieve stable revenue for the practice, while actually improving the cost structure for a health plan.

227
Can molecular profiling increase the ability to provide cost effective health care in gynecologic oncology?
A. Walter, K. Wood, K. Manahan, J. Geisler
University of Toledo Medical Center, Toledo, OH

Objective: As our understanding of genomics and proteonomics has increased, more specific targets for chemotherapy have been discovered. The purpose of this study was to see if using tests to obtain a specific tumor's molecular profile could help provide more cost-effective care for women with ovarian cancer.

Methods: A decision model was developed based on Gynecologic Oncology Group (GOG) protocol 182. Regimen I is 8 cycles of carboplatin (C)/paclitaxel (P) (CP). Regimen II is 8 cycles of CP with gemcitabine (G) (CPG). Regimen III is 8 cycles of CP with 3 cycles of pegylated liposomal doxorubicin (D) (CPD). Regimen IV is 4 cycles of CG followed by 4 cycles of CP (CGCP). Regimen V is 4 cycles of C/topotecan (T) (CT) followed by 4 cycles of CP (CTCP). Parameters analyzed included overall survival (OS), cost, and complications. Sensitivity analyses were performed. Base cost of profile was $3,550. Base survival increase was 30% from the literature for using regimens based on correct targets. A willingness to pay threshold of $50,000/quality-adjusted life year (QALY) was used.

Results: Using the base case analysis, the incremental cost-effectiveness ratio (ICER) for CP versus CPD was $80,415/QALY gained, which dominated all other regimens. If a molecular profile demonstrated that a tumor had low ERCC1 expression and low PGP expression, the patient’s tumor would potentially benefit from treatment with CP, which dominated all other therapies. If the molecular profile instead suggested the use of CPD, CPG, CGCT, or CTCP, the ICERs changed from dominated to $11,334, $14,113, $15,706, and $8,721/QALY, respectively. Even with as little as a 10% gain in survival, using a molecular profile to choose therapy was cost-effective for CPD and CTCP.

Conclusions: Recent advancements have allowed us to understand the genes and/or proteins that are targets for various chemotherapy agents. Using a molecular profile to determine a patient’s therapy can be potentially cost-effective. With GOG 182 as a reference, use of a molecular profile to determine therapy rather than random selection showed that both CPD and CTCP could be cost-effective with as little as 10% increased survival over CP. Thus, a large negative study could have potentially been positive if the drugs were chosen by indicated targets.
Patient, care, and discharge factors associated with risk of hospital readmission after surgical cytoreduction for ovarian carcinoma

Massachusetts General Hospital/Harvard University, Boston, MA

Objective: Hospital readmissions are potentially avoidable, poorly understood, and a recent target for health care reform. Information on readmissions after surgical cytoreduction for ovarian cancer is limited. Our goal was to identify the patient, care and discharge factors driving readmission in this population.

Methods: All patients at our institution with stages II-IV ovarian cancer who underwent debulking between 2003 and 2011 were identified. A retrospective chart review extracted relevant clinical variables (Table). Linear and logistic regression was used to correlate these variables with risk of readmission.

Results: A total of 460 patients were included in the analysis. Mean patient age was 61 years, with 1.2 systemic comorbidities. The majority had serous histology and 87% (n=401) presented at stage III or higher disease. Eight-one percent (n=373) were optimally cytoreduced to <1 cm of disease; 50% (n=233) underwent a bowel resection and/or radical upper abdominal procedure. Average length of stay was 8.62 days (range, 2-55 days). Perioperative complications were frequent and observed in 148 patients (32%); the most common were cardiopulmonary events, infection, and small bowel obstruction/ileus. Of the entire cohort, 55 (12%) were readmitted within 30 days. There was no difference in age, stage, grade, histology, estimated blood loss, or optimal debulking status between patients who were readmitted and those who were not. Neither increasing surgical radicality did not (P=0.54) nor number of comorbidities (P=0.28) increased the risk of readmission. Multivariate analyses suggested that only reoperation (odds ratio [OR] 10.74, 95% CI 3.4-34.2) and cardiopulmonary events (OR 3.15, 95% CI 1.4-7.1) were associated with an increased risk of readmission. Patients who were discharged with a visiting nurse were just as likely to be readmitted as those who went home without any services (OR 1.03, 95% CI 0.55-1.8), even when controlling for age, comorbidities, and perioperative complications (OR 0.78, 95% CI 0.42-1.43).

Conclusions: Readmission after cytoreduction affected 12% of our population. Of all variables, only perioperative complications, particularly reoperation and cardiopulmonary event, were linked to an increased risk of readmission. Furthermore, discharge with home nursing services did not have any significant impact on the risk of readmission. This analysis was unable to identify any preoperative or intraoperative factors that could predict readmission and underscores the need for prospective studies.

**Table. Clinical Variables Included in Analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age</th>
<th>Comorbidities</th>
<th>Stage</th>
<th>Grade</th>
<th>Histology</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61</td>
<td>87%</td>
<td>25</td>
<td>0.28</td>
<td>2</td>
<td>0.03</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td>Estimated blood loss</td>
<td>Placement of intraperitoneal catheter</td>
<td>Surgical procedures performed</td>
<td>0.02</td>
<td>Readmission diagnoses</td>
</tr>
<tr>
<td>Grade</td>
<td>0.67</td>
<td>Optimal debulking status</td>
<td>Readmission diagnoses</td>
<td>Postoperative complications</td>
<td>Discharge with nursing care</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>0.05</td>
<td>Pelvic ultrasound</td>
<td>Adnexal ultrasound</td>
<td>Postoperative interventions</td>
<td>Discharge to rehabilitation</td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>0.03</td>
<td>Time to first postoperative appointment</td>
<td>Discharge to rehabilitation</td>
<td>Time to surgery</td>
<td>0.03</td>
<td></td>
</tr>
</tbody>
</table>

231 Referral patterns and association with excessive imaging and delays to surgical treatment among patients with gynecologic malignancies

G. Miroshnichenko¹, R. Kupets¹, L. Paski²
¹University of North Texas Health and Science Center, Fort Worth, TX, ²Sunnybrook Odette Cancer Center, Toronto, Ontario, Canada

Objective: To study the patterns of imaging by gynecologists and non-gynecologists (family physicians and others) following a pelvic ultrasound in women aged 45 years and older before a surgical intervention.

Methods: Provincial databases of health-care utilization were linked to establish patterns of imaging and surgical outcomes between 2006 and 2008. Women 45 years and older without any surgical or imaging history were included in the study.

Results: A total of 193,261 women met the inclusion/exclusion criteria. Of those, 19,125 underwent a laparotomy and 18,632 women underwent surgery for a gynecologic indication. Eighty-seven percent of women had imaging initiated by a non-gynecologist, with the reminder initially imaged by a gynecologist. Comparing percentages of further imaging incurred by patients as categorized by initial imaging physician, non-gynecologist vs. gynecologist, additional imaging differed as follows: repeat pelvic ultrasound 42% vs. 24%; abdominal ultrasound 30% vs. 12%; computed tomography (CT) scan abdomen/pelvis 13% vs. 4%; and magnetic resonance imaging (MRI) pelvis 4% vs. 1.5%. Time to surgery also increased in malignant cases when imaging ordered: uterine malignancy mean time to surgery with pelvic ultrasound alone was 138 days vs. 213 days when CT scan and MRI were ordered; for malignant adnexal disease, time to surgery increased from 100 days to 180 days (P=0.001).

Conclusions: There is an important discrepancy between gynecologists and non-gynecologists with regard to patterns of imaging involving gynecologic pelvic pathology and pelvic gynecologic malignancies in particular. Educational interventions are needed to reduce potentially unnecessary imaging tests, which lead to treatment delay of serious underlying conditions, including cancer.
Racial disparities and patterns of ovarian cancer surgical care in California

F. Liu, R. Bristow
UC Irvine Medical Center, Orange, CA

Objective: To investigate differences according to racial classification in ovarian cancer-related surgical procedures and in access to high-volume medical centers among women undergoing initial surgery for ovarian cancer.

Methods: The California Office of Statewide Health Planning and Development database was accessed for women undergoing a surgical procedure that included oophorectomy for a malignant ovarian neoplasm between 1/1/06 and 12/31/10. Multivariate logistic regression analyses were used to evaluate odds ratios (OR) of selected surgical procedures and access to high-volume hospitals (≥20 cases/year) and academic medical centers according to racial classification. Analyses were adjusted for disease-related characteristics and medical morbidity.

Results: A total of 8,573 patients were identified who underwent a primary surgical procedure that included oophorectomy for a malignant ovarian neoplasm. White=5,488 (64.0%), African-American=309 (3.6%), Hispanic/Latino=1,540 (18.0%), Asian=907 (10.6%), and Other=329 (3.8%). White patients served as reference for all comparisons. All minority ethnic groups were statistically significantly less likely to undergo important ovarian cancer-specific surgical procedures compared to White patients.

Conclusions: The use of RB may serve as a predictive indicator for prediction of FDA approval. Additionally, the RB of drugs has not significantly improved.

Hereditary Cancers

234 Timing of genetic counselling in patients with ovarian, fallopian tube, or primary peritoneal carcinoma

Washington University School of Medicine, St. Louis, MO

Objective: To describe the timing of genetic counseling (GC) for patients diagnosed with epithelial ovarian, fallopian tube, or primary peritoneal cancer and to assess patients’ opinions of the optimal timing of GC and genetic testing (GT) in relation to their cancer diagnosis, treatment, and recurrence.

Methods: Patients with ovarian cancer or a related disease were managed between January 2010 and December 2011 by a certified genetic counselor and were identified from encounter logs. An introductory letter, consent form, and written questionnaire were mailed to all women to gather information regarding the factors influencing the timing of GC and GT as well as patient’s opinions regarding optimal timing to offer GC and to schedule GC. The medical records of consenting patients were reviewed to collect relevant demographic and clinical data. Descriptive data were reported from contingency tables.

Results: Of 46 consenting women, 44 underwent genetic testing, and 80% had ovarian, 4% had fallopian tube, and 15% had primary peritoneal carcinoma. Nine (20%) patients were found to have a genetic mutation. The median age at the time of GC was 58.9 years (interquartile range [IQR] 52.3-64.7 years), and the median time between surgery and genetic counseling was 1 year (IQR 0.3-4.1 year). Approximately 50% of responders underwent GC at the time of recurrence. Women lacked consensus about the optimal time for GC referral, with 15% preferring before surgery, 22% after surgery but before chemotherapy, 22% during chemotherapy, and 28% after chemotherapy. Similarly, women’s opinions varied as to the best time for GC, including before surgery (11%), after surgery but before chemotherapy (18%), during chemotherapy (24%), and after chemotherapy (40%). More than half the women said they were comfortable receiving the GT results by phone, but one third of responders considered an office visit to be the preferred setting to disclose GT results.

Conclusions: Patients views regarding the best time to be referred for and to undergo GC vary greatly. Due to the high mortality of this disease, clinicians should discuss referral for GC early and personalize the timing of the referral to their patients’ desires. While many patients are comfortable receiving their results over the phone, the subset of patients who prefer an office visit should be identified at the time of their initial GC.
235 Evaluation of immune function in patients with hereditary cancers
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1University of Louisville, Louisville, KY, 2Naval Medical Center San Diego, San Diego, CA

Objective: Patients with hereditary cancers have been shown to have relatively better outcomes than those with sporadic cancers. Strong lymphocytic infiltration has been reported as a characteristic of colon cancers in patients with Lynch syndrome or sporadic tumors with high microsatellite instability. The purpose of this study was to evaluate gene expression profiles for genes involved in T- and B-cell activation in patients with hereditary cancer syndromes.

Methods: Ten patients with a diagnosis of Lynch syndrome, BRCA1 mutation, BRCA2 mutation, or juvenile polyposis syndrome confirmed by genetic testing or by immunohistochemical staining of tumor were enrolled in the institutional review board-approved trial. Blood (10 mL) was drawn into heparinized tubes from study participants. Peripheral blood mononuclear cells (PBMC) were isolated by centrifugation on Ficoll-Hypaque. RNA was isolated from the PBMC’s by the Trizol method. T- and B-cell activation was studied by polymerase chain reaction array containing 84 relevant genes.

Results: Thirty-four genes were expressed significantly less than the controls in all of the 10 patients tested. Most affected genes were CCR3, CD40, CD5, CD8A, CXCR3, IL12B, TLR9, and TNFSF14. These genes are all involved in pathways related to T-cell activation. In addition, CSF-2 and IL12B were not expressed or expressed in very low levels in all of the patients. CSF-2 is involved in T-cell polarization while IL12B plays a role in Th1, Th2 differentiation. A subgroup of BRCA1 patients were characterized by the lack of expression of CD28, CD80, CD40, HDAC5, and KIF13B.

Conclusions: A pilot study of patients with hereditary cancers demonstrates that pathways related to T-cell activation may play a central role in the susceptibility and manifestation of malignancies associated with this group.

236 Screening endometrial cancer for Lynch syndrome in a Brazilian public health care system cancer center
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Barretos Cancer Hospital, Barretos, Brazil

Objective: Lynch syndrome (LS) is a hereditary cancer syndrome that increases the risk for colorectal and endometrial cancer (EC). To our best knowledge, our department is the first in Brazil with an organized screening program to select EC patients for genetic counseling in the context of the public health care system.

Methods: Our gynecologic oncology department started to screen patients systematically for genetic counseling in April 2011. Data were prospectively collected from all patients referred due EC during their first consultation. A 6-item questionnaire was employed (history of dilatation and curettage, age, other primary cancer, family history of LS-related cancer, and relatives with history of cancer before 50 years of age or with confirmed LS). Patients younger than 60 years or with at least 1 relative with LS-related cancer were contacted after completing their primary treatment to schedule an appointment at the oncogenetic department. After genetic counseling, patients younger than 60 years, those who had 1 first-degree relative with LS-related cancer, or those who had at least 2 second-degree relatives with LS-related cancer and 1 who had cancer before 50 years of age were asked to test for LS using immunohistochemistry for expression of MLH1, MSH2, MSH6, and PMS2 and a blood test for microsatellite instability (MSI).

Results: From April 2011 to February 2012, 50 patients were referred due EC. Thirty-five with endometrioid histology and 2 patients with undifferentiated tumors were screened using the 6-item questionnaire. Two (5.4%) screened patients had another primary cancer (1 colorectal and 1 pancreatic). Seventeen (45.9%) patients had first-degree relatives with LS-related cancer, and 12 (32.4%) had at least 2 second-degree relatives with LS-related cancer. Only 1 patient had a relative with cancer before age 50 years. None had a relative with confirmed LS. Median age of the screened patients was 60 years (range, 31-82 years), with 18 patients younger than 60 years. Thirty-one were screened for genetic counseling, but 3 died before the screening, 4 did not accept the invitation, and 3 did not attend the appointment. Among 11 tested women, 4 had LS with 2 having mutations in MSH2 and 2 in MSH6 genes. Among the total of cases of endometrioid EC, 10.8% had LS.

Conclusions: The application of wide criteria to screen women with EC resulted in selection of fewer than one third for genetic testing. Because 10.8% of patients received the diagnosis of LS, we can assume that the detection rate for LS was adequate in this sample.

237 Endometrial cancer screening in Lynch syndrome: Do patients report symptoms prior to diagnosis?
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Objective: With increasing awareness and testing for Lynch syndrome in patients with colorectal and endometrial cancer, an increasing number of individuals have been identified who carry germline mismatch repair (MMR) gene mutations. Current guidelines for endometrial cancer screening include annual endometrial sampling. The study objectives were to evaluate patient compliance with current screening guidelines and to evaluate symptoms before diagnosis of endometrial cancer in patients undergoing screening.

Methods: Clinicopathologic data for patients enrolled in a Lynch registry from 2007 through 2011 at a single institution were reviewed retrospectively. Data were collected from medical records as well as yearly surveys sent to patients enrolled in the registry.

Results: Of 203 patients enrolled, 113 patients with no previous diagnosis of endometrial cancer had clinicopathologic data available for analysis. Mean age at entry to the registry was 44 years (range, 19-84 years). Germline MMR mutations were found in MLH1 in 44 patients (38.9%), MSH2 in 41 patients (36.3%), MSH6 in 8 patients (7.1%), and PMS2 in 3 patients (2.7%). The remaining 17 patients (15.0%) were enrolled in the registry based on family history that met Amsterdam II criteria. Thirty-eight patients (33.6%) had a previous history of colon cancer. Eighty-four patients (74.3%) reported having at least 1 endometrial biopsy (EB) following diagnosis of Lynch syndrome. Fifty patients (44.2%) had a prophylactic hysterectomy performed, and 10 patients (8.8%) reported a hysterectomy before diagnosis of Lynch syndrome. Of the 51 patients who chose screening, only 18 patients (35.3%) reported an annual endometrial biopsy over 2 years. Five cases (4.4%) of endometrial cancer or complex atypical hyperplasia (CAH) were identified. Three cases (2.7%) of endometrial cancer were found: 2 prevalent cases and 1 incident case. In addition, of the 2 cases (1.8%) of CAH, 1 was a prevalent case and 1 incident. Only 1 of the patients (20.0%) diagnosed with cancer or CAH reported heavy bleeding, irregular bleeding, or unusual discharge before diagnosis.

Conclusions: When screening was chosen, compliance with annual endometrial biopsy was low. The majority of patients diagnosed with cancer or hyperplasia did not report symptoms before diagnosis, reinforcing the importance of screening in this high-risk population.

238 Diagnostic value of microsatellite instability analysis in uterine cavity washings to detect endometrial cancer in Lynch syndrome
A. Batg, H. Blons, C. Narjoe, M. Le Frère-Belda, P. Laurent-Puig, F. Lecuru
Hôpital Européen Georges-Pompidou, Paris, France
Objectives: To assess the feasibility of microsatellite instability (MSI) analysis in uterine washings and its diagnostic value to detect atypical hyperplasia and endometrial cancer in patients with Lynch syndrome (LS).

Methods: Prospective study in patients with LS and indication of total hysterectomy (June 2010–February 2012). Washings of the uterine cavity were performed at the beginning of surgery, using injection-aspiration of 10 mL of saline solution. Washings were analyzed for MSI. The uterus had a pathologic examination to determine its benign, premalignant, or malignant feature. Furthermore, immunohistochemistry to assess expression of mismatch repair protein and MSI analysis were performed on the tumor.

Results: Ten patients, with a median age of 51 years (range, 48–56 years), were included in the study. Indications of surgery were prophylactic surgery (n=5), endometrial cancers (n=3), and symmetrical myomomas (n=2). Final histologic report identified 5 normal specimens, 3 cases of unstable endometrial cancers, and 2 myomatous uteri. MSI analysis of uterine cavity washings was feasible and performed in all cases (10 patients). The result could not be interpreted in 1 case. All benign cases exhibited stable phenotype of uterine cavity washings. In the 3 endometrial cancers, 2 patients had instability detected in uterine cavity washings and 1 patient had an uninterpretable result. Sensitivity, specificity, positive predictive value, and negative predictive value for endometrial cancer reached all 100%.

Conclusions: We report the first 2 cases of MSI detection in uterine cavity washings in patients with MSI-positive endometrial carcinoma. This promising result suggests that molecular tests could be interesting in gynecologic screening of LS.

### Table. Comparison of Screening Strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Costs (Millions)</th>
<th>Effectiveness (Overall Survival)</th>
<th>Cost-Efficiency</th>
<th>ICER</th>
<th>Lynch Syndrome Detected</th>
<th>Colorectal Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bethesda</td>
<td>$168.8</td>
<td>279.8 months</td>
<td>$603,472</td>
<td>186</td>
<td>1,245</td>
<td></td>
</tr>
<tr>
<td>IHC</td>
<td>$190.7</td>
<td>280.3 months</td>
<td>$680,371</td>
<td>$3,361,073</td>
<td>357</td>
<td>1,186</td>
</tr>
<tr>
<td>Sequence None</td>
<td>$205.1</td>
<td>277.1 months</td>
<td>$740,285</td>
<td>Dominated</td>
<td>0</td>
<td>1,625</td>
</tr>
<tr>
<td>Sequence All</td>
<td>$208.6</td>
<td>282.0 months</td>
<td>$739,656</td>
<td>$894,580</td>
<td>450</td>
<td>909</td>
</tr>
</tbody>
</table>

Conclusions: Accuracy and diagnostic performance of diagnostic hysteroscopy appear similar with or without GA.


241
The incidence of occult cancer in specimens from patients with genetic predisposition to ovarian and fallopian tube cancer
L. Douglass1, G. Rodriguez, C. Kirschner, J. Hurteau
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Objective: To identify the incidence of occult ovarian and fallopian tube cancer in high-risk women at the time of risk-reducing salpingo-oophorectomy (RRSO) and to compare the age at diagnosis with current guidelines.

Methods: Hospital database was reviewed between January 2004 and April 2012 to identify women undergoing RRSO for either documented BRCA1/2 gene mutation or strong personal or family history of breast and ovarian cancer. A retrospective chart review was performed to obtain patient demographics, personal history of breast cancer or any other malignancy, social history, oral contraceptive (OCP) or hormone replacement therapy (HRT) use, BRCA status, detailed family history, surgical findings, and follow-up. Characteristics were compared between women with cancer and those without.

Results: Of the 124 women identified undergoing RRSO, pathology findings of occult malignancy were noted in 4. Two of the 4 specimens were consistent with metastatic breast cancer. The incident of occult malignancy was 3.2%, with the incident of ovarian and fallopian tube cancer of 1.6%. Both cases were early stages (IB, IIB), and women underwent complete surgical staging followed by chemotherapy. All peritoneal washings were negative. One premalignant finding of serous tubal intraepithelial carcinoma (STIC) was also identified. There were no differences in characteristics between women with and without cancer. The mean age at diagnosis was 49.5 years (range, 43 to 62 years), and the average follow-up for all women was 38.4 months. No post-RRSO malignancy or recurrence has been observed.

Conclusions: The incidence of occult ovarian and fallopian tube cancer in high-risk women at the time of RRSO was low at 1.6%. In our study, the age at which women underwent RRSO was almost a decade later compared to current guidelines.

242
Best practices in risk-reducing bilateral salpingo-oophorectomy: The influence of surgical specialty
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Objective: Risk-reducing BSO (RRBSO), or prophylactic removal of the adnexae in women at increased genetic risk of ovarian cancer, diminishes ovarian cancer risk. While many general gynecologists (GG) perform these procedures, some argue that they should be performed exclusively by gynecologic oncologists (GO). Crucial aspects of the procedure include attention to removing all adnexal tissue, systematic methods and processing to detect occult disease, and communication between surgeon and pathologist. After compiling a “best practices” protocol for performing RRBSO, we sought to identify how often these practices were followed and whether surgeons’ training affected implementation.

Methods: All cases of RRBSO from 2006 to 2010 at a single institution were identified. We abstracted data from the medical record, including type of surgeon and year of procedure. We reviewed operative reports to determine if pelvic washings were obtained; whether the upper abdomen, and peritoneal surfaces were inspected; and whether a retroperitoneal approach was used to skeletonize the infundibulopelvic (IP) ligament and maximize length of the pedicle. The pathology report was used to determine if the applicable preoperative diagnosis was noted and whether the entirety of the fallopian tubes and ovaries was sectioned or if only representative sections were reviewed. Fisher’s exact test and chi-square were used as appropriate to compare differences between groups (InStat, LaJolla, CA).

Results: Among 290 RRBSOs, 26 were performed by GGs and 264 by GOs. When performed by GOs, the ovaries and fallopian tubes were more likely to be completely sectioned compared with GG cases: 231/264 (88%) vs. 17/26 (65%) (P<0.003). GOs were more likely to perform pelvic washings 228/264 (86%) when compared to GGs 13/26 (50%) (P<0.0001). GOs were more likely to use a retroperitoneal approach to skeletonize the IP ligaments 172/264 (65%) when compared to GGs 6/26 (23%) (P<0.0001). GOs were more likely to include a description of the upper abdomen and peritoneal surfaces in the operative report: 228/264 (86%) vs. 16/26 (62%) of GGs (P<0.0025). The use of a retroperitoneal approach among GOs increased over the study period when analyzed by year with 14/28, 46/76, 35/69, 48/59, and 32/32 cases performed in the years 2006 through 2010, respectively (chi-square for trend, P<0.0001).

Conclusions: RRBSOs performed by GOs are more likely to adhere to best practice standards than those performed by GGs.

243
Ten-year experience with a multidisciplinary high-risk program
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Objective: The management of women at increased genetic risk for gynecologic cancer is complex. In 2001, a multidisciplinary high-risk program (HRP) was established at our institution to counsel families at risk for hereditary gynecologic cancer. Our objective was to review the characteristics of the hereditary breast and ovarian cancer population over time.

Methods: After obtaining institutional review board approval, data regarding demographics, personal and family cancer history, genetic counseling and testing, and risk management strategies were collected from all patients seen in the HRP from 2001 to 2011. These data were analyzed using descriptive statistical methods.

Results: Among a total of 499 patients, the median age was 44 years (range, 21-73 years). The most common referral source was gynecology practitioners (GYN) (42.3%), followed by self-referrals (20.2%), genetic counselors (15.2%), oncologists (9.4%), and primary care providers (PCP) (8.2%). Most patients (82.4%) had 1 visit, while 10% had 2, and 7.6% had ≥3 visits. The table provides data about patients who were offered and completed genetic testing. Of the 233 tested patients, 116 (49.8%) were found to carry BRCA mutations (68 BRCA1, 48 BRCA2). Variants of uncertain significance were noted in 6 patients (2.6%). Among 47 (9.4%) who were Ashkenazi Jewish, 32/47 (68.1%) completed genetic testing and 14/32 (43.8%) were found to carry mutations. Prior breast cancer was noted in 18% of patients; 19.6% had breast surgery for cancer treatment, prophylactic mastectomy, or both before HRP presentation. Breast cancer was diagnosed after the first visit in 2.2%. Three patients (0.6%) developed ovarian cancer after HRP presentation; all were diagnosed during risk-reducing salpingo-oophorectomy (RRSO). A total of 106 patients (21.2%) underwent RRSO; 59 (55.7%) were known mutation carriers. RRSO was performed by a gynecologic oncologist in 66% of cases. Of the 106 RRSO performed, 54 patients (50.9%) opted for hysterectomy as well. Of the 116 BRCA mutation carriers, 36 (31%) underwent RRSO, 11 (9.5%) underwent prophylactic bilateral mastectomy (PBM), and 18 (15.5%) opted for both.

Conclusions: In our HRP, more than 50% of patients were referred by GYN or PCP, while another 20% self-referred. Over the 10-year period, more patients were offered genetic testing and more patients completed testing. RRSO is chosen much more often than PBM. The rate of incidental cancer diagnosis at RRSO was low at 2.8%.
Table. Patients Offered and Completing Genetic Testing

<table>
<thead>
<tr>
<th>Genetic Testing</th>
<th>2001-2005 (n=200)</th>
<th>2006-2011 (n=299)</th>
<th>2001-2011 (n=499)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Offered</td>
<td>100/200 (50%)</td>
<td>213/299 (71.2%)</td>
<td>313/499 (62.7%)</td>
</tr>
<tr>
<td>Completed</td>
<td>65/100 (65%)</td>
<td>168/213 (78.9%)</td>
<td>233/313 (74.4%)</td>
</tr>
</tbody>
</table>

244

When you hear hoof beats, don’t forget the zebra: The role of nonserous ovarian cancer in BRCA mutation carriers
K. Ring, M. Daniels, B. Batte, K. Lu
The University of Texas, MD Anderson Cancer Center, Houston, TX

Objective: The predominance of high-grade serous ovarian carcinoma in BRCA mutation carriers has been previously documented, but recent studies suggest that BRCA mutations are confined exclusively to this histologic subtype. Our study objectives were to characterize the histologic subtypes of ovarian, fallopian tube (FT), and primary peritoneal (PP) cancers in a cohort of known BRCA1 and BRCA2 mutation carriers and to correlate with family history and cancer outcome.

Methods: Patients with ovarian, FT, or PP cancer and a known BRCA mutation were identified through an institutional genetics database. Clinicopathologic data for patients were collected through retrospective chart review. Only specimens that underwent gynecologic pathology review at our institution were included in analysis.

Results: A total of 180 patients with BRCA1 or BRCA2 mutation and ovarian, FT, or PP cancer were identified. Germline mutations were found in BRCA1 in 127 patients (70.6%), BRCA2 in 52 patients (28.9%), and BRCA1 and BRCA2 in 1 patient (0.6%). The mean age at diagnosis was 52 years (range, 28-79 years). One hundred thirty-one patients (72.8%) reported a family history of breast cancer and 66 patients (36.7%) reported a family history of ovarian cancer in a first-, second-, or third-degree relative. Fifteen patients (8.3%) reported a family history of Ashkenazi Jewish lineage. Twelve patients had stage I disease (6.7%), 11 had stage II disease (6.1%), 127 had stage III disease (70.6%), and 30 (16.7%) had stage IV disease at diagnosis. One hundred eighteen cases (65.6%) were of high-grade serous histology, while 43 (23.9%) were of mixed histology, with at least 1 component being serous. Nineteen cases (10.6%) had no serous component and included 1 endometrioid (0.6%), 2 clear cell (1.1%), 3 transitional cell (1.7%), 3 carcinosarcoma (1.7%), and 10 undifferentiated cancers (5.6%). Of the patients with nonserous histology, 11 patients (57.9%) reported a family history of breast cancer and 8 patients (42.1%) reported a family history of ovarian cancer. There were no significant differences in family history of breast or ovarian cancer, recurrence, or vital status at last follow-up in patients with serous and nonserous cancers.

Conclusions: Although the majority of patients with germline BRCA mutations and ovarian cancer were high-grade serous or mixed histologic subtypes, 10% of BRCA mutation carriers in our cohort would potentially be missed if serous histology was used as an exclusion criterion for BRCA testing.

245

Does postmenopausal risk-reducing salpingo-oophorectomy reduce the risk of BRCA-associated breast cancer?
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Objective: In addition to protecting against pelvic serous cancer, premenopausal risk-reducing salpingo-oophorectomy (RRSO) in BRCA mutation carriers is associated with a significant reduction in the risk of breast cancer. As the ovaries maintain substantial androgenic function after both natural and chemotherapy-induced menopause, it is plausible that surgical ovarian ablation after menopause may also impact the risk of subsequent breast cancer. Our objective was to determine the effect of postmenopausal RRSO on the incidence of subsequent breast cancer in women with BRCA mutations.

Methods: From 8/18/1995 through 3/21/2011, 199 postmenopausal women, with breast tissue at risk and ovaries in situ, were identified as having a deleterious BRCA1 or BRCA2 mutation and enrolled on an institutional review board-approved prospective follow-up (f/u) study. At any time following receipt of genetic testing results, participants could self-select to have an RRSO. The occurrence of new breast cancer through 6/26/2012 was obtained by annual questionnaire, telephone contact, and medical record review. For participants with prior breast cancer, only the contralateral breast was considered to be at risk. Each woman was considered to be “at risk” for all ages starting at her age at genetic testing (left censoring) until age at breast cancer diagnosis (the event of interest) or the first of bilateral mastectomy, last f/u, or death (right censoring). A left- and right-censored Cox survival analysis was performed with age as the time variable to examine the impact of RRSO on subsequent breast cancer risk. For women who elected RRSO, “survival time” was allocated to the no-RRSO group from her age at genetic testing until her age at RRSO and then to the RRSO group with left censoring at her age of RRSO.

Results: During a median f/u of 32.8 months, breast cancer was diagnosed in 18 of the 134 women who chose RRSO and in 8 of the 65 women who did not have an RRSO. A Kaplan-Meier survival plot is shown in the Figure. The age-associated Cox survival analysis suggested that postmenopausal RRSO was associated with an approximately 57% reduction in BRCA-associated breast cancer risk (HR 0.43, 95% CI 0.18-1.02, P=0.055).

Conclusions: Our study suggests that postmenopausal RRSO in BRCA mutation carriers may confer significant protection against subsequent breast cancer. Additional work toward understanding the impact of postmenopausal ovarian hormone production on BRCA-associated breast cancer risk is needed.

246

Acceptability of salpingectomy alone as risk-reducing surgery for BRCA mutation carriers
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1The University of Texas, MD Anderson Cancer Center, Houston, TX, 2Facing Our Risk of Cancer Empowered (FORCE), Tampa, FL

Objective: Based upon the adverse effects of surgical menopause and the evidence for the fimbria as the site of origin for serous carcinomas, there is interest in studying salpingectomy without oophorectomy as risk-reducing surgery for women at high risk for ovarian cancer (OC). We aimed to determine the acceptability of a study of salpingectomy among BRCA mutation carriers.
Methods: We performed a retrospective study of the results of an online survey of salpingectomy as OC prevention. This survey was conducted by Facing Our Risk of Cancer Empowered (FORCE), a patient advocacy group, for its members from October 2010 to August 2012. Women with BRCA mutations were included. Exclusion criteria were postmenopausal status, history of OC, or prior bilateral salpingo-oophorectomy (BSO).

Results: To date, 204 women completed the survey. Of these, median age was 35 years, 92.3% were white, 25.7% were Jewish, and 16.7% had a history of breast cancer (BC). Overall, 34.3% reported definite interest in a study of salpingectomy; 33.5% were unsure, and 30.4% said they would not be interested in the study. Women who reported interest in the study noted the possibility of lowering OC risk without menopause as the most compelling reason to participate (83.8%). Of the women who would not participate in a salpingectomy study, 46.6% were concerned about surgical complications, 42.2% worried about potential ovarian damage, 32.4% were planning BSO soon, and 32.8% had concerns about surgical costs. Among all women queried, 77.2% found salpingectomy followed by oophorectomy later an acceptable risk, 68% said the potential of undergoing the procedure but not lowering the risk of OC was acceptable, and 66.5% reported potential disruption of ovarian blood supply to be acceptable. Nulliparous women were more likely to find potential ovarian damage (P=0.02) and salpingectomy followed by later oophorectomy (P=0.025) unacceptable and less likely to find undergoing salpingectomy but not lowering OC risk (P=0.012) acceptable.

Conclusions: Many BRCA carriers eligible for risk-reducing surgery indicated interest in participating in a study of salpingectomy alone. Potential study risks were acceptable to most women. These findings suggest that adequate patient accrual for a clinical trial of risk-reducing salpingectomy would be possible.

247 Patterns of care for risk-reducing salpingo-oophorectomy (RRSO) for BRCA mutation carriers and subsequent surveillance
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Cedars-Sinai Medical Center, Los Angeles, CA

Objective: RRSO is the most effective strategy to reduce cancer risk in BRCA mutation carriers. Factors influencing how physicians counsel women regarding RRSO and recommendations for hysterectomy are poorly understood. We endeavored to better define practice patterns of gynecologic oncologists regarding counseling and performance of RRSO and subsequent surveillance.

Methods: A 20-item survey was emailed to all Society of Gynecologic Oncology members (n=1,100). Data were collected and analyzed using descriptive statistics.

Results: A total of 247 (22%) members responded of whom 96% were gynecologic oncologists. Half of the respondents reported that their patients always had consultation with a genetic counselor. Ninety percent of respondents (96%) always had consultation with a genetic counselor. Ninety percent of respondents (96%) had a history of breast cancer. Of these, 27 (57%) chose coordinated surgeries, 12 (26%) underwent sequential surgeries, and 8 (17%) elected against RRSO with a median follow-up time of 3.5 years (range, 1.4-11.9 years). Patients who elected coordinated surgery were 4.4 years older than their sequential peers and 10 years older than their non-RRSO peers (P=0.02). There were no significant differences in medical comorbidities or use of neoadjuvant therapy among the 3 groups. Total operating time was significantly different in each of the groups; sequential surgery patients had the longest operating times (median=8.43 hours), followed by combined surgery patients (median=7.42 hours) and patients who declined RRSO (median=3.97 hours) (P=0.0007). Estimated blood loss and total length of hospital stay were not significantly different among groups. There were 8 minor postoperative complications in the coordinated group and no complications in the sequential group (P=0.04).

Conclusions: Coordinating RRSO with breast surgery is associated with increased age and decreased total operating room time. These findings are important factors to consider in counseling this unique group of patients.

248 Comparing coordinated versus sequential salpingo-oophorectomy for BRCA1 and BRCA2 mutation carriers with breast cancer
J. Chapman1, A. Panighetti2, S. Hwang1, B. Crawford1, B. Powell1, J. Chan1, L. Chen2
1University of California San Francisco, San Francisco, CA, 2University of Washington Medical Center, Seattle, WA

Objective: Women with breast cancer who carry BRCA1 or BRCA2 (BRCA1/2) mutations must also consider risk-reducing salpingo-oophorectomy (RRSO) and how to coordinate this procedure with their breast cancer surgery. This retrospective study investigated the factors that contribute to a patient's decision to have coordinated vs. sequential surgery and compared the surgical outcomes of each.

Methods: We queried our Cancer Risk Program database for patients who had a breast cancer and a known BRCA1/2 mutation prior to undergoing breast surgery. Women who chose concurrent RRSO at the time of breast surgery were compared to those who did not.

Results: There were 47 patients who knew their mutation carrier status before undergoing breast cancer surgery. Of these, 27 (57%) chose coordinated surgeries, 12 (26%) underwent sequential surgeries, and 8 (17%) elected against RRSO with a median follow-up time of 3.5 years (range, 1.4-11.9 years). Patients who elected coordinated surgery were 4.4 years older than their sequential peers and 10 years older than their non-RRSO peers (P=0.02). There were no significant differences in medical comorbidities or use of neoadjuvant therapy among the 3 groups. Total operating time was significantly different in each of the groups; sequential surgery patients had the longest operating times (median=8.43 hours), followed by combined surgery patients (median=7.42 hours) and patients who declined RRSO (median=3.97 hours) (P=0.0007).

Conclusions: Coordinating RRSO with breast surgery is associated with increased age and decreased total operating room time. These findings are important factors to consider in counseling this unique group of patients.
Methods: From 1/1/02 to 2/28/11, all women undergoing counseling and testing for BRCA mutations at our institution were offered participation in an institutional review board-approved prospective cohort study. For the current analysis, participants were included if they personally had a diagnosis of either BC \( \geq \) age 60 years (yrs) or OC at any age, had at least one additional first- or second-degree female relative with BC \( \geq \) age 60 yrs or OC at any age, and were BRCA(-). Pedigrees were reviewed and kindreds were classified as site-specific breast (SSB) or hereditary breast-ovary (HBO). Participants were contacted via mailed questionnaire and asked to report on new cancer diagnoses since genetic testing. For women with prior BC, only the contralateral breast was considered to be at risk. If a participant had bilateral mastectomy, bilateral oophorectomy, or bilateral BC prior to receipt of genetic testing results, the relevant tissue was not considered to be at risk. For each participant with tissue at risk, woman-years at risk were calculated as the time from genetic testing to date of completion of the questionnaire. Expected cancer incidence was determined using age-specific SEER data. The rates of observed-to-expected cancers were analyzed using a Poisson distribution events test.

Results: Of 2,559 BRCA(-) women ascertained during the study period, 664 met the personal and family history inclusion criteria. Follow-up questionnaires were completed by 419 (63%) participants a median of 5.3 years after genetic testing. Among 320 women with breast tissue at risk, there were 13 new BC in SSB kindreds (3.76 expected, \( P < 0.001 \)) and 2 new BC in HBO kindreds (1.46 expected, \( P = 0.43 \) (Table). Among 347 women with ovarian tissue at risk, there were 0 new OC in SSB kindreds (0.45 expected), and 2 new OC in HBO kindreds (expected 0.10, \( P = 0.005 \)).

Conclusions: Affected women from BRCA(-) SSB kindreds were confirmed to have an increased rate of new BC but not OC. Additionally, these results suggest that BRCA(-) women from HBO kindreds have an increased risk of OC, but not BC.

### Table. Rate of Observed-to-Expected New Cancers

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Site-specific Breast Kindreds n=309</th>
<th>Hereditary Breast-ovary Kindreds n=110</th>
</tr>
</thead>
<tbody>
<tr>
<td>With breast tissue at risk</td>
<td>320</td>
<td>13 (3.76 expected, P &lt; 0.001)</td>
<td>2 (1.46 expected, P = 0.43)</td>
</tr>
<tr>
<td>With ovary tissue at risk</td>
<td>347</td>
<td>2 (0.45 expected, P = 0.11)</td>
<td>2 (0.10 expected, P = 0.005)</td>
</tr>
</tbody>
</table>

250

Is BRCA mutation screening a cost-effective strategy to improve targeted therapy in serous epithelial ovarian cancer?  
I. Scalici(1), J. Straughn(1), J. Estes(1), C. Leah(1), M. Finan(1), R. Rocconi(1)  
1University of South Alabama-Mitchell Cancer Institute, Mobile, AL, 2University of Alabama at Birmingham, Birmingham, AL.

Objective: Germ-line BRCA mutation testing is recommended for all patients with serous epithelial ovarian cancer (EOC). Screening may identify patients who would benefit from targeted therapy such as poly adenosine diphosphate ribose polymerase (PARP) inhibitors. The aim of this study was to analyze the cost-effectiveness of BRCA screening as a triage tool for targeted therapy.

Methods: A decision analysis model evaluated 4 strategies to screen serous EOC patients for germ-line BRCA mutations: 1) SCREEN ALL - patients underwent full-length BRCA analysis; 2) HIGH-RISK SCREENING - full sequencing was performed on patients who met criteria by personal or family history; 3) NO SCREENING - no patients were tested; 4) ALTERNATE SCREENING - patients were screened by a validated massively parallel sequencing approach to detect 16 genes implicated in hereditary ovarian cancer. Clinical estimates and testing probabilities were calculated from published literature. Costs were estimated from published literature and Medicare reimbursement rates. All

Results: Using a cohort of 16,000 serous EOC patients, the most cost-effective strategy was NO SCREENING, with a total cost of $563.2 million (M) and an overall survival (OS) of 56 months. Although HIGH-RISK SCREENING and SCREEN ALL were more effective (OS of 57 months), they had higher total costs. The incremental cost-effectiveness ratio (ICER) for both strategies was unacceptably high at $14.6 M and $9.8 M per life-year saved, respectively. While the most effective strategy was ALTERNATE SCREENING with an OS of 59 months and total cost of $942.7 M, the ICER was $6.0 M per life-year saved. ALTERNATE SCREENING identified the most mutation-positive patients, but incurred the highest cost due more patients receiving targeted therapy. As the cost of targeted therapy decreased from $96,750 to $24,000, ALTERNATE SCREENING dominated TEST ALL and HIGH-RISK SCREENING, making it the only acceptable alternative to NO SCREENING.

Conclusions: Currently, it is not cost-effective to offer BRCA mutation screening to serous EOC patients to direct therapy. Advances in genomic technology should accelerate the discovery of cancer susceptibility genes and increase the feasibility of evaluating multiple genes simultaneously at lower cost. It is imperative that the cost of targeted therapy be considered relative to its clinical benefit because improved recognition of inherited risk should identify more individuals who are candidates for treatment.

251

Frequencies of nonovarian cancers within the Gilda Radner Familial Ovarian Cancer Registry  
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Objective: To determine if the frequency of nonovarian cancers (NOC) within families in the Gilda Radner Familial Ovarian Cancer Registry (GRFOCR) is significantly different from the frequencies listed in the SEER database. Methods: The GRFOCR is a familial ovarian cancer registry established in 1981. The families within this national database are those with 2 or more close relatives who have a diagnosis of ovarian cancer, 3 or more cases of cancer on one side of the family with at least 1 being ovarian, at least 1 female with 2 or more primary cancers in which one is ovary, or a history of 2 or more cancers in the family with at least one being ovarian cancer diagnosed before the age of 45 years. These data were analyzed using Statistical Analysis System (SAS) to find relative rates of 10 of the most common cancers found within the database, with the exception of ovarian and breast. These include bladder, central nervous system, cervical, colorectal, liver, lung, pancreas, prostate, stomach, and uterine. These data were used to compare frequencies of the cancers within the database with that listed in the SEER 18 database. The data were further adjusted into age-specific frequencies of each cancer, as seen in the SEER database.

Results: There are 2,693 pedigrees and a total of 50,277 individuals within the GRFOCR. There are 2011 families with 2 or more relatives with ovarian cancer, accounting for 4,989 individuals with ovarian cancer. The total number of individuals with ovarian cancer is 5,613. The frequencies of the NOCs within the registry were higher than that of the general population, as described in the SEER database. In particular, the overall frequencies of cancers of the bladder, cervix, prostate, and uterus were higher within the GRFOCR at 2.3, 7.4, 25.2, and 11.9 per 1,000, respectively, vs. 1.8, 1.6, 16.4, and 3.8 within SEER. Furthermore, the data show that both cervical and uterine cancers occurred in a higher proportion at an earlier age within the GRFOCR (Table). Compared with the age-adjusted frequencies in the SEER database, our frequencies were statistically significant with a \( P \) value of \(< 0.01\) for all values.

Conclusions: The GRFOCR is a powerful, versatile platform that has proven useful for studying not only ovarian, but NOC. To further validate our findings, we will enhance our collection of information on NOC within the GRFOCR. Additional future steps will include conducting segregation analysis as well as genome-wide linkage studies on families with NOC.
Novel Surgical Techniques

252 Comparison of aortic nodes yields and metastasis rates above and below the inferior mesenteric artery in clinically low stage carcinomas
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Objective: Compare aortic lymph node metastasis identified above and below the inferior mesenteric artery when aortic lymphadenectomy is indicated in clinically early high-risk endometrial cancer, epithelial ovarian cancer, and fallopian tube carcinoma.

Methods: Included were 95 women with clinical stage I and II uterine, 34 with IB cervical carcinoma, and 34 with tubal/ovarian cancer with no gross metastatic lesions. One hundred sixty-three had bilateral pelvic lymphadenectomy, 82 had bilateral infracolonic (IM) aortic lymphadenectomy, and 71 had bilateral infrarenal (IR) lymphadenectomy. All underwent LH, bilateral salpingooophorectomy, appendectomy, and peritoneal washings for cytology with or without infracolic omentectomy. Statistical analysis was performed using independent t-test and ANOVA for comparison of means and chi-square for categorical variables.

Results: The mean age was 56 years (range, 27-90 years), mean body mass index was 28.3 (range, 17.2-50.3). There was no difference in procedures or nodal yields between the 3 primaries, so all were considered together. Lymph node metastasis was found in 34 (21%) patients: 29/163 (18%) pelvic, 18/82 (22%) IM, and 13/71 (18%) IR. Among the 29 with positive pelvic nodes, 15 (52%) had positive aortic nodes, 13 (45%) had positive IM nodes, and 11 (38%) had positive IR nodes. Among the 134 with negative pelvic nodes, 5 (4%) had positive aortic nodes, 4 (5%) had positive IM nodes, and 2 (1.5%) had positive IR nodes. Among the 17 with positive IM nodes, 13 (76%) had positive pelvic nodes and 10 (59%) had positive IR nodes. Among the 13 with positive IR nodes, only 2 had negative IM nodes, and 2 had negative pelvic nodes. Ten of 13 with positive IR nodes had high-grade endometrial carcinoma. The rate of nodal metastasis increased significantly with the number of nodes harvested (95% CI 0.093-0.26, P<0.0001). A total of 7/34 (21%) of stage IB cervical cancer patients, 23/95 (24%) stage I or II endometrial cancer patients, and 4/34 (12%) patients with ovarian/tubal carcinoma were upstaged from lymphadenectomy alone.

Conclusions: Comprehensive laparoscopic lymphadenectomy for early pelvic carcinomas is feasible, with acceptable nodal yields. Nodal metastasis was identified up to the renal vessels in 18% of cases, most often when the pelvic and inframesenteric nodes were involved. Obtaining more nodes resulted in higher rates of upstaging and more appropriately aggressive therapy.

254 Impact of obesity on surgical outcomes of laparoscopic radical pelvic lymphadenectomy for women with cervical, endometrial, or ovarian cancer
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Objective: Gynecologic oncologists performing traditional laparotomy for staging hysterecomy with radical pelvic lymphadenectomy who desire to transition to minimally invasive approaches may be deterred by the increasing rates of obesity in women today. We document the impact of obesity on surgical adequacy and complication rates from a minimally invasive approach to laparoscopic radical pelvic lymphadenecomy across the body mass index (BMI) spectrum.

Methods: Institutional review board approval was maintained at the primary hospital. Data were abstracted from medical records for all patients undergoing a laparoscopic radical pelvic lymphadenectomies for cervical, endometrial, tubal, or ovarian carcinoma from 9/1/1996 to 7/26/2012. Statistical analysis was performed using independent t-test and ANOVA for comparison of means and chi square for categorical variables.

Results: A total of 159 women underwent laparoscopic radical pelvic lymphadenecomy. The mean age was 54 years (range, 27-90 years), weight was 74 kg (range, 43-135 kg), and BMI was 28.5 (range, 17.8-50.3). At final pathology, 92 (58%) had endometrial carcinoma/sarcoma, 34 (21%) had cervical carcinoma, 30 (19%) had ovarian/tubal carcinoma, and 3 (1.9%) had endometrial and ovarian primaries. Women were stratified by obesity: 107 (67%) had BMI <29.9, 45(28%) had BMI 30-39.9, and 7(4%) had BMI>40. Complications occurred in 13 (8%) patients; 7 were reoperative, including 1 pelvic abscess, vaginal cuff bleed, ureteral stenosis, bowel obstruction, and cystotomy repair and 2 incisional hernias. Six complications were not reoperative, with 1 each subcutaneous hematoma, colotomy repair, and cystotomy repair, and 3 with pelvic cellulitis, not related to BMI (NS). The mean surgical duration for ideal/overweight was 202 minutes (NS). The mean blood loss was: 183 mL for ideal/overweight, 129 mL for obese, and 314 mL for morbidly obese (P=0.0104). Three patients required transfusion, unrelated to BMI (NS). The mean hospital stay for all BMI categories was 1.4 days (NS). The mean pelvic node yield was 23 (NS). Pelvic nodes were positive in 22/107 (21%) of ideal/overweight, 6/45 (13%) of obese, and 0/7 (0%) of morbidly obese (P=0.0001). Notably, the chance of finding positive nodes increased significantly with increasing number of pelvic nodes harvested (P=0.0001).

Conclusions: Surgeons can expect to successfully perform radical pelvic lymphadenectomy across the BMI spectrum with low complication and transfusion rates. These data affirm existing data suggesting that complete lymphadenectomy more accurately reveals nodal positivity.

253 Transperitoneal versus retroperitoneal approach for staging aortic lymphadenecomy
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Objective: Assess safety and feasibility of transperitoneal and retroperitoneal aortic lymphadenectomy up to the renal veins in early endometrial, tubal, and ovarian cancer patients.

Methods: A retrospective chart review was undertaken. Statistical analysis was performed using independent t-test and ANOVA for comparison of means and chi square for categorical variables.

Results: Seventy-two patients underwent laparoscopic hysterectomy with comprehensive staging from 12/1996 to 8/2012. A total of 30 (42%) aortic...
lymphadenectomies were performed by initial transperitoneal approach, and 42 (58%) were performed by retroperitoneal approach. Omectomy was performed in 36/72 patients, with no difference between groups. Two (4%) of the retroperitoneal approaches were converted to open procedures due to a transection of the renal artery in one patient and bleeding with loss of pneumoretroperitoneum in another. All transperitoneal approach dissections were successful. Non-reoperative complications included 1 ureteral kinking requiring stenting, 1 vaginal cuff bleed, and 1 pelvic cellulitis. Total surgical duration (includes total laparoscopic hysterectomy/bilateral salpingo-oophorectomy/appendectomy/pelvic lymphadenectomy) for the both groups was 227 minutes (NS). Mean estimated blood loss totals for the entire procedure (including hysterectomy on all) for the transperitoneal and retroperitoneal approach groups was 214 mL for each (NS). Mean length of hospital stay was 1.3 days for all patients (NS). All aortic dissections were bilateral and divided in 2 segments: from the ureter up to the inferior mesenteric artery and from the inferior mesenteric artery up to the renal veins. There was no difference in nodule yields by approach (Table).

Conclusions: Aortic inframesenteric and infrarenal lymphadenectomy are both essential for patients with early endometrial, tubal, and ovarian carcinoma and were safely accomplished in 97% of cases, with 6% positive at each level. Both approaches yielded an equal number of nodes, although there was a trend for more nodes to be removed on the left by the retroperitoneal approach.

Table. Nodal Yields

<table>
<thead>
<tr>
<th>Right</th>
<th>Left</th>
<th>Total</th>
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<tbody>
<tr>
<td>Mean # nodes (%)</td>
<td>Mean # nodes (%)</td>
<td>Mean # nodes (%)</td>
</tr>
<tr>
<td>Transperitoneal</td>
<td>Retroperitoneal</td>
<td>Transperitoneal</td>
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<tr>
<td>(%) Positive nodes</td>
<td>(%) Positive nodes</td>
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<td>Inframesenteric</td>
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<tr>
<td>6 (8%)</td>
<td>6 (2%)</td>
<td>12 (5%)</td>
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<tr>
<td>Total</td>
<td>Total</td>
<td>Total</td>
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<tr>
<td>11 (8%)</td>
<td>13 (4.2%)</td>
<td>24 (6%)</td>
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Does IORT at the time of pelvic exenteration impact survival for patients with recurrent, previously irradiated cervical, vaginal, or vulvar cancer?

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Objective: To determine whether intraoperative electron radiation therapy (IORT) at the time of pelvic exenteration (PE) improves survival in patients with recurrent, previously irradiated cervical, vaginal, or vulvar cancer.

Methods: We conducted a single-institution retrospective chart review of all patients who had undergone pelvic exenteration. Patients with cervical, vaginal, or vulvar cancer without evidence of distant disease at the time of surgery were included. Patient characteristics, procedures performed, pathologic factors, and recurrence and survival data were collected. IORT was given using beveled cones applying 10-20 Gy delivered with 6-MeV electrons.

Results: Of the 30 patients identified, 20 (67%) had cervical cancer, 7 (23%) had vaginal cancer, and 3 (10%) had vulvar cancer. Of these, 20 (67%) received IORT with 10-20 Gy delivered with 6-MeV electrons. The mean age was 52 years (standard deviation, 11 years); patients who received IORT were slightly younger than those who did not (48 vs. 60 years, P = 0.004). Eight patients had a laterally extended endopelvic resection (LEER). Median progression-free survival (PFS) for those with no IORT/no LEER was 33 months vs. 8 months for IORT/no LEER and 12 months for IORT/LEER. Of patients who had IORT/LEER, 83% had a treatment-free interval of <24 months vs. 30% of those without IORT (P = 0.03). 50% had close <1 mm or positive margins, 75% had lymphovascular space involvement (LVSI), and mean maximal tumor diameter was 6.3 cm for both. Of the patients who had a LEER and IORT, 12.5% had positive or close margins and 50% had a treatment interval of <24 months. Of the patients who had IORT/LEER, none recurred only locally whereas 62.5% had distant ± local recurrence. Patients with no IORT/no LEER had mainly local (40%) and a few (10%) distant recurrences compared to 33% local and 42% distant ± local recurrences for those with IORT/no LEER. For the 8 patients who had a LEER (all had IORT), close <1 mm or positive margins was the only significant factor to influence survival. Median PFS and overall survival were not reached for those with no IORT and negative margins. If IORT was given, PFS was similar for patients with positive/close versus negative margins (risk ratio 0.97, 95% CI 0.30-2.77).

Conclusions: IORT at the time of PE counteracted the negative impact of positive/close margins on survival. However, patients who had a clinical indication for IORT at the time of PE had a worse prognosis compared those who did not require IORT, possibly secondary to the (lateral) extension of the tumor. If the need for IORT is anticipated, the surgeon may consider performing a LEER if cure is the ultimate goal of this radical procedure.

256

CyberKnife for single extracranial ovarian or uterine cancer metastases

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Objective: To report disease control, overall survival, and toxicity following CyberKnife for single extracranial ovarian or uterine cancer metastases.

Methods: Patients presenting with biopsy-proven single extracranial ovarian or uterine cancer metastasis, treated using the CyberKnife system, were retrospectively reviewed. A metastasis was considered single if there was no evidence of additional gross disease when CyberKnife treatment was completed. A prescribed dose of 30 to 50 Gy was delivered to the gross tumor volume (GTV) in 5 fractions. Clinical examination and imaging were performed at 3- to 6-month follow-up intervals.

Results: Twenty patients were treated over a 6-year period extending from August 2005 to August 2011: 10 with single ovarian cancer metastases (4 papillary serous carcinoma, 2 mucinous carcinoma, 2 granulosa cell tumor, 1 clear cell carcinoma, and 1 undifferentiated carcinoma) and 10 with single uterine cancer metastases (6 endometrioid adenocarcinoma, 2 carcinosarcoma, and 2 leiomyosarcoma). The metastases involved the liver (6), abdominal cavity (4), lung (4), spine (3), pelvis (2), and thigh (1). The mean GTV was 52.7 cc (range, 41.1 – 273.0 cc). The mean dose delivered to the GTV was 37 Gy (range, 30 - 50 Gy). At a median follow-up of 23 months, the 2-year Kaplan-Meier local control, disease-free survival, and overall survival estimates were 86%, 47%, and 68%, respectively. Two metastases recurred locally approximately 1 year following relatively low-dose treatment (30 Gy). Seven patients developed additional metastases. Two with second single metastases completed CyberKnife alone and 5 with multiple metastases received chemotherapy. All deaths were attributed to the development of successive metastases. No grade 3 or greater toxicities were attributed to CyberKnife in this cohort of patients.

Conclusions: CyberKnife is a well-tolerated effective local treatment option for single extracranial ovarian and uterine cancer metastases. Sixty-five percent of treated patients remained disease-free following CyberKnife treatment alone. Remission has been maintained beyond 5 years in 2 patients to date, suggesting durable local control and possibly cure. At a minimum, CyberKnife has improved quality of life by delaying chemotherapy in these patients. Whether this treatment approach is superior to metastectomy, conventional radiation therapy, or chemotherapy deserves further study.

257

First case of pregnancy following a modified Strassman procedure

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Objective: To describe a novel surgical concept, modified Strassman procedure (MSP), which may treat patients diagnosed with a placental trophoblastic tumor (PSTT) as well as preserve their fertility.

Methods: Six patients were diagnosed with a presumed solitary uterine PSTT. The temporary occlusion of the main uterine arterial supply, using either a Foley catheter under the round ligament that avoided the ovarian vessels or with vascular slings at the uterine arteries, coupled with application of vascular bulldog clips to the ovarian ligaments, allowed for uterine isolation. The abnormality was identified using intraoperative ultrasound and MRI as well as cutting diathermy for all and cold knife for the last 2 operations. Pelvic lymph node sampling was performed.

Results: Two patients remained in remission with their fertility intact, with 1 delivering a healthy term baby. Four underwent a completion hysterectomy after their fertility-sparing procedure failed due to incomplete excision of the disease, as shown by histologic margins. No residual disease was later found in 2 of these 4 uteri. This changed our practice to using cold knife and intraoperative frozen section analysis of the margins.

Conclusions: PSTTs are a rare form of gynecologic malignancy, accounting for 0.2% of all gestational trophoblastic disease (GTD). It differs from other GTD with respect to its relative insensitivity to standard chemotherapy. The standard management for localized disease is a radical hysterectomy with pelvic lymph node sampling. Performing fertility-sparing surgery in the form of a MSP has demonstrated the possibility of preserving fertility in some of these women. Our results are promising, but this treatment should only be offered after extensive counseling. The fact that 2 patients had complete excisions but with margins that were too narrow demonstrates the difficulties of performing histopathology on electrodiathermed biopsies.

258
A 10-year experience of cecal neovagina procedures for the restoration of sexual function on a gynecologic oncology service
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Objective: To describe a gynecologic oncology service’s 10-year experience with cecal neovaginas in women who desired vaginal reconstruction due to surgical removal, radiation fibrosis, or stricture formation.

Methods: Using a prospectively recorded database, 26 cases that included “neovagina” as part of the procedure were reviewed. Fourteen of these were cecal neovaginas and were selected for data evaluation. The operative technique was similar in all cases. A 15-cm segment of the cecum and ascending colon was mobilized into the pelvis on either its ileocolic or right colic arterial pedicle and anastomosed to the introitus. An ileocolic anastomosis was then performed. Perforating-fertility-sparing procedure failed due to incomplete excision of the disease, as shown by histologic margins. No residual disease was later found in 2 of these 4 uteri. This changed our practice to using cold knife and intraoperative frozen section analysis of the margins.

Conclusions: PSTTs are a rare form of gynecologic malignancy, accounting for 0.2% of all gestational trophoblastic disease (GTD). It differs from other GTD with respect to its relative insensitivity to standard chemotherapy. The standard management for localized disease is a radical hysterectomy with pelvic lymph node sampling. Performing fertility-sparing surgery in the form of a MSP has demonstrated the possibility of preserving fertility in some of these women. Our results are promising, but this treatment should only be offered after extensive counseling. The fact that 2 patients had complete excisions but with margins that were too narrow demonstrates the difficulties of performing histopathology on electrodiathermed biopsies.

259
Urologic outcomes following modified Indiana pouch during pelvic exenteration for gynecologic malignancies
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Objective: Urinary reconstruction may be a major cause of morbidity associated with pelvic exenteration. The objective of this study was to report on the urologic outcomes following the creation of a modified Indiana pouch (MIP) using a ureteral substitution segment.

Methods: We reviewed the medical records of all gynecologic oncology patients (pts) who underwent pelvic exenteration during the MIP technique between 12/2002 and 06/2012. All procedures were done by a single surgeon. The MIP was created using the standard ileocecal segment. The tapered ileum is exteriorized as a stoma. However, ureters are not directly implanted into the pouch but instead on the segment of viable ileum similar to the ileal conduit. The segment of ileum with implanted ureters is connected to the pouch as an afferent limb. This technique creates a continent pouch and allows use of nonradiated portions of ureter and ileum. The urologic complications were examined up to the last date of follow-up, graded per our institutional grading system, and categorized as early (<30 days) and late (>30 days).

Results: We identified 9 pts who received a MIP diversion. All had received prior pelvic radiation. The median age was 55 years (range, 41–69 years). The primary tumor site was: cervix, 5 (56%); vagina, 3 (33%); and uterus, 1 (11%). The type of exenteration performed was: total, 6 (67%) and anterior, 3 (33%). Intraoperative radiation therapy was used in 6 pts (67%). A neovagina was created in 5 pts (56%). The median estimated blood loss was 700 mL (range, 350–2,000 mL), and the median operating time was 671 minutes (range, 460–750 minutes). After a median follow-up of 33 months (range, 7–93 months), the following urologic complications were observed: early, grade 3: 1 pt (pouch leak) and late, grade 1: 2 pts (1 stomal stenosis, 1 difficulty with catheterization), grade 2: 1 pt (pyelonephritis), grade 3: 1 pt (pouch calculus). None of the pts developed uretero-enteral anastomotic stricture, leak, or renal failure. At the time of data retrieval, 4 pts were alive without evidence of disease, 2 were alive with disease, and 3 were dead of disease.

Conclusions: The MIP technique was associated with a low incidence of major urologic complications (1 case of pouch leak). Specifically, the absence of uretero-enteric complications in this previously irradiated population is encouraging. A larger number of pts with prolonged follow-up is needed to establish the long-term safety of this procedure.

260
Modified gluteral fold advancement V-Y flap for vulvar reconstruction after surgery for vulvar malignancies
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Objective: To assess the feasibility and complications of the modified V-Y advancement gluteral flap in vulvoperineal reconstruction among women operated for vulvar malignancies.
Methods: From December 2008 to April 2012, women who underwent excisional radical surgery for invasive vulvar cancer were considered for the study. The inclusion criteria were: vulvar cancer histologically proven FIGO stage I-IVA; performance Status (World Health Organization) <2; life expectancy >3 months; informed consent; patient compliance on follow-up. After the excisional surgery, patients were submitted to reconstructive time (group A). A bilateral or monolateral V-Y advancement fasciocutaneous flap from the gluteal fold was performed according to dimension and site of defect.

Results: The surgical results were compared to a historical group of patients (group B) with the same characteristics who did not have reconstructive time. Twenty-nine patients underwent radical surgery follow by reconstruction (group A), and they were compared to a cohort of 78 patients (group B) who underwent excisional surgery only. There were no significant differences in terms of clinical characteristics and perioperative complications between the 2 groups. The average length of hospital stay was 7 and 10 days, respectively, for group A and B (P<0.05). The mean operating time was higher in group A: 210 minutes (range 60-270 minutes) vs. 120 minutes (range, 60-125 minutes) (P<0.05). Among women with tumor size >4 cm (27 group A, 30 group B), group A had a lower complication rate (dehiscence 10% vs. 40%; incontinence 6% vs. 11%; P<0.05).

Conclusions: Vulvar reconstructive surgery using modified gluteal fold advancement V-Y flap is a safe and feasible surgical technique based on the size and location of the skin defect created by vulvar excision. Lesions >4 cm had benefits in terms of a lower rate of complications.

262
Distal pancreatectomy as part of cytoreductive surgery in patients with ovarian cancer: Morbidity and evolution of a surgical technique
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Objective: To investigate the postoperative morbidity after distal pancreatectomy as part of cytoreductive surgery in patients with ovarian, primary peritoneal, and tubal cancer.

Methods: Medical records for primary advanced or current ovarian cancer patients who were treated at the National Cancer Center between December 2000 and July 2012 were retrospectively reviewed. Postoperative outcomes of distal pancreatectomy with visceral and/or parietal peritonectomy to minimize residual tumor were reviewed.

Results: The median age of the patients was 55.6 years (range, 39.3-71.3 years). Serous adenocarcinoma was the main histology (n=29, 76.3%). Preoperative CA-125 was 1635.5 U/mL (range, 46.5-18,300 U/mL). Thirty-four patients underwent distal pancreatectomy as part of cytoreduction: 25, 8, and 1 for primary, secondary, and tertiary cytoreductive surgery (Figure), respectively. Of 34 patients, 2 (5.9%) developed pancreatic enzyme leakage requiring percutaneous drainage and delaying adjuvant chemotherapy. These cases developed in the earlier surgical experience. Better postoperative recovery in recent cases might be explained by improved surgical technique of using a minimizing touch for remaining pancreatic tissue, reinforcing the pancreatic duct, securing placement of a peripancreatic drain, and applying adequate glue.

Conclusions: Distal pancreatectomy can be incorporated with acceptable morbidity into upper abdominal cytoreductive surgery in the surgical management of ovarian cancer.
The blood supply of the remaining uterus after radical abdominal trachelectomy

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Objective: Abdominal radical trachelectomy (ART) is similar to type C radical hysterectomy, with the uterine vessels ligated at their origin from the hypogastric artery. In selected patients, selective ligation of the descending branches of the uterine artery with preservation of the uterine artery can be performed. The purpose of our study was to determine the changes of the pelvic arterial network after ART and to evaluate the relationship between the anatomy alteration and uterine function after ART by computed tomography angiography (CTA).

Methods: Between April of 2004 and August of 2012, ART was performed on 124 patients (pts) with cervical malignancies at our institution. Surgical approaches to the uterine arteries included preservation or ligation of uterine vessels (either bilateral or unilateral). A preliminary evaluation was carried out to study the vascular pattern of the remaining uterus by CTA.

Results: Two pts underwent a CTA scan preoperatively and another 11 pts were scanned during their follow-up visits. Preoperative CTA scan demonstrated patent uterine arteries and indistinct ovarian arteries using the reconstructed 3-dimensional pelvic arterial network technique (Fig. 1). On the postoperative CTA scan, ovarian arteries were found to be compensatively dilated while the uterine arteries were not visualized (Fig. 2). Of the 5 pts who preserved their bilateral uterine arteries, 1 showed a distinct left uterine artery without ovarian vessels, and the other 4 pts were noted to have absent display while the ovarian arteries were compensatorily dilated in bilateral (3 pts) or in unilateral (1 pt) vessels. For the 6 pts with ligated uterine vessels, all displayed dilated ovarian arteries bilaterally (in 4 pts) or unilaterally (in 2 pts) (Fig 3). Among the 11 postoperative patients, 1, whose uterine vessels were ligated, complained of oligomenorrhea. Her endometrium was found to be thin on ultrasound evaluation. Further evaluation of this patient noted patent cervical os and normal hormonal levels. Her CTA showed narrowing of the caudal-half of her right ovarian artery while the cranial-half of her right ovarian artery and the left ovarian artery were invisible.

Conclusions: Our preliminary study demonstrated that ovarian arteries are dilated after ART. These dilated vessels serve as the major blood supply for the remaining uterus. The patency of these ovarian arteries is important in maintaining the menstruation function of those undergoing ART.

PET probe-assisted surgical debulking in patients with recurrent gynecologic tumors

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Objective: To investigate the utility of PET probe-assisted surgical debulking for small-volume recurrent gynecologic tumors in heavily pretreated patients. Methods: Twenty-two patients from 2007-2012 with small-volume isolated recurrent gynecologic cancers were debulked using the PET probe. 18F-fluorodeoxyglucose was administered 4-6 hours before surgery. A high-energy gamma probe was used to locate the tumor intraoperatively. A tumor-to-background-ratio of 1.5 counts-per-second (CPS) and above was used for confirmation of the target lesion identified on PET CT scan performed the day of surgery.

Results: Among the 22 patients, there were 13 epithelial ovarian cancers, 5 cervical cancers, 2 uterine cancers, 1 vulvar cancer, and 1 neuroendocrine tumor. All of the patients had received prior chemotherapy, with an average of 1.8 separate lines. Ten of the 22 patients had radiation. Nine of the ovarian cancer patients were platinum-resistant, with a median overall survival of 28 months (range, 5.3-61 months). Twenty-one of the cases were operatively performed via traditional laparotomy while 1 was performed robotically. The tumors were completely removed in all but 1 case and were confirmed by both frozen and permanent sections by a pathologist. The median overall survival of all 22 patients was 19.6 months (range, 1-48 months). A total of 48 separate tumors were removed, 10 of which showed no active disease. The mean CPS of the malignant tumors was significantly higher than the tumors with no active disease 950 CPS vs. 501 CPS (P=0.0028).

Conclusions: This is the largest series to date involving PET probe debulking of gynecologic malignancies. These results show that patients with isolated small volume recurrent gynecologic tumors can potentially do well if the tumor can be accurately located and completely excised prior to adjuvant treatment, even in these heavily pretreated patients.

Estrogen receptor expression and increased risk of lymphovascular space invasion in high-grade serous ovarian carcinoma

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Objective: We have recently demonstrated that lymphovascular space invasion (LVSI) is associated with increased risk of nodal metastasis and poor clinical outcome for women with epithelial ovarian cancer. Given the suspected role of estrogen in promoting ovarian cancer metastasis, we examined potential links between estrogen receptor and LVSI in high-grade serous ovarian carcinoma.

Methods: Tumoral expression of tumor suppressor gene (p53), multidrug resistance 1 (MDR1), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), and progesterone receptor (PR) was examined for 131 cases of high-grade serous ovarian carcinoma samples obtained at primary cytoreductive surgery. DNA ploidy and S-phase fraction were also examined. Proportion expression (0-100%) and staining intensity (0-3+) were examined, and positive expression was defined as proportional expression of ≥5% and staining intensity of ≥1+. Biomarkers were examined with Spearman's correlation coefficient, correlated to LVSI (binary logistic regression) and survival outcomes (Cox's proportional hazard regression).

Results: LVSI was observed in 108 (82.4%) of all cases and correlated with stage (odds ratio [OR] 8.14, 95% CI 2.17-30.5, P<0.002). Expression of biomarkers...
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

266 How oncologists communicate information to women with recurrent ovarian cancer in the context of treatment decision making in the medical encounter

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Objective: To explore from oncologists’ perspectives: 1) the extent to which they give patients either the same or different information; and 2) any explicit or implicit criteria they use to decide whether and how to tailor the information to individual patients.

Methods: A qualitative, exploratory approach was used with gynecologic and medical oncologists in Ontario, Canada. Individual interviews were conducted, transcribed, and coded and themes identified.

Results: Fifteen gynecologic and 5 medical oncologists participated. Theme 1 involved the extent to which oncologists gave the same or different information to their patients. Theme 2 focused on the factors that influenced what information was given. Subthemes were: the oncologist’s ongoing assessment of how the patient was assimilating the information shared during the medical encounter, the oncologist’s perception of his or her relationship with the patient, and the oncologist’s assessment of what role he or she should take in decision making. Theme 3 involved the factors that influenced how information was given. Subthemes included: oncologist’s perception of the patient’s vitality; comprehension of the information, and emotional well-being; making the information relevant; patient- or family-initiated question; and competing demands for the oncologist.

Conclusions: Oncologists provide women with information on their disease status, their treatment options, and the adverse effects of treatment. The demands for the oncologist. The oncologists use perceptions to determine what information and how to provide information. The question this paper raises is whether the oncologist’s perceptions reflect the individual patient’s information and decision making needs.

268 Pretreatment assessment of primary ovarian cancer with [18F]fluorodeoxyglucose positron emission tomography/computed tomography

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Objective: To assess the diagnostic and therapeutic impact of pretreatment fluorine-18 fluorodeoxyglucose ([18F]FDG) positron emission tomography and computed tomography (PET/CT) in the pretreatment assessment of patients with primary ovarian cancer.

Methods: This retrospective study was approved by the ethics committee. One hundred thirty-four consecutive patients with suspected primary ovarian cancer were entered onto the study. Abdominopelvic CT and [18F]FDG PET/CT were performed in all patients. All findings were histologically confirmed or followed up with serial imaging studies. Correlation between parameters was calculated using Pearson’s correlation coefficient. P < 0.05 was considered statistically significant.

Results: [18F]FDG PET/CT identified a primary tumor in all patients. PET/CT detected 99 patients with pelvic and/or para-aortic lymph node metastases and had a sensitivity of 98.1%, specificity of 75.8% and accuracy of 92.5%. PET/CT also identified distant metastases (supraclavicular lymph node, lung, and liver).
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

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269
Obesity is associated with worse overall survival in women with low-grade papillary serous epithelial ovarian cancer
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Objective: To evaluate prognostic risk factors for survival in women diagnosed with low-grade serous epithelial ovarian cancer (LGSC).

Methods: A multicenter retrospective analysis of patients with LGSC was conducted. Potential epidemiologic risk factors were evaluated, including obesity, age, parity, race, smoking, history of oral contraceptive pill and/or hormone replacement therapy use, and previous hysterectomy or surgery on fallopian tubes and/or ovaries. Additional factors included stage, extent of debulking, residual disease, and disease status.

Results: Eighty-one eligible patients were identified and pathology was independently confirmed at each institution. Median age of diagnosis was 56 years (range: 21-86 years). Twenty-five percent were obese, and 90% had optimally debulked disease. Thirty-seven percent were alive, 11% with disease; 20% were dead of disease; 2% died of intercurrent disease; and 26% had an unknown status. Optimal tumor reduction (P < 0.001), obesity (P = 0.05), and body mass index (BMI) (P = 0.03) were significant univariate predictors of overall survival (OS) in Cox proportional hazards models. On multivariate analysis, optimal debulking (HR 0.03, 95% CI 0.007-0.17, P = 0.0001), and obesity (HR 2.6, 95% CI 1.04-6.6, P = 0.04) were significant predictors of OS. Unlike optimal tumor reduction (P = 0.02), neither obesity (P = 0.35) nor BMI (P = 0.31) were associated with worse disease-specific survival (DSS).

Conclusions: Optimal tumor debulking and obesity were significant predictors of OS for women with LGSC. However, obesity was not associated with worse DSS, suggesting that mortality of obese patients with LGSC may result from other comorbidities. Interventions addressing obesity may improve survival for women diagnosed with LGSC, and further study is warranted to address the role of obesity in LGSC.

270
Factors leading to racial disparities in treatment and outcomes of epithelial ovarian cancer
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Objective: Population-based studies suggest that black women have worse survival and are less likely than white women to receive standard of care for the treatment of epithelial ovarian cancer (EOC). The objective of this study was to determine factors that lead to disparities between black and white women in a National Comprehensive Cancer Network (NCCN) cancer center serving a diverse racial and socioeconomic population.

Methods: Following institutional review board approval, a retrospective review of women with EOC diagnosed between 2004 and 2009 undergoing treatment with follow-up at our institution was performed. Records were reviewed for demographics, tumor characteristics, treatment, progression-free survival (PFS), and overall survival (OS). NCCN-adherent care was defined as a combination of surgical cytoreduction and 6 cycles of taxane/platinum based chemotherapy. Chi-square and Student’s t-test were used to compare variables between groups. PFS and OS were calculated using Kaplan-Meier (KM) estimates and compared with the log-rank test.

Results: Of 369 women identified, 54 (14.6%) were black and 311 (84.3%) were white. Black women were less likely to receive NCCN-adherent care than white women (68.5% vs. 80.4%, P = 0.049). However, black women were more likely to die in the 30-day postoperative period (11.1% vs. 3.2%, P = 0.01) and when these patients were removed from analysis, NCCN-adherent care did not differ between groups (77.1% vs. 83.1%, P = 0.31). The most common reasons for not receiving NCCN-adherent care were comorbidities (47.5%), chemotoxicity (19.7%), and disease progression (13.1%). Compared to white women, black women had higher body mass index (29.8 vs. 27.8, P = 0.03), lower rates of optimal surgical cytoreduction (53.7% vs. 75.9%, P < 0.001), lower rates of intraperitoneal (IP) chemotherapy (0% vs. 9.0%, P = 0.02), and were less likely to have private or supplemental insurance (53.7% vs. 82.9%, P < 0.001). Median PFS was similar between races (12.1 vs. 14.9 months, P = 0.12), but white women had significantly higher OS (24.9 vs. 46.8 months, P < 0.001).

Conclusions: In an NCCN cancer center serving a diverse socioeconomic population, black women were more likely to die postoperatively and less likely to undergo optimal surgical cytoreduction and receive IP chemotherapy, providing some explanation for differences in survival. Further research is needed to understand the cultural, health, and tumor characteristics that contribute to these disparate findings.

271
Long-term survival outcomes in patients with advanced epithelial ovarian, fallopian tube, and primary peritoneal malignancies as related to preoperative nutritional status
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Objective: Patients with poor global functioning and nutritional status are thought to have decreased survival following the diagnosis and treatment of advanced epithelial ovarian, fallopian tube, and primary peritoneal malignancies. The purpose of this study is to evaluate the overall survival of patients with these malignancies as a function of nutritional status at the time of primary surgery.

Methods: A retrospective cohort of 253 consecutive women treated within our institution from 2001 to 2011 for advanced epithelial ovarian, fallopian tube, and primary peritoneal cancers was included in this study. Inclusion criteria were: surgical stage III or IV, age >18 years, treatment with primary surgery, at least 1 follow-up visit, and minimum 30-day survival after cancer diagnosis. Exclusion criteria were: previous malignancy, preexisting conditions affecting nutritional status, or treatment with neoadjuvant chemotherapy. Data collected included demographics, medical comorbidities, surgical details, subsequent adjuvant therapy, and survival outcomes. Surrogate markers of nutritional status were body mass index and preoperative serum levels of albumin, total protein, hemoglobin, platelets, and total lymphocyte counts. Statistical analysis was performed with SAS 9.3 software.

Results: Preoperative laboratory values were evaluated for their impact on patient survival. Serum albumin of <3.3 g/dL was not associated with decreased patient survival (P = 0.7). Similarly, total lymphocyte counts of <1,500/μL showed no association with survival (P = 0.45) nor did total serum protein of <6.2 g/dL (P = 0.78) or platelet counts of <150x10^3/μL or hemoglobin <13g/ dL. These variables also showed no significant correlation with stage, grade, or tumor histology. Multivariate analysis using Cox regression showed no correlation between overall survival and age, body mass index, or preoperative laboratory evaluations.
Conclusions: Univariate analysis of several surrogate markers for a patient’s nutritional status showed no statistically significant association between these markers, when known preoperatively, and a patient’s overall survival. Poor nutritional status is also not indicative of variations in tumor stage, grade, or histology. Multivariate analysis likewise showed no single variable that significantly affected survival.

272 Optimal but visible residual disease: Is extensive debulking warranted?

Objective: Our primary objective was to determine if the need for extensive surgery affected overall survival (OS) for patients left with ≤1 cm but visible disease. Our secondary objective was to evaluate if leaving optimal but visible residual throughout the small bowel (SB) conferred a worse prognosis, since mortality in ovarian cancer is often associated with malignant SB obstruction.

Methods: With institutional review board approval, all stage IIIB-IV ovarian cancer patients who had visible but ≤1 cm residual disease at time of primary cytoreductive surgery from 2001-2010 were identified. Standard demographic and clinical data were extracted. Extensive upper abdominal surgery (UAS) included diaphragm peritonectomy/resection, splenectomy, distal pancreatectomy, liver resection, porta hepatis resection, or cholecystectomy. Based on operative reports, residual SB serosal and/or mesenteric involvement was recorded. Operating room (OR) tumor index was scored from 0-2, with 1 point for bulky upper abdominal disease and 1 point for carcinomatosis. Kaplan-Meier and Cox regression analyses were performed.

Results: The 219 patients identified with optimal but visible residual disease had a median OS of 51 months. Of these 219 patients, 127 had extensive UAS performed, and 87 had residual disease involving the SB. Univariate OS analysis was performed on the following factors: UAS performed, SB residual disease, OR tumor index, size of residual (≤5 mm vs. 6-10 mm), age, American Society of Anesthesiologists (ASA) score, family history of breast and ovarian cancer, and stage. There was no significant difference in OS between patients who did or did not have extensive UAS (45 vs. 52 months, P=0.56) (Figure) or between patients with or without residual SB disease (45 vs. 51 months, P=0.84). Factors that were significantly associated with OS were age, ASA score, family history, and stage.

Conclusions: Optimal debulked patients with visible residual disease that required upper abdominal surgical procedures did not have a worse OS. OS was similar if residual disease involved the SB. For ovarian cancer patients with disease not amenable to a complete gross resection, extensive surgery should still be considered to achieve optimal but visible residual disease status.

273 Which is the price of an upper abdomen optimal cytoreduction for advanced ovarian cancer? Analysis of complications
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Objective: To evaluate the complication rate in patients undergoing extensive upper abdominal surgery for treatment of advanced ovarian cancer.

Methods: From January 2003 to December 2007, all patients who had undergone upper abdominal surgery during primary, interval, or secondary cytoreduction, including diaphragm stripping/resection, splenectomy, distal pancreatectomy, partial gastric resection, partial liver resection, and cholecystectomy, were considered for the study. Inclusion criteria were: diagnosis of advanced ovarian cancer (FIGO stage IIIC-IV) histologically confirmed, age >18 and <80 years, at least 1 metastasis in the upper abdomen, and Eastern Cooperative Oncology Group Performance status (Oken MM, 1982) ≤2. Intraoperative as well as early and late postoperative complications were evaluated through physical and gynecological examination, laboratory evaluation, and abdominopelvic ultrasonography.

Results: A total of 78 patients affected by FIGO stage IIIC-IV ovarian cancer were included: 35 (44.9%) had primary cytoreduction, 16 (20.5%) had interval debulking surgery, and 27 (34.6%) had secondary cytoreduction for recurrent disease on upper abdomen. One hundred thirty-seven upper abdominal surgical procedures were performed: 16 (11.7%) diaphragmatic peritonectomy, 28 (20.4%) diaphragmatic resections, 12 (8.8%) gllionian resections, 19 (13.8%) liver resections, 8 (5.8%) gastric resections, 8 (5.8%) partial pancreatectomies, 31 (22.6%) splenectomies, and 15 (11.1%) cholecystectomies. Pulmonary, cardiovascular, hematologic, gastrointestinal, and infective postoperative early and late complications were reported respectively in 20 (25.7%) and 7 (9.1%) patients, 4 (5.2%) and 2 (2.6%) patients, and 6 (7.7%) and 2 (2.6%) patients. The overall grade 1-2, grade 3-4, and grade 5 complications rate was 15.5% (12/78), 19.3% (15/78), and 1.3% (1/78), respectively. Median follow-up time was 60 months.

Conclusions: Extensive upper abdominal surgery is associated with a global postoperative complications rate of 38%, but only 20% of patients presented with grade 3-5 complications. Upper abdomen surgery for treatment of ovarian cancer is feasible and safe, with an acceptable complication rate.

274 Comprehensive epigenetic analysis of Notch pathway in high-grade serous ovarian cancer
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Objective: Gene methylation and other epigenetic modifications of gene regulation have been implicated in the growth of ovarian cancer, but the clinical significance of such modifications in the Notch pathway in high-grade serous ovarian cancer (HGS-OvCa) is not well understood. We used The Cancer Genome Atlas (TCGA) data to study the clinical relevance of epigenetic modifications of Notch pathway genes.

Methods: We analyzed the interaction of DNA methylation and microRNA (miRNA) with gene expression data for Notch family members with the Spearman rank correlation test and explored potential relationships with overall survival (OS) with the log-rank test. We downloaded clinical data, level 3 gene expression data, and level 3 DNA methylation data for 480 patients with stage II-IV HGS-OvCa from the TCGA data portal. Patients were randomly divided into training and validation cohorts for survival analyses. In each set, patients were grouped into percentiles according to methylation and miRNA or messenger RNA (mRNA) levels. We used several algorithms to predict miRNA-mRNA interaction.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

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A cost-effectiveness analysis of the adjuvant treatment of advanced epithelial ovarian carcinoma

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Objective: To compare the cost-effectiveness of current adjuvant treatments of advanced stage epithelial ovarian carcinoma.

Methods: TreeAgePro 2009 software was used to compare 4 evidence-based treatment strategies for the primary treatment of advanced-stage ovarian epithelial carcinoma: intravenous (IV) carboplatin/paclitaxel, IV carboplatin and dose-dense paclitaxel, IV paclitaxel and intraperitoneal cisplatin and paclitaxel, and IV carboplatin and paclitaxel with bevazucimab maintenance. Each treatment represents a current option based on National Comprehensive Cancer Network guidelines, and each was found to be the superior arm in a phase III trial. Progression-free survival (PFS) was the primary outcome used to compare the 4 regimens because overall survival data were not available for all the trials. In the absence of trials comparing the 4 treatments of interest, an indirect treatment comparison methodology was used to obtain useful evidence of the difference in treatment effects among the competing interventions. Cost calculations were based on drug cost from pharmacy billing information. Costs were varied over a range for sensitivity analysis. Cost-effectiveness ratios (ICER) were calculated for each treatment arm and then expressed as incremental cost-effectiveness ratios (ICER).

Results: The cost of treating one woman with IV carboplatin and paclitaxel was $700. The pooled PFS for this treatment was 15.6 months and resulted in a CER of $45 per month PFS. The cost of IV paclitaxel and IP cisplatin and paclitaxel, as given in GOG 172, cost approximately $1,250 and had a pooled PFS of 18.0 months. This resulted in a CER of $69 per month PFS and ICER of $230. The dose-dense regimen in the JGOG study cost $1,200 and resulted in a PFS of 24 months. This resulted in a CER of $50 per month PFS and ICER of $60. The bevazucimab arm in GOG 218 cost $142,000 and had a pooled PFS of 16.3 months, resulting in CER of $8,712 per month PFS and ICER of $201,857. The ICON 7 regimen cost $81,612, had a pooled PFS of 16.3 months, and resulted in a CER of $5,007 per month PFS and an ICER of $115,588.

Conclusions: IV carboplatin and dose-dense paclitaxel, as studied by the JGOG, appears to be the most cost-effective regimen. When compared to IV carboplatin and paclitaxel, it increased costs by $60 per month of PFS. IV/ IP cisplatin and paclitaxel was the next most cost-effective regimen based on ICER, costing $230 per month of PFS. Bevacucimab-containing regimens were the least cost-effective, with both ICERS exceeding $100,000.

Serous tubal vs. ovarian vs. peritoneal vs. uterine cancers - A study of 12,369 women

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Objective: Recent studies have suggested that the distal fallopian tube may serve as a site of tumor origin in those with primary ovarian, peritoneal, and uterine cancers. To further study this potential relationship, we proposed to determine the survival of patients with these cancers.

Methods: Data were obtained from the SEER of the National Cancer Institute between 2004 and 2009. Kaplan-Meier and Cox proportional hazards model were used for survival analyses.

Results: All patients had high-grade serous cancers, of which 337 were tubal (TC), 9,765 ovarian (OC), 980 primary peritoneal (PPC), and 1,347 uterine cancer (USC). The median ages of these patients were 64, 63, 68, and 70 years, respectively. The majority of patients were white (86% vs. 89% vs. 91% vs. 76%). The overall 5-year disease-specific survival was 38%. Based on tumor site of origin, the survivals of those with TC, OC, PPC, and USC were 50%, 38%, 26%, and 41%, respectively (P=0.01). In subset analysis of those with complete staging information, the 5-year disease-specific survival of stage I, II, III, and IV TC were 72%, 61%, 40%, and 23%, respectively (P=0.01); OC were 80%, 64%, 37%, and 21%, respectively (P=0.01); and USC were 70%, 52%, 32%, and 12%, respectively (P=0.01). There was no staging diagnosis available for PPC cancers. Adjusted for stage of disease, the survival of those with stage I - II were 68%
(TC), 73% (OC), and 66% (USC) and those with stage III-IV were 36% (TC), 31% (OC), and 23% (USC).

Conclusions: In this study of women with serous tubal, ovarian, peritoneal, and uterine cancers, the survival was only 38%. Those with tube cancers had better survival compared to uterine, ovarian, and peritoneal cancers. The prognostic differences in these tumor warrant further studies to evaluate molecular pathogenesis of these tumor types.

278 Comparative effectiveness of upfront treatment strategies for advanced-stage ovarian cancer

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Objective: Although a randomized trial has suggested the outcomes of primary cytoreduction and neoadjuvant chemotherapy are equivalent, the comparative effectiveness of these 2 treatments in women in the United States remains controversial. Prior observational studies have been severely limited by strong selection bias and unmeasured confounding. We used a novel statistical methodology, instrumental variable analysis, to examine the comparative effectiveness of upfront treatment strategies for ovarian cancer in elderly women.

Methods: Instrumental variable analysis (IVA) uses an exogenous factor (instrument), area of residence in the current analysis, that affects treatment choice but not outcome. Variation in the instrument (regional variation in use of neoadjuvant chemotherapy) can be leveraged to function as a quasi-randomization to overcome selection bias and confounding. Women >65 years of age with stage II-IV epithelial ovarian cancer treated with primary surgery or chemotherapy from 1991-2007 and recorded in the SEER-Medicare dataset were examined. Survival was compared using traditional multivariable analysis as well as a 2-stage IVA. An intention-to-treat analysis of all patients as well as an analysis of intended treatment (only patients who received both chemotherapy and surgery) was performed.

Results: A total of 7,583 women, including 5,345 (70.5%) who underwent primary surgery and 2,238 (29.5%) who underwent primary chemotherapy, were identified. Use of neoadjuvant chemotherapy increased over time from 19.7% in 1991 to 31.8% in 2007 (P<0.0001). Using traditional multivariate Cox modeling, women who received primary chemotherapy were 24% (HR 1.24, 95% CI 1.16-1.33) more likely to die from ovarian cancer than those who received surgery. A comparable analysis based on IVA revealed no difference in cancer-specific survival between primary chemotherapy and surgery (HR 1.05, 95% CI 0.82-1.33). In the IVA of intended treatment, patients who received primary chemotherapy were at increased risk of death (HR 1.19, 95% CI 1.08-1.32).

Conclusions: Among elderly women with advanced-stage ovarian cancer, the effectiveness of primary chemotherapy and primary surgery are similar. For women who ultimately receive both surgery and chemotherapy, a strategy of primary surgery is superior.

279 Impact of underweight after the completion of primary treatment on prognosis in patients with advanced-stage epithelial ovarian cancer

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Objective: To investigate the impact of body mass index (BMI) on prognosis in patients with advanced-stage epithelial ovarian cancer (EOC).

Methods: A total of 380 patients with FIGO stage III to IV disease were enrolled from 2000 to 2011. All patients were divided into underweight (BMI <18.5), normal weight (BMI ≥18.5 to <23.0), overweight (BMI ≥23.0 to <27.5), and obese (BMI ≥27.5) according the World Health Organization criteria for Asian populations. We compared progression-free survival (PFS) and overall survival (OS) based on the criteria of BMI at 3 points during primary treatment: at diagnosis, after surgery, and after the completion of treatment. We then investigated prognostic factors by multivariate analyses. Moreover, we evaluated the association between BMI and serum biomarkers, including CA-125 and neutrophil-to-lymphocyte ratio (NLR).

Results: Among all patients, underweight, normal weight, overweight, and obese were identified as 12 (3.4%), 160 (44.7%), 150 (41.9%), and 36 (10.1%) at diagnosis; 32 (9.1%), 177 (50.4%), 115 (32.8%), and 27 (7.7%) after surgery; and 29 (8.1%), 144 (40.4%), 155 (43.5%), and 28 (7.9%) after the completion of treatment. Underweight after the completion of primary treatment showed poorer OS than normal weight to obese groups (median, 53.7 vs. 65.5 months; P=0.02), and it was an independent poor prognostic factor (adjusted HR 2.21, 95% CI 1.05 to 4.66). In particular, 58.3% of patients who were underweight at diagnosis also showed underweight after the completion of treatment. Furthermore, underweight after the completion of treatment showed higher level of NLR (mean, 2.32 vs. 2.15; P=0.05).

Conclusions: Underweight after the completion of treatment is associated with poor prognosis and elevated systemic inflammation in patients with advanced-stage EOC. Moreover, more than half of the patients who are underweight at diagnosis may fail to gain weight after the completion of treatment.

280 Determinants of emergency department (ED) diagnosis of ovarian cancer and subsequent surgical morbidity and mortality

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Objective: The majority of patients with ovarian cancer are diagnosed in an outpatient setting. However, a subset of diagnoses is made via ED admissions. We sought to identify predictors for ED presentation among women diagnosed with ovarian cancer and to compare subsequent surgical morbidity and mortality to those diagnosed in an outpatient setting.

Methods: Information on inpatient hospitalizations was drawn from complete 2005-2009 hospital discharge files from the Healthcare Cost and Utilization Project (HCUP) for California. Our cohort consisted of all patients admitted with an ovarian cancer diagnosis who underwent initial surgery for their cancer. Our outcomes were ED admission, surgical morbidity, and inpatient mortality. We used ICD9 codes as a proxy for surgical morbidity. Our independent variables included age, race, insurance status, and cancer-associated and medical comorbidities. We performed descriptive analysis and created multivariable regression models to account for confounders.

Results: Our study population included 6,667 patients, 9.54% of whom were admitted via the ED (6.66% of the privately insured, 19.70% of Medicaid beneficiaries, 29.52% of the uninsured). Medicaid beneficiaries and the uninsured were significantly more likely than the privately insured to be admitted through the ED (adjusted odds ratio (AOR) 3.08, 95% CI 2.38-4.00 for Medicaid, and AOR 6.53, 95% CI 4.11-10.37 for the uninsured). Ascites and obstruction doubled the likelihood of ED admission. Inpatient mortality was 0.94% overall (2.83% for ED admissions and 0.75% for admissions elsewhere). Admission via the ED was an independent risk factor for inpatient mortality (AOR 2.73, 95% CI 1.51-4.94). Admission via the ED was also associated with an increased risk of having 1 or more indicators for surgical morbidity (75.31% vs. 49.69%, AOR 2.32, 95% CI 1.86-2.88). The average length of stay was 7.14 days; on average, ED admission increased the length of stay by 1.7 days (P<0.001).

Conclusions: The failure of patients with ovarian cancer to access the health-care system in a timely fashion can result in higher morbidity and mortality. Admission through the ED appears to be independently influenced by being uninsured or on Medicaid and is also associated with higher cancer-associated comorbidities and subsequent surgical morbidity and in-hospital mortality. These data suggest that limited access to medical care may negatively impact the diagnosis of ovarian cancer, resulting in poorer outcomes.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

282 The efficacy of serum multivariate markers to diagnose ovarian cancer in patients with ovarian tumor

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Objective: The development of method to distinguish women with ovarian cancer from those with benign conditions is important because most women with a clinical presentation consistent with ovarian cancer have benign conditions. The objective of this study was to analyze the concentration of serum multivariate markers and find the effective combination to diagnose ovarian cancer.

Methods: We collected serum samples prospectively, under appropriate institutional review board approval, from patients treated with ovarian tumors. A total of 398 samples, including malignant and benign ovarian tumor and normal controls, were analyzed for their ovarian cancer-specific proteins, CA-125, CA-19-9, epidermal growth factor receptor, myoglobin, tenascin C, ApoAI, ApoCIII, and c-reactive protein (CRP) by Luminess methods, which is a multiplexed immunoassay.

Results: More than half of the biomarkers tested were found to differ significantly between benign and malignant cases. The individual markers CA-125, tenascin C, and CRP provided the greatest level of discrimination between benign and malignant cases, and ApoAI was significantly decreased in malignant cases compared with benign cases. The combination of these 4 biomarkers provided a higher level of discriminatory power than either marker considered alone. Multivariate statistical analysis identified that these multimarker panels could discriminate ovarian cancers from benign cases with 83.33% sensitivity (SN), 80.00%, specificity (SP), 93.33% positive predictive value, and 87.64% accuracy. This was slightly improved SN/SP levels to the CA-125 alone.

Conclusions: We describe a blood-based assay using 4 markers that can distinguish women with ovarian cancer from those with benign conditions. Preliminary evaluation of the multimarker panels suggests it has the potential to improve the accuracy of diagnosing ovarian cancers. While promising, the performance needs to be assessed in a blinded clinical validation study.

283 Serous tubal intraepithelial carcinoma frequency in endometriosis-associated epithelial ovarian cancer

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Objective: With the discovery of serous tubal intraepithelial carcinoma (STIC), the fallopian tube has been identified as the site of origin for many serous ovarian cancers. We hypothesized that endometriosis-associated ovarian cancer would have the equivalent or lower frequency of STICs as epithelial ovarian cancer alone because its site of origin is outside the fallopian tube.

Methods: Under institutional review board approval, all patients with ovarian cancer and endometriosis treated between January 1, 1999 and August 31, 2011 were identified. Of 33 identified patients, 21 were evaluable. Samples of the patients’ fallopian tubes were obtained from the pathologic archive and examined histologically for STICs by a blinded pathologist. All questionable samples were examined by a second pathologist and stained for p53 to confirm the diagnosis of a STIC. Twenty-two age-matched samples from patients with ovarian cancer alone evaluated in the same manner served as our control group. Statistical analysis was performed using a one way ANOVA and Fisher’s exact test.

Results: Two STICs were identified: 1 in a papillary serous ovarian cancer patient and 1 in an endometrioid ovarian cancer patient with endometriosis.

The histologic distribution of the 2 groups was well matched between the patient with and without endometriosis (clear: 4 vs. 8, endometrioid: 11 vs. 7, serous 6 vs. 5, carcinomascarcoma: 1 vs. 1; P=0.52). Stage (P=1.0), grade (P=0.41), and body mass index (29.2 vs. 27.0, P=0.30) were also well-matched between patients with and without endometriosis.

Conclusions: There was no difference in the number of STICs between ovarian cancer patients with and with endometriosis. Although limited by sample size, this study shows that the STIC frequency between epithelial ovarian cancer alone and those cancers associated with endometriosis are not extremely different. It is worth noting that the 1 ovarian cancer patient with endometriosis with a STIC had an endometrioid histology that is typically not associated with STICs. Further study is needed.

284 Altered recurrence patterns after extended treatment with bevacizumab for ovarian, fallopian tube, and primary peritoneal cancer

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Objective: To evaluate patterns of recurrence in patients undergoing extended treatment with bevacizumab for ovarian, fallopian tube, and primary peritoneal cancer.

Methods: A retrospective chart review of patients with primary ovarian, peritoneal, or fallopian tube cancer treated with bevacizumab from 2001 to 2011 was performed. Qualified patients were identified by chemotherapy records. Electronic medical records, laboratory results, and imaging reports were reviewed. Clinical characteristics, CA-125 at preoperative time and at time of recurrence, radiologic studies, physical examination findings, patient report of symptoms, site of recurrence, size of largest lesions, and which clinical aspect was the first evidence of recurrence were abstracted.

Results: Of 108 patients identified, 89 patients met the criteria for the study. The most common recurrent symptoms with bevacizumab treatment were abdominal pain/bloating and ascites. Most common recurrent sites were abdominal lymph node, upper abdomen and liver, and lung. Patients who received more than 12 cycles of bevacizumab presented with fewer symptoms at time of recurrence (P=0.002) compared to those receiving 12 cycles or less. Radiologic imaging was more capable of detecting recurrence than CA-125 among patients who were treated with bevacizumab at first recurrence (P=0.006). For patients who initiated bevacizumab after their second recurrence, radiologic imaging was even more significantly associated with detection of recurrent disease than CA-125 (P=0.0001). CA-125 was not predictive for distant metastasis (P=0.19) or number of metastatic sites (P=0.36).

Conclusions: Extended treatment with bevacizumab in ovarian, fallopian tube, and primary peritoneal cancers leads to alterations in the patterns of recurrence. CA-125 may become a less reliable marker to identify recurrent disease and patients may present with fewer symptoms suggesting recurrence with prolonged treatment. As agents with novel mechanisms of action continue to be employed, the biology of recurrent disease and guidelines for cancer surveillance must continue to be reexamined.

285 Ovarian low-malignant potential tumors: The clinical value of serum CA-125

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Objective: Ovarian low-malignant potential (LMP) tumors comprise 15% of epithelial ovarian neoplasms, with a low recurrence rate and excellent survival. Serum CA-125 is often assessed but has not been well studied. The purpose of
this study was to determine the clinical value and association with recurrence of preoperative and postoperative CA-125 levels in patients with LMP.

**Methods:** After institutional review board approval, women diagnosed with ovarian low-malignant potential tumors between January 1984 and June 2003 were identified. Medical records were retrospectively reviewed for data extraction. Statistical analysis was performed for continuous and dichotomized CA-125 values.

**Results:** One hundred thirty-one women were diagnosed with ovarian LMP. Forty-nine (63%) preoperative CA-125 levels were abnormal. Collapsed tumor stage, presence of microinvasion, and staging surgery were associated with continuous preoperative CA-125. There was no association of preoperative CA-125 with recurrence, histology, or tumor size. Of 547 postoperative CA-125 values, 423 (77%) were normal and 124 (23%) were abnormal. When excluding women who had recurrence (n=8), 377 (94%) values were normal and 25 (6%) were abnormal. Eight women had recurrence. Four (50%) had abnormal CA-125 values detected before recurrence, 1 (12.5%) had normal CA-125 before recurrence, and the remaining 3 had no postoperative CA-125 recorded before recurrence.

**Conclusions:** CA-125 has clinical value in patients with ovarian LMP. Preoperatively, CA-125 is associated with early vs. late stage disease and tumor microinvasion. We advocate preoperative CA-125 testing for women with suspicious adnexal masses. The role CA-125 plays during the postoperative period may have limited clinical value. The ability to predict recurrence is not evident with preoperative CA-125 and remains unproven for postoperative CA-125.

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286 Metabolic tumor volume measured by preoperative 18F-fluorodeoxyglucose positron emission tomography and computed tomography predicts for recurrence in endometrial cancer

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**Objective:** To evaluate whether metabolic tumor volume (MTV) and total lesion glycolysis (TLG) measured by 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography and computed tomography (PET/CT) have prognostic value in patients with endometrial cancer.

**Methods:** Between 2004 and 2009, 84 patients with endometrial cancer underwent preoperative 18F-FDG PET/CT at our institution. Patients' clinicopathologic data were reviewed from medical records retrospectively (Table). We measured the SUVmax, SUVavg, MTV, and TLG of the primary tumor. Cox proportional hazards analysis were used to identify the predictors for recurrence. Receiver operating curve (ROC) analysis was used to determine the cutoff value of continuous variables for predicting recurrence.

**Results:** The median progression-free survival (PFS) duration was 48 months (range, 1-85 months). There were 12 cases of recurrence. In univariate analysis, factors predicting for recurrence were myometrial invasion (P=0.012), lymphovascular space invasion (P=0.029), lymph node metastasis (P<0.001), nonendometrioid histology (P=0.002), advanced FIGO stage (P=0.001), MTV (P=0.001), and TLG (P=0.052). However, multivariate analysis showed that only lymph node metastasis (P=0.001, HR 9.286, 95% CI 2.614-32.986) and MTV (P=0.009, HR 1.007, 95% CI 1.002-1.013) remained as independent risk factors for recurrence. The Kaplan-Meier survival graph showed that patients with a high MTV (>17.15) had a significantly lower PFS rate than those with a low MTV (<17.15; P=0.034, log-rank test) (Figure).

**Conclusions:** MTV measured by preoperative 18F-FDG PET/CT was an independent prognostic factor predicting for recurrence in endometrial cancer. This functional tumor parameter may be considered to plan further treatment and follow-up after operation.

### Table. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>84</td>
</tr>
<tr>
<td>Median age at diagnosis, year (range)</td>
<td>51 (24-76)</td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
</tr>
<tr>
<td>I (%)</td>
<td>58 (69.0)</td>
</tr>
<tr>
<td>II (%)</td>
<td>11 (13.1)</td>
</tr>
<tr>
<td>III (%)</td>
<td>13 (15.5)</td>
</tr>
<tr>
<td>IV (%)</td>
<td>2 (2.4)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Endometrioid (%)</td>
<td>63 (75)</td>
</tr>
<tr>
<td>Papillary serous (%)</td>
<td>10 (11.9)</td>
</tr>
<tr>
<td>Carcinosarcoma (%)</td>
<td>9 (10.7)</td>
</tr>
<tr>
<td>Clear cell (%)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Adenocarcinoma (%)</td>
<td>1 (1.2)</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
</tr>
<tr>
<td>1 (%)</td>
<td>31 (36.9)</td>
</tr>
<tr>
<td>2 (%)</td>
<td>25 (29.8)</td>
</tr>
<tr>
<td>3 (%)</td>
<td>28 (33.3)</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Hysterectomy+BSO (%)</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td>Hysterectomy+BSO+PLND (%)</td>
<td>28 (33.4)</td>
</tr>
<tr>
<td>Hysterectomy+BSO+PLND+PALND (%)</td>
<td>51 (60.8)</td>
</tr>
<tr>
<td>Myometrial invasion</td>
<td></td>
</tr>
<tr>
<td>&lt;1/2 (%)</td>
<td>56 (66.7)</td>
</tr>
<tr>
<td>≥1/2 (%)</td>
<td>28 (33.3)</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td></td>
</tr>
<tr>
<td>Absent (%)</td>
<td>70 (83.3)</td>
</tr>
<tr>
<td>Present (%)</td>
<td>14 (16.7)</td>
</tr>
<tr>
<td>LVSI</td>
<td></td>
</tr>
<tr>
<td>Absent (%)</td>
<td>63 (75)</td>
</tr>
<tr>
<td>Present (%)</td>
<td>21 (25)</td>
</tr>
<tr>
<td>Recurrence (%)</td>
<td>12 (14.3)</td>
</tr>
</tbody>
</table>

BSO=bilateral salpingo-oophorectomy, PLND=pelvic lymph node dissection, PALND=para-aortic lymph node dissection, LVSI=lymphovascular space invasion
Ovarian Cancer (Chemotherapy)

287

Time from completion of chemotherapy to disease progression as a clinically relevant endpoint in women with epithelial ovarian, primary peritoneal, and fallopian tube cancers treated with and without bevacizumab

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Objective: To explore a common definition of recurrence, time from completion of chemotherapy to disease progression (progression-free interval [PFI]) as an endpoint for meaningful clinical benefit in women treated with and without bevacizumab on GOG Protocol 218.

Methods: An unplanned exploratory analysis of PFI, defined as time from last carboplatin dosing to investigator-reported disease progression or death, was performed on data collected from GOG-0218, a double-blind phase III trial evaluating progression-free survival (PFS) in women with FIGO stage III or IV epithelial ovarian, primary peritoneal, or fallopian tube cancers randomized to either intravenous carboplatin and paclitaxel plus placebo cycles 2-22 (CPP [control]; n=625), CP + bevacizumab cycles 2-6 and placebo cycles 7-22 (CPB; n=625), or CP + bevacizumab cycles 7-22 (CPB+B; n=623).

Results: Median PFI (months) in each group was as follows: CPP=6.3, CPB=7.5, CPB+B=10.0. HR estimated using Cox regression and stratified for stage (III optimal, III suboptimal, or IV) and performance status (0, 1, or 2) for CPB vs. CPP was 0.85 (95% CI 0.73-0.98) and for CPB+B vs. CPB was 0.71 (95% CI 0.61-0.82). After censoring for patients whose progression was defined by CA-125 alone or for those receiving nonprotocol therapy (NPT), the HR for CPB vs. CPP was 0.81 (95% CI 0.69-0.97) and for CPB+B vs. CPP was 0.61 (95% CI 0.51-0.74). The proportion of patients achieving a PFI of at least 6 months was CPP=53%, CPB=66%, and CPB+B=71%, and that of at least 12 months was CPP=26%, CPB=32%, and CPB+B=42% (Table 1). This trend was not observed in the very platinum-sensitive group (PFI at least 24 months). A similar trend was found after censoring for CA-125-defined progression and NPT.

Conclusions: A higher proportion of patients receiving any bevacizumab were free of progression at 6 months and at 12 months as compared to control. This could potentially prolong the time to subsequent cytotoxic chemotherapy. PFI is a clinically relevant endpoint that warrants further study in prospective trials.

Table 1: Distribution of PFI at Relapse - Time from Last Dose of Carboplatin to Progression or Death - Not Censored for CA-125 or NPT

<table>
<thead>
<tr>
<th>Time from last dose of carboplatin to progression or death (months)</th>
<th>CPP</th>
<th>CPB</th>
<th>CPB+B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>52.7 (46.8-57.6)</td>
<td>65.4 (61.6-70.0)</td>
<td>76.0 (66.7-84.9)</td>
</tr>
<tr>
<td>12</td>
<td>25.0 (22.0-28.0)</td>
<td>42.1 (37.3-47.1)</td>
<td>41.7 (36.8-46.7)</td>
</tr>
<tr>
<td>24</td>
<td>14.5 (10.9-19.1)</td>
<td>18.5 (13.7-23.3)</td>
<td>28.2 (24.1-34.3)</td>
</tr>
</tbody>
</table>

PFI: Progression-free interval; CP: carboplatin + placebo cycles 2-22; CPB: carboplatin + paclitaxel + 6 cycles of placebo; CPB+B: carboplatin + paclitaxel + 6 cycles of bevacizumab + 16 cycles of placebo. NPT: Nonprotocol specified cancer therapy.

The goal of this study was to test whether CT57 (ACTL8) and CT55 (CXorf48) are potential targets for immunotherapy. ACTL8 is similar in structure to actin and interacts with molecular chaperones and transcription regulators. CXorf48 has 2 RNA variants and may interact with the BRCA2 gene in DNA repair and cell cycle regulation.

Methods: One-step reverse transcriptase polymerase chain reaction was performed with RNA from a panel of 17 normal and 91 EOC tissues obtained between 1994 and 2007. Specific primers were used to amplify a 260-bp product for ACTL8, a 432-bp product for CXorf48 variant 1 (V1), and a 337-bp product for CXorf48 variant 2 (V2). Enzyme-linked immunosorbent assay was performed on sera derived from an expanded panel of 241 EOC patients treated within the same period. Associations between antigen expression and covariates were assessed using the Wilcoxon rank sum and Pearson chi-square tests. Kaplan-Meier analysis and Cox proportional hazards were used to model overall and progression-free survival (OS and PFS).

Results: Spontaneous antibody responses to ACTL8 and CXorf48 were detected in 6% and 10% of EOC patients, respectively. Both genes demonstrated restricted expression in normal tissues. In EOC patients, ACTL8 was expressed in 96.7%, CXorf48 V1 in 56%, and V2 in 46.2%. The majority of patients had stage III disease (72.5%) as well as serous histology (62.6%) and were treated uniformly (Table). There was no difference in PFS for patients expressing either gene or in OS for those expressing ACTL8 or CXorf48 V1. However, patients who expressed CXorf48 V2 had a significantly improved OS compared to those who did not (median survival, 93 vs. 40 months; P=0.0069), which correlates with a 46% improvement (HR 0.54, 95% CI 0.28-1.04) (Figure).

Conclusions: Our results indicate that ACTL8 and CXorf48 have attributes of cancer/testis genes with restricted expression in normal tissues and a high frequency of expression in ovarian cancer. Patients with CXorf48 V2-expressing tumors may have improved OS. The high frequency of expression and evidence of spontaneous immunity to both antigens indicate that they are potential targets for ovarian cancer immunotherapy.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

289 A dose-dense carboplatin and paclitaxel regimen is highly active in the treatment of recurrent ovarian cancer
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Objective: To evaluate the efficacy and toxicity of monthly carboplatin and weekly paclitaxel for women with recurrent ovarian cancer.

Methods: Retrospective chart review of women with recurrent ovarian cancer treated with carboplatin (AUC 5 - day 1) and paclitaxel (80 mg/m^2 - days 1, 8, 15) of a 28-day cycle between 2001 and 2012 at a single institution. Primary endpoints included response rate (RR), progression-free survival (PFS), and overall survival (OS). PFS was calculated from date of onset of the dose-dense regimen, and OS was calculated from date of original diagnosis of ovarian cancer.

Results: Forty-seven women were treated between 2001 and 2012. The majority (87%) were stage III/IV. All had received a platinum and taxane chemotherapy regimen as their initial therapy. The overall response rate to dose-dense carboplatin and paclitaxel was 83% (28 complete responses [CR] and 11 partial responses [PR]). Patients with tumors categorized as platinum-sensitive had a response rate of 87% (33 CR/38 PR). Even among those predicted to have platinum-resistant tumors, the response rate was 67% (6 CR/9 PR), and half of these were CR. Median follow-up time was 51.5 months (range, 12-120 months). For all patients, the median PFS was 13 months and median OS was 60 months. Women with platinum-sensitive disease had a PFS and OS of 16 and 73 months, respectively. For those with platinum-resistant tumors, PFS and OS were 7 and 36 months, respectively. Seven women were treated with carboplatin and dose-dense paclitaxel 2 times over their clinical course. All 7 had had CR when treated for their first recurrence. Of these, 4 women responded to the dose-dense regimen the second time (3 CR and 1 PR). Eight women experienced grade 3 neutropenia and 1 patient was hospitalized for a severe infection. The most common adverse event was mild neuropathy (grade 1), which was seen in 25 patients.

Conclusions: A monthly carboplatin and weekly paclitaxel regimen is highly active for women with recurrent platinum-sensitive and platinum-resistant epithelial ovarian cancer and compares favorably to results of other published regimens. Given the excellent response rate and general tolerability of this regimen, it should be considered as the regimen of choice for first recurrences of ovarian cancer.

290 The effectiveness of intraperitoneal chemotherapy in treating retroperitoneal stage IIIC ovarian carcinoma
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Objective: Intraperitoneal (IP) chemotherapy has been shown to improve survival of women with stage IIIC ovarian carcinoma as compared to intravenous (IV) chemotherapy. The objective of this study was to examine the effectiveness of IP chemotherapy in patients with stage IIIC disease by retroperitoneal nodal metastasis.

Methods: This was a retrospective cohort study of patients with stage IIIC ovarian carcinoma treated with surgical cytoreduction followed by IV or IP chemotherapy between 2004 and 2010. Data were collected, Kaplan-Meier curves generated, and multivariate analyses performed.

Results: Of 393 patients with advanced-stage ovarian carcinoma, 202 had stage IIIC disease. Of those patients, 95 received IV chemotherapy and 114 received IP chemotherapy. Of 20 patients who had stage IIIC disease due to retroperitoneal lymph node involvement, 10 received IV chemotherapy and 10 received IP chemotherapy. Survival was superior in women treated with IP chemotherapy as compared to IV chemotherapy (P=0.004). Patients with stage IIIC disease by abdominal involvement or stage IIIC disease by retroperitoneal nodal involvement who were treated with IP chemotherapy had equivalent survival (P=0.34). Patients with stage IIIC disease by retroperitoneal nodal involvement had improved survival if they were treated with IP chemotherapy as compared to IV chemotherapy (P=0.04).

Conclusions: IP chemotherapy appears equally effective in patients with stage IIIC ovarian carcinoma due to retroperitoneal nodal metastasis as it is in patients with stage IIIC ovarian carcinoma due to abdominal metastasis. Women with stage IIIC disease by retroperitoneal nodal involvement experienced improved survival when treated with IP chemotherapy as compared to IV chemotherapy.

291 Feasibility of interval cytoreduction following neoadjuvant chemotherapy with carboplatin, weekly paclitaxel, and bevacizumab for advanced ovarian cancer – A phase I study
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The Ohio State University, Columbus, OH

Objective: We sought to evaluate a feasible dosing schedule of neoadjuvant chemotherapy using weekly paclitaxel with carboplatin and bevacizumab (bev) in women with advanced ovarian cancer. Furthermore, we evaluated treatment toxicities and assessed outcomes of interval cytoreductive surgery (ICS) following therapy in women with advanced ovarian cancer.

Methods: Using a “3+3” design, cohorts of 3 to 6 patients with advanced ovarian cancer received carboplatin (AUC 5), bev (15 mg/kg) every 3 weeks with weekly paclitaxel (60, 70, and 80 mg/m^2) for 3 cycles. Patients then received 1 cycle of carboplatin and paclitaxel without bev followed by ICS. The primary objective was to determine a feasible dosing schedule. Secondary objectives included defining toxicity, response rates based on imaging, and surgical outcomes defined by residual disease following ICS and 30-day postoperative outcomes.

Results: Nine patients, 3 on each dose level, were enrolled and had a median age of 64 years. No patient experienced a dose-limiting toxicity, indicating that the regimen using weekly paclitaxel 80 mg/m^2 was deemed feasible. During chemotherapy treatment, there were a total of 7 attributable grade 3 toxicities, which most commonly included neutropenia and thromboembolism and were distributed evenly across all 3 paclitaxel dose groups. All patients demonstrated a response (based on imaging before chemotherapy to before surgery), with a median reduction in disease of 56.4% (range 36.9%-100%). Optimal ICS was performed in all patients, and 78% had no gross residual tumor. There were no intraoperative complications, but 1 patient experienced an anastomotic leak (grade 4) 10 days after surgery that required repeat operation.

Conclusions: ICS was feasible following the administration of intravenous weekly paclitaxel and carboplatin with the addition of bev in the neoadjuvant setting. Optimal ICS was achieved in all patients, and both chemotherapy and surgery were associated with acceptable morbidity.

292 Patterns of crossover to antiangiogenesis agents in recurrent ovarian cancer patients: An analysis of a Gynecologic Oncology Group ancillary data study (GOOg218, abstract)
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Objective: To determine pattern of cross-over to antiangiogenesis agents for recurrent cancer after GOG#218 trial.

Methods: Data were extracted and chi-squared tests were used for statistical analysis.

Results: Of 580 patients enrolled on GOG 218 Arm 1, 486 (84%) recurred (median age: 61 years). Of these, 71% and 29% had stage III and IV disease, respectively; 89% had serous disease; and 76% had grade 3 tumors. Recurrence rates were 49.8%, 30%, and 20.2% at ≤6, 6–12, and ≥12 months after last chemotherapy treatment, respectively. Of 486 patients in Arm 1 who recurred, 188 (39%) crossed over to an antiangiogenesis agent, including bevacizumab (89%), sorafenib (1%), AMG386 (1%), afibbercept (0.5%), cediranib (0.5%), and others (10.6%), with some having >1 agent. The percentages of women who crossed over were 58%, 25%, and 13%, respectively, at first, second, third or more, and unknown recurrence. Crossover rates were 37.6%, 45.9%, and 30.6%, respectively, for recurrence at <6 months, 6–12 months, and ≥12 months (P=0.04). Of those who received bevacizumab in Arms 2 and 3 of GOG 218 and subsequently recurred, 29% were retreated with antiangiogenesis agents, with bevacizumab as the most common (91%) agent.

Conclusions: The rate of crossover to antiangiogenesis agents at recurrence was 39% in the reference and 29% in experimental arms in GOG 218, with bevacizumab as the most common agent. Crossover was more frequent in younger patients, at initial relapse, and during earlier recurrence. Closer monitoring of subsequent therapy with novel agents may be an important factor in the design, outcomes, and interpretation of future trials.

293 Common genes and pathways associated with in vitro/in vivo ovarian cancer chemo-response and overall survival

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Objective: Clinical outcome from epithelial ovarian cancer (OVCA) is substantially affected by response to chemotherapy, but molecular determinants of this response remain to be fully delineated. We sought to identify genes and molecular signaling pathways associated with OVCA chemo-response in a series of databases with OVCA gene expression information.

Methods: This is an in silico analysis involving different sources (multiplatform) of serous OVCA gene expression data. The objective was to determine common signaling pathways within the differential gene expression between patients (or cells) responding to chemotherapy or not responding to treatment. Previously reported in vitro differential gene expression from OVCA cell lines (n=48) subjected to incremental cisplatinum was used. Also, publically available datasets of differential gene expression of OVCA were used: Gene Expression Omnibus (GEO, www.ncbi.nlm.nih.gov/geo) database GEO, accession number GSE8991 (n=267), and The Cancer Genome Atlas OVCA database (TCGA, n=569). Finally, a clinicogenomic database of 142 patients with OVCA from our institution was also used. Genes differentially expressed between patients (or cells) with complete response to therapy (CR) and those with incomplete response (IR) were identified. Common genes associated with in vitro and in vivo chemo-response where introduced in a pathway enrichment analysis with MetaCore (www.genego.com) and significant pathways for chemosensitivity were recorded.

Results: We identified 15 common genes (P ≤0.4) associated with OVCA in vitro and in vivo chemo-response: TIMP3, OLFML3, C10orf26, COP22, PDGF, OMD, PKD2, SNRPA, COL8A1, GCNT1, CDSR4, PRP4A0, RAB35, MAPK14, and PARN. They included the molecular representation of 3 different pathways: 1) O-glycan biosynthesis (P=0.007), described in our previous in vitro studies of chemo-sensitivity; 2) Transport RAB1A regulation (P=0.005) that controls vesicle traffic within the cell; and 3) MAPK signaling (P=0.0001) pathways, involved in the initiation of a G2 delay and also identified in our previous in vitro studies.

Conclusions: We have identified genes and molecular signaling pathways associated with OVCA chemo-response in vitro and in vivo. More studies to identify interactions with regulatory elements of gene expression and to validate these results are underway.

294 Prognostic significance of dose reductive chemotherapy in epithelial ovarian cancer

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Objective: We investigated the significance of dose intensity on survival compared with treatment delay in adjuvant chemotherapy.

Methods: Medical records of 429 patients diagnosed with epithelial ovarian cancer (EOC) between 2005 and 2011 were reviewed retrospectively. Relative dose intensity (RDI) was calculated with the ratio of delivered dose intensity to standard dose intensity. Multivariate analysis was performed to identify a prognostic significance of treatment delay and dose reduction to tumor recurrence.

Results: Ninety-nine EOC patients received 6 cycles of postoperative adjuvant chemotherapy with paclitaxel and carboplatin. Mean values of RDI, treatment time intensity, and injected dose intensity were 93% (range, 70%-110%), 106% (range, 97%-127%), and 98% (range, 87%-110%), respectively. Most common causes of decreased RDI were neutropenia and thrombocytopenia. Median progression-free survival (PFS) of patients who received chemotherapy with <90% of dose intensity was 11 months compared with 21 months for patients who received >90% of dose intensity. In contrast with treatment time delay, dose intensity was an independent prognostic factor for tumor recurrence with multivariate analysis (P=0.030, 95% CI 1.307-208.203).

Conclusions: Dose reductions and treatment delays are the main ways to achieve an RDI for patients with chemotherapy-induced toxicity. Maintaining more than 90% of dose intensity is a significant factor in prolonging PFS.

295 Successful oxaliplatin salvage for recurrent ovarian cancer after carboplatin/cisplatin allergy

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Objective: Hypersensitivity reactions preclude platinum re-challenge for up to 44% of patients receiving second-line and higher carboplatin/cisplatin salvage therapy. Our center has used oxaliplatin challenge for platinum hypersensitivity since 2006. The objective of this study was to evaluate our patient experience in recurrent or progressive ovarian or fallopian tube cancer with oxaliplatin salvage.

Methods: This is a single-institution, retrospective chart review of all patients from 1995 to 2012 receiving oxaliplatin for treatment of recurrent or progressive ovarian or fallopian tube carcinoma. Data collected included patient demographics, diagnosis date, prior chemotherapy regimens, platinum-free interval, prior hypersensitivity reactions, oxaliplatin toxicity, length of therapy, disease response, and last follow-up. All patients who received oxaliplatin for 1 or more cycles were included. A response to therapy was determined after 2 or more cycles.

Results: We identified 44 patients who received oxaliplatin as treatment for epithelial ovarian or fallopian tube carcinoma. All patients had prior carboplatin therapy and 38.6% (17/44) had prior cisplatin therapy. Platinum hypersensitivity reactions were seen in 52.3% (23/44). Patients received a
median of 2 prior platinum-containing chemotherapy regimens and a median of 5 chemotherapy lines before oxaliplatin exposure. No grade 3 or grade 4 toxicities were noted. No patients had treatment delays for pancytopenia. Nausea and dysesthesias were controlled medically and were not dose-limiting. No platinum-associated toxicities, such as nephropathy or neuropathy, progressed on oxaliplatin therapy or were dose-limiting. Disease response was seen in 56.8% of patients, with a median reduction in CA-125 to 55.3% of the starting level. In patients who responded to therapy, the median nadir of CA-125 was 19.1% of the starting level. Of those patients who responded to oxaliplatin therapy, 42.3% had a prior platinum hypersensitivity reaction and were not candidates for other platinum-containing regimens. Patients were followed for a median of 15.5 months (range, 1-46 months) after initiation of oxaliplatin therapy.

Conclusions: In our institution's experience, oxaliplatin is well tolerated and should be considered for platinum challenge desensitization after carboplatin/cisplatin hypersensitivity with a reasonable chance of response.

296 Platinum dosing for epithelial ovarian cancer: Is it appropriate to use actual body weight?
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Objective: Rates of obesity in the United States continue to rise. Historically, obese patients with ovarian cancer have received adjusted-dose (AD) chemotherapy due to concerns for increased toxicity without corresponding benefit. However, there is evidence that chemotherapy pharmacokinetics in obese patients differ from those in normal-weight patients, and dose restriction (DR) may lead to poorer outcomes. Recently published guidelines by the American Society for Clinical Oncology recommend using the patient's actual, as opposed to ideal, body weight. We sought to determine the rate of DR in our epithelial ovarian cancer (EOC) patient population and if that influenced outcomes.

Methods: We conducted a retrospective review of EOC patients diagnosed between 2004 and 2009 at a single institution. Demographic data, tumor characteristics, and primary treatment details, including chemotherapy dosing, were abstracted. Only women who received 4 or more cycles of intravenous platinum/taxane regimens were included. Patients were considered DR if their total platinum dose was <90% of that predicted based on actual body weight. Student's T-test and chi-square analysis were used to compare variables as appropriate.

Results: Of 211 patients who met inclusion criteria, 98 (46%) were platinum dose-restricted. On average, DR women received 25% less platinum than their actual body weight dose would have predicted. The mean body mass index (BMI) of DR women was 32.3 compared to 23.9 among appropriately dosed (AD) women (P <0.01). The 2 groups were the same in regard to race, stage, debulking status, and histology, although DR women were significantly younger (60.0 vs. 65.5 years, P <0.01). Progression-free survival (PPS) and overall survival (OS) were not different (PPS 24.1 vs. 22.66 months, P=0.59; OS 34.1 vs. 35.4 months, P=0.61). AD women with a BMI >30 had a significantly shorter OS compared to DR women with a BMI >30 (26.8 vs. 37.3 months, P=0.03). These groups did not differ in terms of debulking status, stage, or histology. However, the AD/BMI >30 group were significantly older than the AD/BMI >30 group (70.6 vs. 59.7 years, P=0.02).

Conclusions: Obese patients with EOC commonly receive substantially lower doses of platinum when treated based on ideal body weight, but this does not appear to affect PPS or OS. However, older women with a BMI >30 have a significantly worse survival when dosed on actual body weight. This issue warrants further investigation.

297 Hyperthermic intraperitoneal chemotherapy with carboplatin for recurrent epithelial ovarian cancer: A pilot study
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Objective: To evaluate the feasibility and tolerability of hyperthermic intraperitoneal carboplatin (HIPC) following secondary cytoreduction for recurrent, platinum-sensitive ovarian cancer.

Methods: A single-institution prospective pilot study. Ten patients underwent secondary cytoreductive surgery followed by HIPC with carboplatin at 1,000 mg/m². Consolidation (6 cycles) was with standard platinum-based regimens. Adverse events (AE) were monitoring according to CTCAE v4.0 guidelines. Quality of life was measured before surgery, within 1 week of HIPC-carboplatin, and at the conclusion of therapy using FACT-O tool.

Results: Twelve patients were enrolled of which 2 were excluded (1 each for extra-abdominal disease identified before surgery and suboptimal cytoreduction). All 10 remaining patients received prescribed HIPC. There were no intraoperative complications or AEs attributable to HIPC therapy. Grade 1/2 nausea was the most common postoperative toxicity (6/10 patients), but this was managed with oral and/or antiemetics. Two patients had grade 4 postoperative neutropenia and thrombocytopenia, but only 1 experienced transient treatment delay. The median hospital stay was 5.5 days. A total of 69/70 (98%) planned chemotherapy doses were ultimately delivered, with 1 patient electively forgoing her final treatment. At a median follow-up of 16 months (range, 6-23 months), 3 patients have recurred at 8, 14, and 16 months from surgery. The median disease-free and overall survival have not been reached. FACT-O scores, as expected, demonstrated a significant decrease in the week following surgery (126 vs. 108, P<0.01) but improved at or near the completion of therapy (108 vs. 113, P=0.27).

Conclusions: HIPC-chemistry using carboplatin at 1,000mg/m² following optimal cytoreduction for ovarian cancer is feasible. Surgical complications were not observed, and postoperative AEs were largely within expected ranges. Consolidation using standard platinum-based regimens was feasible following HIPC, and preliminary survival data suggest efficacy. Further investigation of HIPC in the setting of debulkable cancer recurrence is warranted.

298 A phase I study of intraperitoneal carboplatin with intravenous paclitaxel and bevacizumab in patients with previously untreated epithelial ovarian carcinoma or primary peritoneal carcinoma
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Objective: To determine the maximum tolerated dose (MTD) of intraperitoneal (IP) carboplatin, dose-dense (dd) intravenous (IV) paclitaxel, and bevacizumab (C/T/Bev) during the first 2 cycles of treatment in patients with chemo-naïve epithelial ovarian, primary peritoneal, or fallopian tube carcinoma (EOC).

Methods: This was a phase I prospective study of patients with EOC with either optimal (≤1 cm maximum diameter) or suboptimal (>1 cm maximum diameter) residual disease following initial surgery. In part A, patients were treated with IP carboplatin/IV paclitaxel/IV bevacizumab (15 mg/kg) on day 1. IV paclitaxel was again administered on days 8 and 15 of 21-day cycles. Dose escalation first occurred with IP carboplatin from AUC 5 to 6, followed by dd paclitaxel (60, 70, 80 mg/m²). Bev was held for cycle 1. Thus, MTD was based on toxicity from cycle 1 or 2. After presentation of GOG 213, the addition of maintenance Bev (part B) was optional after completion of 6 cycles.

Results: A total of 9 patients were enrolled in the study. On the third dose level (IP carboplatin AUC 6, IV paclitaxel 70 mg/m²), 2 dose-limiting toxicities (febrile neutropenia and 15-day delay secondary to neutropenia) occurred. Seven of nine patients completed all 6 cycles of C/T/Bev. After primary therapy, 2 patients
Class III beta-tubulin overexpression within the tumor microenvironment is a prognostic biomarker for poor overall survival in ovarian cancer patients treated with neoadjuvant carboplatin/paclitaxel

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Objective: In advanced ovarian carcinoma, there is concern that neoadjuvant chemotherapy (NACT) followed by interval debulking may select for resistant clones or cancer stem cells when compared to cytoreduction followed by chemotherapy. Choice of adjuvant regimen may become problematic in instances of poor response to NACT, even if optimal debulking is achieved. Class III beta-tubulin overexpression has been linked to hypoxia and chemoresistance through reduced binding of paclitaxel and modulation of prosurvival pathways. In this study, we described changes of class III beta-tubulin expression in response to NACT in relationship to oncologic outcome and comparatively between patients who underwent NACT vs. primary debulking.

Methods: Patients with clinical stage III/IV disease who received carboplatin/paclitaxel in neoadjuvant fashion or following primary debulking from 2003 to 2012 were identified retrospectively. Demographics/oncologic outcomes were recorded. Class III beta-tubulin expression in tumor/stroma was quantified by immunohistochemistry in matched formalin-fixed paraffin-embedded tissues representing pre-NACT biopsies and post-NACT specimens obtained at interval debulking. Reverse transcriptase-polymerase chain reaction (RT-PCR) was used to quantify expression in fresh-frozen tissues obtained from patients treated with NACT vs. primary debulking.

Results: Patient characteristics for matched samples are provided in the Table. Among 22 paired specimens obtained before/after NACT, class III beta-tubulin expression decreased within stroma ($P=0.04$) but was unchanged in tumor ($P=0.76$) (Figure 1a). At time of interval debulking, reduced median overall survival (OS) was predicted by increased class III beta-tubulin staining by both tumor (high $[2+,3+]$ vs. low $[0,1+]$: 596 days vs. not reached; HR 3.56; 95% CI 1.08,11.8; $P=0.04$) and stroma (high $[1+,2+,3+]$ vs. low $[0]$: 596 vs. 1,354 days; HR 4.32; 95% CI 1.23,15.3; $P=0.02$) (Figure 1b). Class III beta-tubulin expression by RT-PCR was higher among patients who received NACT ($n=12$) compared to those who underwent primary cytoreduction ($n=14$) (mean±SD copy number: 491.2±115.9 vs. 224.1±55.66, $P=0.037$) (Figure 1c).

Conclusions: Overexpression of class III beta-tubulin in patients receiving NACT compared to primary cytoreduction likely reflects intrinsic phenotype.

Decreases in stromal expression may represent normalization of the tumor microenvironment as a result of therapy. Class III beta-tubulin expression by tumor and stroma at time of interval debulking predicts OS following NACT and may guide choice of adjuvant therapy.

Table. Patient Characteristics

<table>
<thead>
<tr>
<th>Age, years (mean±SD)</th>
<th>65.0±12.6</th>
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<tbody>
<tr>
<td>NACT Cycles of Carboplatin / Paclitaxel (mean±SD)</td>
<td>5±6±8.9</td>
</tr>
<tr>
<td>Debulking Status</td>
<td></td>
</tr>
<tr>
<td>- No residual disease</td>
<td>70%</td>
</tr>
<tr>
<td>- ≤5 mm residual or miliary disease</td>
<td>22%</td>
</tr>
<tr>
<td>- 6-10 mm residual</td>
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<td>- ≥2 cm</td>
<td>4%</td>
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<td>Histology</td>
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<tr>
<td>- Serous</td>
<td>75%</td>
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<tr>
<td>- Clear cell</td>
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<tr>
<td>- Endometrioid</td>
<td>4%</td>
</tr>
<tr>
<td>- Mixed</td>
<td>4%</td>
</tr>
<tr>
<td>- Undifferentiated</td>
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<td>Adjuvant Consolidation Regimen</td>
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<tr>
<td>- Carboplatin/paclitaxel</td>
<td>82%</td>
</tr>
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<td>- Other</td>
<td>21%</td>
</tr>
<tr>
<td>- Treatment at outside facility/unknown</td>
<td>17%</td>
</tr>
</tbody>
</table>
Objective: The high rate of relapse in patients with advanced ovarian cancer likely reflects the chemoresistance of cancer stem cells (CSCs), which are central to disease recurrence. This theory prompted researchers to develop therapies to target both chemosensitive and chemoresistant ovarian cancer cells. We evaluated the monoclonal antibody (mAb) 376.96, which recognizes a B7-H3 epitope with selective expression on ovarian carcinoma cells, in combination with the tyrosine kinase inhibitor sunsitibin and standard chemotherapy.

Methods: Eight ovarian cancer cell lines, including 2 chemoresistant cell lines A2780.c2p0 (platinum-resistant) and SKOV3.ip2.TR (taxane-resistant) were incubated with mAb376.96 and analyzed by flow cytometry to establish B7-H3 expression. We performed in vitro studies using flow cytometry to assess the effect of carboplatin, paclitaxel, or sunsitibin on B7-H3 expression. Additionally, the effects of mAb 376.96 alone and in combination with sunsitibin on cell growth inhibition and proportion of CSCs were performed on chemosensitive and chemoresistant cell lines.

Results: The B7-H3 epitope recognized by mAb 376.96 was expressed by chemosensitive and chemoresistant cell lines. Treatment of SKOV3.ip1 with 25 μM paclitaxel resulted in a 1.7-fold increase in mean fluorescence of B7-H3 expression, while treatment of A2780 cells with the same dose resulted in a 1.6-fold increase. Monotherapy with mAb 376.96 (1 mg/mL) resulted in nearly 50% growth inhibition of SKOV3.ip2.TR cells and more than 30% inhibition of A2780.c2p0 cell growth. The addition of mAb 376.96 to sunsitibin increased growth inhibition of SKOV3.ip1 cells from 10% to 28%. Furthermore, treatment of A2780 cells with carboplatin resulted in a 7-fold increase in the proportion of CSCs, while treatment with mAb 376.96 decreased the population by 50%.

Conclusions: The B7-H3 epitope bound by mAb 376.96 was expressed on all chemosensitive and chemoresistant ovarian cancer cell lines tested. In vitro studies using mAb376.96 showed an inhibitory effect against chemosensitive and chemoresistant ovarian cancer cells and reduced the proportion of CSCs. The consistent expression of B7-H3 by ovarian cancer cells warrants further studies examining B7-H3 as a potential therapeutic target.

Objective: To study the relation ARID1A expression with CCC molecular and pathologic features as well as the effect of ARID1A mutation on the response to treatment and survival of patients.

Methods: Specimens from 123 ovarian cancer cases (56 CCC, 25 endometrioid [EC], 20 serous [SAC], 22 mucinous [MAC]) were examined for ARID1A, HNF1-beta, ER-alpha, P53, PAKT, and Ki67 by immunohistochemistry, after obtaining informed consent from all patients. mRNA expression microarray analyses were performed on 14 CCC samples merged with GSE2109 and GSE6008 data sets. This study was approved by the institutional review board of Kyoto University.

Results: ARID1A showed positive staining in 22 (48%), 21 (84%), 20 (100%), and 22 (100%) cases of CCC, EC, SAC, and MAC. ARID1A was correlated to HNF1-beta, ER-alpha, P53, and Ki67 but not to pAKT. CCC has 3 architectural patterns: tubulocystic, papillary, and solid. Solid one had higher ARID1A (P=0.0169) and lower HNF1-beta (P=0.025) expression than other patterns. Unsupervised hierarchical clustering of microarray data of 14 samples merged with GSE2109 and GSE6008 showed 2 main clusters, with ARID1A accumulated in 1 cluster. Univariate analyses suggested that cases lacking ARID1A had a shorter progression-free survival compared with cases expressing ARID1A, although the difference was not statistically significant. Overall and progression-free survival rates were not affected by ARID1A status.

Conclusions: CCC has a unique molecular profile which distinguishes it from the other histologic types of ovarian cancer. There are 2 CCC subtypes based on ARID1A that are related to the morphologic pattern. ARID1A expression is preserved in the solid pattern of CCC, which may be related to a more aggressive tumor. This suggests that independent therapeutic strategies are needed based on CCC molecular subtypes.
303
Celecoxib and paclitaxel synergistically induce apoptosis in the human ovarian cancer cell line OVCAR-3
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Objective: Celecoxib, a highly selective cyclooxygenase (COX-2) inhibitor, regulates apoptosis of several human cancer cell types. The aim of this study was to investigate whether celecoxib alone or in combination with paclitaxel modulates apoptosis of ovarian cancer cells and to identify the signal pathway by which celecoxib mediate s apoptosis.

Methods: OVCAR-3 cells were exposed to paclitaxel (20 mcM) in the absence or presence of celecoxib (10 mcM). Cell viability was evaluated using a cell counting kit-8 (CCK-8) assay. Apoptosis was examined by Annexin-V/7-AAD staining and cellular DNA fragmentation enzyme-linked immunosorbent assay (ELISA). Caspase-3 was evaluated using the Caspase-3/7 Colorimetric Assay kit. Caspase-9 and cleavage of poly ADP-ribose polymerase (PARP) were determined by western blotting. Expression of nuclear factor-kappa-B (NF-kappa-B) was assessed using Trans AM kits and immunofluorescence. Vascular endothelial growth factor (VEGF) and Akt activation were studied by reverse transcriptase-polymerase chain reaction (RT-PCR) and western blotting.

Results: Celecoxib enhanced paclitaxel-induced growth inhibition of OVCAR-3 cells. Celecoxib significantly increased paclitaxel-induced apoptosis of OVCAR-3 cells. Pretreatment with celecoxib also increased activation of caspase-9, -3, and cleaved PARP following paclitaxel-treatment. Exposure of OVCAR-3 cells to celecoxib in combination with paclitaxel resulted in downregulation of NF-kappa-B activation and VEGF expression. Furthermore, combining celecoxib and paclitaxel inhibited phosphorylation of Akt.

Conclusions: Our data indicated that OVCAR-3 cells were sensitized to caspase-9, -3, and NF-kappa-B and Akt activation via a synergistic role in inhibiting different targets. Combining celecoxib with paclitaxel may provide clinical advantages for the treatment of ovarian cancer.
306 Decreased 53BP1 expression predicts improved survival in sporadic ovarian carcinoma

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1University of Washington Medical Center, Seattle, WA, 2Mayo Clinic, Rochester, MN

Objective: 53BP1 is a critical regulator of the balance between homologous recombination (HR) and the more error-prone nonhomologous endjoining (NHEJ) DNA repair. Deletion of 53BP1 in brca1- (but not brca2-) null cells rescues embryonic lethality, partially restores HR, and reverses sensitivity to poly-ADP ribose polymerase inhibitors (PARP). We characterized 53BP1 and BRCA1 expression in a large number of primary and recurrent ovarian carcinomas to determine if 53BP1 expression is associated with clinical outcomes in sporadic and inherited cases.

Methods: We evaluated 53BP1 protein expression using immunohistochemistry in 248 ovarian carcinomas comprehensively characterized for germline mutations in BRCA1 and BRCA2, including 54 paired primary and recurrent samples. We evaluated relative 53BP1 and BRCA1 mRNA expression in a subset of 85 cases with quantitative reverse transcriptase-polymerase chain reaction.

Results: Both primary and recurrent BRCA1-mutated (but not BRCA2-mutated) ovarian carcinomas had significantly higher 53BP1 protein expression than wild type carcinomas. 53BP1 message levels were significantly associated with BRCA1 message levels in wild type and in BRCA1-mutated but not in BRCA2-mutated ovarian carcinomas. In wild type carcinomas, lower 53BP1 mRNA message predicted improved survival (median survival 74 vs. 41 months, HR 0.49, 95% CI 0.27-0.88, P <0.02). Survival was not significantly impacted by BRCA1 message level. Neither 53BP1 protein nor mRNA expression was associated with primary platinum resistance. In 54 paired primary and recurrent cases, 53BP1 protein expression was equally likely to decrease or increase, and there was no association between decreased 53BP1 at recurrence and the development of platinum resistance.

Conclusions: BRCA1-mutated ovarian carcinomas have higher 53BP1 protein expression than wild type or BRCA2-mutated carcinomas, in direct contrast to previous findings in breast carcinomas. Higher 53BP1, which promotes NHEJ DNA repair, could explain the high aneuploidy that is characteristic of BRCA1-mutated ovarian carcinomas. In wild type ovarian carcinomas, decreased 53BP1 mRNA expression predicts improved overall survival, an opposite effect to our prediction. We speculate that if 53BP1 expression correlates with a predominant NHEJ phenotype, low 53BP1 could be a good prognostic factor in sporadic cases secondary to overall decreased aneuploidy and more ordered DNA repair.

Results: High expression of TTP gene expression was significantly associated with worse overall survival (OS) in both training and validation sets (median OS=39 vs. 46.9 months, P=0.004; 55.9 vs. 51.9 months, P=0.002, respectively). Results from the prediction programs identified 46 miRNAs targeting the TTP gene. Analysis of these miRNAs revealed only mir-301a as consistently and significantly inversely correlated with the TTP gene (correlation coefficient=-0.21, P <0.0001). Using CellMiner, mir-301a was also inversely correlated with TTP gene expression in the ovarian cancer cell lines (correlation coefficient=-0.71, P <0.0001). Low mir-301a gene expression was also significantly associated with worse OS (39.3 months vs. 56.4 months, P=0.01). Furthermore, combining high TTP and low mir-301 was associated with poorer OS (median OS=35.2 vs. 68.7 months, P <0.001).

Conclusions: Unexpectedly, the TTP gene appears to have oncogenic properties in ovarian cancer. The mechanism by which TTP and mir-301a impact the malignant course of the disease are being evaluated.

307 Deception of suppression: Unexpected effects of tristetraprolin in ovarian cancer

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Objective: The ZFP36 gene encodes a tumor suppressor protein, tristetraprolin (TTP), which plays a role in mRNA decay of many inflammation- and cancer-associated genes. We used the Cancer Genome Atlas (TCGA) to identify the clinical impact of TTP gene expression and its regulatory microRNA in ovarian cancer.

Methods: The clinical implication of TTP in high-grade serous epithelial ovarian cancer was examined using 479 tumor samples (“training” n=319 and “validation” n=160) sets were used. Candidate miRNAs were identified using multiple parallel prediction programs: miRanda, PITA, TargetScan, and Diana-MicroT. Several ovarian cancer cell lines were also examined using the CellMiner™ database.

Results: PIK3CA activating mutations are more frequent in VTE+ OC at a rate of 39% (P=0.05), and patients with PIK3CA mutations were more times more likely to be VTE+ than patients without a mutation (odds ratio 13.1, 95% CI 2.0-85, P=0.05). The entire cohort was thoroughly reviewed to determine if 53BP1 expression is associated with the highest risk of venous thromboembolism (VTE) and the highest rate of PIK3CA mutations. This study was designed to compare PIK3CA pathway activation in OC with VTE+ and then VTE- and to investigate the impact of VTE on survival.

Methods: With institutional review board approval, 44 OC were retrieved from our pathology files. Macrodissected formalin-fixed paraffin-embedded sections of the tumors were analyzed for mutations in exons 9 and 20 of the PIK3CA gene.

Objective: Ovarian clear cell carcinoma (OCCC) is the subtype of ovarian cancer associated with the highest risk of venous thromboembolism (VTE) and the highest rate of PIK3CA mutations. This study was designed to compare PIK3CA pathway activation in OC with VTE+ and then VTE- and to investigate the impact of VTE on survival.

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Methods: With institutional review board approval, 44 OC were retrieved from our pathology files. Macrodissected formalin-fixed paraffin-embedded sections of the tumors were analyzed for mutations in exons 9 and 20 of the PIK3CA gene.
Identification of differentially expressed genes according to chemosensitivity in advanced ovarian serous adenocarcinomas: Expression of GRIA2 predicts better survival
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¹Samsung Medical Center, Seoul, Republic of Korea, ²Samsung Medical Center, Changwon, Republic of Korea

Objective: To identify genes that are differentially expressed in chemosensitive serous papillary ovarian carcinomas relative to those expressed in chemoresistant tumors.

Methods: To identify novel candidate biomarkers, differences in gene expression were analyzed in 26 stage IIIC/IV serous ovarian adenocarcinomas (12 chemosensitive tumors and 14 chemoresistant tumors). We subsequently investigated the immunohistochemical expression of GRIA2 in 48 independent sets of advanced ovarian serous carcinomas.

Results: Microarray analysis revealed a total of 57 genes that were differentially expressed in chemoresistant and chemosensitive tumors. Of the 57 genes, 39 were upregulated and 18 were downregulated in chemosensitive tumors. Five differentially expressed genes (CD36, LIFR, CHL1, GRIA2, and FGGBP) were validated by quantitative real-time polymerase chain reaction. The expression of GRIA2 was validated at the protein level by immunohistochemistry, and patients with GRIA2 expression showed a longer progression-free and overall survival (P=0.051 and P=0.031, respectively).

Conclusions: We found 57 differentially expressed genes to distinguish between chemosensitive and chemoresistant tumors. We also demonstrated that the expression of GRIA2 among the differentially expressed genes provides better prognosis of patients with advanced serous papillary ovarian adenocarcinoma.
312 Expression of stress-induced phosphoprotein-1 (STIP-1) was associated with tumor progression and poor prognosis in epithelial ovarian cancer

M. Lee, 1 H. Cho, 1 J. Chung, 3 S. Hewitt, 3 D. Chay, 4 Y. Kwon, 1 J. Kim 2

1Kangdong Sacred Heart Hospital, Hallym University, Seoul, Republic of Korea, 2Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea, 3National Cancer Institute, Bethesda, MD, 4Yongin Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

Objective: Our previous study has suggested that stress-induced phosphoprotein-1 (STIP-1) is a putative biomarker candidate in epithelial ovarian cancer (EOC). In this study, we investigated in detail the expression of STIP-1 as well as its functions in EOC.

Methods: STIP-1 expressions were assessed by immunohistochemistry on 126 epithelial ovarian tissues, and the results were compared with clinicopathologic factors, including survival data of 113 EOC patients. The effects of STIP-1 gene silencing with small interfering RNA (siRNA) were examined in EOC cells and xenograft model.

Results: The expression of STIP-1 protein in EOC was significantly higher than in the other study groups (P < 0.001), and this increase of expression was significantly associated with tumor stage (P = 0.005), tumor grade (P = 0.029), and lymph node metastasis (P = 0.020). In multivariate analysis, overall survival in EOC was significantly shorter in cases with high STIP-1 expression (HR 3.05, 95% CI 1.01-9.20, P = 0.047). STIP-1 silencing in EOC cells resulted in the inhibition of cell proliferation and invasion as well as increased apoptosis. In vivo experiments demonstrated that treatment with STIP-1 siRNA inhibited tumor growth and increased apoptosis.

Conclusions: Increased STIP-1 expression is associated with poor survival outcome in EOC, and STIP-1 might represent a useful therapeutic target in EOC patients.

313 A water-soluble analog of triptolide induces ovarian cancer cell death in vitro and in vivo

C. Rivard Hunt, M. Geller, C. Evans, R. Vogel, S. Ramakrishnan, A. Saluja

Objective: Stress proteins known as heat shock proteins (HSP) have been recognized as inhibitors of apoptosis. Heat shock protein 70 (HSP70) has been investigated as a marker of ovarian cancer aggressiveness; elevated expression in both peritoneal and pleural fluid correlates with a worse overall survival. Triptolide, a diterpenoid, inhibits HSP70 and induces programmed cell death in cancer cells. However, triptolide is only soluble in organic solvents, limiting its clinical utility. A water-soluble analog of triptolide (Minnelide) has been synthesized for evaluation of anticancer activity in ovarian cancer.

The objective of this study was to perform the first testing of the water-soluble analog of triptolide in ovarian cancer.

Methods: Immunohistochemistry (IHC) was performed to measure HSP70 expression in serous ovarian cancers vs. normal ovaries. To measure tumor inhibition by Minnelide, A2780 (platinum-sensitive) and C200 (platinum-resistant) ovarian cancer cell lines were established and real-time growth inhibition assays (xCelligence, Roche) performed to measure cell attachment, spreading, and proliferation by determining electrical impedance. An MTT assay was performed to determine cell proliferation following treatment with Minnelide. A2780 cells were implanted subcutaneously in an in vivo mouse model following tumor establishment (174-190 mm³). Mice were administered Minnelide intraperitoneally (0.6 mg/kg) daily for 1 week or carboplatin 60 mg/kg twice weekly (positive control).

Results: HSP70 expression measured by IHC was elevated in serous ovarian cancer compared to normal ovaries. The MTT and real-time growth inhibition assays indicated that Minnelide was active in both platinum-sensitive (A2780) and platinum-resistant (C200) cell lines. Control cells grew from the initial cell index of 0.9 to 1.9 during 2 days in cell culture. Minnelide treatment showed concentration-dependent inhibition of ovarian cancer cell growth. At 500 nM, ovarian cancer cells were completely inhibited. In platinum-resistant cells, growth was inhibited at concentrations as low as 200 nM. In the in vivo model, regression of established ovarian tumors and improved survival were observed in mice administered Minnelide intraperitoneally daily (Figure).

Conclusions: Minnelide is markedly effective at killing ovarian cancer cells in vitro as well as in vivo. The activity of this novel agent in both platinum-sensitive and platinum-resistant ovarian cancer makes it a promising candidate for future investigation.

314 The oncogenic role of human epididymis protein (HE4): Promotion of tumorigenesis, cell survival, and cisplatin resistance in ovarian cancer in an in vivo mouse model


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Objective: The biomarker HE4 is overexpressed in epithelial ovarian cancer. This study delineated the biologic role of HE4 overexpression in ovarian cancer models.

Methods: Stably HE4-overexpressing ovarian cancer cell (SKOV-3, OVCAR-8) clones were developed using pCMV6-HE4 vector under G418 antibiotic pressure. HE4 overexpression was confirmed by western blot, reverse transcriptase-polymerase chain reaction and enzyme-linked immunosorbent assay (ELISA). Cell viability was determined by MTS assay. The growth of tumor and response to cisplatin was evaluated in an ovarian cancer xenograft model in nude mice and relative survival estimated by Kaplan-Meier analysis. HE4 protein expression was examined by western blot, ELISA, and immunohistochemistry. Spatial expression of HE4 in cultured SKOV-3, OVCAR-8, and OVCAR-3 or SKOV-3-derived xenograft tumor tissues was studied by immunostaining.
and microscopy. Protein-protein interaction of HE4 with HIF1-alpha and epidermal growth factor receptor (EGFR) was determined by colocalization and coimmunoprecipitation (co-IP). SiRNAs were used for gene knockdown studies. Antisense phosphorothioiogos (PTOs) targeting HE4 were used to knock down HE4 expression in ovarian cancer (SKOV-3, OVCAR-8) xenografts in mice. **Results:** SKOV-3 and OVCAR-8 clones expressed significantly higher levels of HE4 and showed more chemoresistance against cisplatin treatment than wild type or null vector cells in vitro. HE4 overexpression induced higher HE4 production in mice serum. Significantly faster tumor growth in HE4-overexpressing animals was observed, and Kaplan-Meier analysis showed that higher portions of HE4-overexpressing animals undergoing cisplatin treatment reached an earlier terminal end point (P<0.007) than wild type or null vector groups. Cultured ovarian SKOV-3, OVCAR-8, and OVCAR-3 cancer cells showed cytosolic staining, whereas corresponding xenografts tissues exhibited primarily nuclear presence. HE4 colocalized with HIF1-alpha and phosphorylated EGFR in SKOV-3 xenograft tissues and co-IP of HE4 with HIF1-alpha and phosphorylated EGFR was observed both in SKOV-3 cells and xenograft tissues. HIF1-alpha inhibition by SiRNA and Gefitinib inhibition of EGFR downregulated HE4 expression. HE4 antisense PTO (7 mg/kg) daily treatment suppressed tumor growth in SKOV-3 and OVCAR-8 xenografted mice in 2 weeks without affecting animal weights. **Conclusions:** We have shown for the first time that HE4 overexpression promotes tumor growth and cisplatin resistance in ovarian cancer animal models. We have observed that HE4 colocalizes with HIF1-alpha and EGFR and translocates to the nucleus in the tumor microenvironment.

**316**

**A novel cMET inhibitor, MK8033, potentiates the activity of carboplatin/paclitaxel in ovarian cancer cell lines**

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**Objective:** Elevated serum levels of hepatocyte growth factor (HGF) and high tumor expression of cMET are both indicators of poor overall survival from ovarian cancer (OVCA). We evaluated the role of the HGF signaling pathway in OVCA cell line chemoresistance and OVCA patient overall survival as well as the influence of HGF/cMET signaling inhibition on the sensitivity of OVCA cells to combination carboplatin plus paclitaxel (C/T) therapy.

**Methods:** Pearson’s correlation test of cisplatin-EC50 values and Affymetrix U133a expression profiles was used to identify genes and representative pathways associated with the experimental induction of platinum resistance in OVCA cells (n=8). Expression of the entire HGF pathway was summarized using principal component analysis to generate a pathway expression score, which was evaluated against overall survival in 2 independent clinical OVCA datasets (n=142, n=57). The prevalence of the HGF receptor, cMET, was determined by immunohistochemistry (IHC) in OVCA cell lines (n=41) and primary OVCA tumor samples (n=79). Lastly, the synergistic activity between HGF/cMET signaling inhibition and first-line OVCA chemotherapy (carboplatin + paclitaxel) was determined in a subset of OVCA cells (n=8) by CellTiter-Blue cell viability assays.

**Results:** The HGF pathway was associated with the evolution of OVCA cisplatin resistance (P=0.03). Analysis of 2 clinogenicomic OVCA datasets indicated that the HGF pathway expression was associated with overall survival from OVCA (P=0.002, P=0.04). IHC analysis indicated 83% of OVCA cells and 92% of primary OVCA expressed the HGF receptor, cMET. The HGF/cMET signaling inhibitor, MK8033, exhibited significant antiproliferative effects against a panel of human OVCA cell lines. Combination index values determined by the Chou-Talalay isobologram equation indicated synergistic activity in combinations of MK8033 and carboplatin + paclitaxel.

**Conclusions:** These data indicated that HGF/cMET pathway signaling may influence OVCA chemosensitivity and overall patient survival. Furthermore, HGF/cMET inhibition by MK8033 represents a promising new therapeutic avenue to increase OVCA sensitivity to carboplatin + paclitaxel.
analysis (HuRSTA genechip). OVCA cell sensitivity to PPD±cisplatin was quantified using MTS proliferation assays. Pearson’s correlation was calculated for gene expression and PPD IC50 values. The genes associated with PPD sensitivity were subjected to pathway analysis using GeneGo Metacore software. For identified pathways, principal component analysis (PCA) was used to derive pathway scores to represent overall pathway expression, which was evaluated for associations with survival from 969 patients with OVCA in a series of clinico genetic datasets, including: 1) Moffitt (MCC) (U133Plus, n=142); 2) Total Cancer Care (TCC) (HuRSTA, n=57); 3) The Cancer Genome Atlas (TCGA) (U133A, n=497); 4) MD Anderson (MDA) (U133Plus, n=53); and 5) Australian (AUS, n=220).

Results: PPD exhibited antiproliferative effects against a panel of 12 OvCa cell lines, with IC50s ranging from 0.2 to 1.4 mcM. Furthermore, PPD treatment significantly decreased cisplatin IC50 in all OVCA cell lines (mean IC50 reduction: 2.1 mcM; P<0.02). Pearson’s correlation test followed by biologic pathway analysis identified 48 pathways to be associated with PPD sensitivity (false discovery rate <0.05, P<0.05). Associations were observed between patient survival from OVCA and expression of the following pathways: apoptosis and survival/nitric oxide signaling (MCC, P<0.001, AUS, P=0.03), apoptosis and survival/caspase cascade (MCC, P=0.003, TCC, P=0.02), translation/nongenomic (rapid) action of androgen receptor (MCC, P=0.02, TCC, P=0.03), translation/regulation of EIF2 activity (MCC, P=0.001, TCC, P=0.003), and transcription/receptor-mediated HIF regulation (MCC, P<0.001, AUS, P=0.04).

Conclusions: PPD is a steroidal saponin and a major component of the Chinese herb Paris Polyphylla. PPD exhibited significant antiproliferative effects against OVCA cells and potentiated cisplatin sensitivity. Our data provide insights into the molecular basis of PPD activity against OVCA cells and identify pathways associated with clinical outcome.

318
Nonascites-forming advanced-stage serous ovarian cancer is related to a superior epithelial antigen presentation and enhanced infiltrating T-cell response
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Objective: High-grade serous ovarian cancer (HGSOC) is the most common subtype of ovarian cancer, with ascites a common presenting feature. Little is known of the mechanisms leading to ascites formation. Recent publications on gene expression profiles of HGSOC revealed at least 4 subtypes, suggesting that HGSOC is a heterogeneous disease, but data on ascites production were not included as a clinical parameter in these studies. We sought to identify genes expressed in HGSOC that correlate with differential ascites production in search of possible targets for therapy.

Methods: Whole genome gene expression profiles were obtained for 11 stage III/IV HGSOC primary tumors obtained from patients with substantial ascites, and 9 stage III/IV HGSOC primary tumors obtained from patients who had minimal ascites. Significantly differentially expressed genes were used to interrogate the Cancer Genome Atlas (TCGA) dataset of 488 HGSOCs to determine if a specific subset segregated with ascites-correlated genes. Selected proteins were chosen for validation by immunohistochemistry on tissue microarrays containing samples of ovarian tumors from 26 high-volume ascites and 25 low-volume ascites patients. Antibodies against CD3, CD20, and CD8 were included to compare immune response within the tumors.

Results: Using a t-test (P<0.05) statistic with a 2-fold change cutoff between cases with high and minimal ascites, 52 probes were found differentially expressed. A striking difference was observed for genes that regulate antigen presentation and T-cell function, which were reduced in the high-volume ascites group. The low-volume ascites group resembled the ‘immunoreactive’ subset of cases within the TCGA dataset. Immunohistochemistry confirmed the differential expression of several genes, suggesting an enhanced ability of the tumors in the low-volume ascites group to stimulate an immune response. Tumor-infiltrating T cells were also more abundant in this group, while few B cells were detected in all samples.

Conclusions: HGSOC associated with large ascites volumes may be less able to mount an immune response, as indicated by reduced expression in the tumor epithelium of genes expressed in antigen presentation and lower infiltrating T cells. These molecular signatures resemble subtypes of HGSOC identified in the TCGA dataset, providing support for the idea that these are clinically relevant subtypes of HGSOC.

319
Drug screening identifies growth inhibition of ovarian tumor-initiating cells by niclosamide
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Objective: Recent studies underscore the need to target tumor progenitors that have been shown to be resistant to conventional chemotherapeutic agents. The present study was designed to discover novel compounds with activity against drug-resistant ovarian tumor-initiating cells (OTICs).

Methods: We performed high throughput drug screening against OTICs derived from cells lines and patient tumors. We isolated and characterized OTICs for expression of multiple ‘stemness’ markers and functional phenotypes (membrane dye efflux, drug resistance, sphere formation, potent tumorigenicity, and serial transplantation). We screened >1,200 agents to identify clinically approved drugs specifically targeting OTICs. Time serial gene expression arrays after drug treatment were used for the mechanistic pathway analysis.

Results: The combination of surface markers, dye-exclusion, and spheroid formation assays identified OTICs fulfilling current definitions of cancer stem cells. OTICs were then subjected to high throughput drug screening, and 61 potential compounds were identified. Further in-depth analyses demonstrated that the anthelmintic niclosamide selectively targets OTICs in vitro and in vivo. Mechanistic analysis revealed niclosamide disrupted multiple metabolic pathways affecting bioenergetics, biogenesis, and redox regulation. The combination of niclosamide with compounds targeting cancer metabolism synergized the therapeutic effects.

Conclusions: These studies support niclosamide as a promising therapy for ovarian cancer. Further preclinical and clinical studies using this clinically proven drug in ovarian cancer therapy are warranted. The combination of multiple compounds targeting multiple metabolic pathways may provide a new approach for ovarian cancer therapy.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

Objective: Emerging evidence highlights the importance of chemokine microenvironment in tumor immune response. Our aim was to map the chemokine microenvironment in advanced-stage papillary serous ovarian cancer and to determine the chemokines that play a central role in mounting a successful tumor immune response.

Methods: Gene-expression profiling on 63 patients treated for primary ovarian cancer was performed using Affymetrix GeneChip. Publicly available Affymetrix array data on 222 human ovarian cancer patients from the Australian Ovarian Cancer Study was used as a validation cohort. Unsupervised clustering and classification and regression trees were performed using R. To determine the chemokine expression of ovarian cancer cells, gene expression analysis was done on 17 primary papillary ovarian cancer cell lines and results were validated by quantitative polymerase chain reaction. The presence of the 9 most highly expressed chemokines were further validated by using tissue microarray constructed from 50 patients with advanced-stage papillary serous ovarian cancer undergoing primary resection at our institution and was correlated with CD3 cell infiltration. Kaplan–Meier curves were computed and the log-rank test was used to determine whether the survival curves were significantly different.

Results: Unsupervised hierarchical clustering in the 2 Affymetrix array datasets showed 3 predominant clusters, but there was no statistically significant difference in overall survival between these clusters. The most highly expressed chemokines were CXCL16, CXCL10, CXCL12, CXCL5, and CX3CL1, where CXCL16, CXCL5, and CX3CL1 were also constitutively and highly expressed by ovarian cancer lines. Classification and regression tree analysis showed CXCL6 as the most predictive chemokine associated with overall and disease-free survival, which was further validated on the tissue microarray dataset (P <0.05). High levels of CX3CL1, CXCL6, and CXCL5 expressed in tumor islet with the presence of CD3 cells was more significantly associated with disease-free and overall survival than the presence of CD3 cells alone.

Conclusions: Chemokines play a paramount role in tumor immune response. The high expression of CXCL6 is associated with increased overall and disease-free survival. The presence of CX3CL1, CXCL5, and CXCL6 in tumor islets infiltrated with CD3 cells results improved overall survival, indicating that these chemokines play an important role in mounting a successful antitumor immune response.

Objective: The 2 most common ovarian cancer histologies are serous and endometrioid adenocarcinoma. Data from The Cancer Genome Atlas (TCGA) have been used to extensively study the molecular profile of serous ovarian carcinomas. mRNA expression profiling is included in this analysis for genes unique to the serous histology. We sought to identify genes unique to endometrioid adenocarcinomas of the ovary through microarray analysis and to compare the expression profiles to serous carcinomas in an attempt to identify if these 2 histologic subtypes have distinct and different expression patterns.

Methods: Affymetrix Human Exon 1.0 ST microarrays were used to evaluate more than 22,000 genes in patient samples. Included were 8 samples from histologically benign ovaries and 24 samples from patients diagnosed with endometrioid ovarian cancer divided as follows: stage I (7), stage II (7), stage III (9), and stage IV (1). TCGA datasets were used to obtain gene expression profiles on samples from serous carcinoma patients with similar clinical characteristics (n=54). Analyses included hierarchical clustering and the use of ANOVA to determine associations between genes. GeneGo was used to assist in the search for pathways of interest. Included were genes that had a fold change of ±2 or greater. Significance was set at a P value of ≤0.05.

Results: Out of approximately 400 genes that defined prognosis, we identified only 4 genes (RBPI, MATN2, SHMT2, and WARS) that had prognostic significance within both histologies. Upon examining only endometrioid carcinomas, hierarchical clustering analysis showed distinct, differentially clustered genes that were separated by stage. We identified 16 genes that were differentially expressed between good vs. bad prognosis and benign vs. advanced disease.

Conclusions: Ovarian endometrioid adenocarcinomas possess a unique gene expression profile that is separate and distinct from ovarian serous adenocarcinomas. Specific genes are differentially expressed and separate noncancerous and early-stage samples from advanced-stage disease. Specific genes within this study may be identified as therapeutic targets for patients diagnosed with ovarian endometrioid adenocarcinoma.

321 Endometrioid ovarian carcinoma has a distinct gene expression profile separate and unique from serous ovarian carcinoma
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Objective: The 2 most common ovarian cancer histologies are serous and endometrioid adenocarcinoma. Data from The Cancer Genome Atlas (TCGA) have been used to extensively study the molecular profile of serous ovarian carcinomas. mRNA expression profiling is included in this analysis for genes unique to the serous histology. We sought to identify genes unique to endometrioid adenocarcinomas of the ovary through microarray analysis and to compare the expression profiles to serous carcinomas in an attempt to identify if these 2 histologic subtypes have distinct and different expression patterns.

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322 Methylation profiling of ovarian cancer-initiating cells identifies DNA methylation as a prognostic biomarker
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Objective: Epigenetic changes of ovarian cancer-initiating cells remain unexplored. In this study, we aimed to discover novel DNA methylation in ovarian cancer initiation cells and tested its potential as a prognostic biomarker.

Methods: We compared the methylation profiles between an ovarian cancer-initiating cell line (CP70/psps) and its parental line (CP70) by bead arrays (Illumina). Quantitative reverse-transcriptase polymerase chain reaction (QRT-PCR), quantitative methylation-specific PCR (Q MSP), and pyrosequencing were used for the validation of gene expressions and DNA methylation in cell lines and clinical samples. We assessed the clinicopathologic correlation of potential DNA methylation sequences as markers.

Results: We identified gene H as a potential candidate. Methylation status of H gene by QMSP was tested in 113 ovarian cancer tissues, which revealed an independent prognostic significance of H gene methylation for progression-free survival (PFS) and overall survival (OS). Kaplan–Meier analysis and multivariate Cox regression analysis showed that low levels of H gene methylation conferred a poor PFS (HR 5.02, 95% CI 1.19-21.27, P <0.05) and OS (HR 7.85, 95% CI 1.07-57.63, P<0.05), which suggests the existence of a more stemlike phenotype defined by H gene with reduced therapeutic responses.
Conclusions: Our data demonstrate that the methylation of H gene is an independent prognostic biomarker for ovarian cancer patients. H gene may provide a novel therapeutic target for ovarian cancer.

323 Human leukocyte antigen polymorphisms predict NY-ESO-1 tumor antigen serology and overall survival in epithelial ovarian cancer
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Objective: The generation of antitumor immune responses, spontaneously or by vaccination, determines the outcome of patients with epithelial ovarian cancer (EOC). HLA genes are crucial to tumor surveillance, whereby tumor antigens are presented by Human leukocyte antigen (HLA) class I and II molecules to T cells, resulting in an orchestrated cellular and humoral immunity. NY-ESO-1 (ESO), a highly immunogenic member of the “cancer testes” antigen family, elicits spontaneous immune responses in a subset of patients with EOC. We hypothesized that the generation of spontaneous immunity to ESO and the clinical outcome of EOC patients are determined by HLA genetic polymorphisms.

Methods: A total of 116 patients with ESO-expressing tumors, as determined by immunohistochemistry, were included in this study. Matched serum samples were assessed by enzyme-linked immunosorbent assay for the ESO antibody. Low-resolution HLA typing was performed using sequence-specific polymerase chain reaction. The relative odds of the ESO serologic response correlating with HLA type was analyzed using a multivariate logistic model. A proportional hazards model was used to assess the association between HLA allele groups and survival.

Results: ESO humoral immunity was detected in 47% (54/116) and was absent in 53% (62/116) of EOC patients. The HLA class II alleles, DRB1*13 and DRB4*01, were significantly more frequent in ESO-seropositive patients (70% [16/23] and 63% [19/30], respectively) than in ESO-berogative patients (30% [7/23] and 37% [11/30], respectively) (odds ratio [OR] 0.223, 95% CI 0.08-0.619, P=0.008 and 0.029, 95% CI 0.119-0.722, P=0.004, respectively). HLA class I allele frequencies were similar in seropositive and seronegative patients. Improved survival was observed in patients with the A*01 subtype as compared to other HLA-A subtypes (HR 0.491, 95% CI 0.226-0.832).

Conclusions: HLA polymorphisms are associated with antitumor immunity and may influence clinical outcomes in EOC. The HLA-DRB1*13 and HLA-DRB4*01 alleles are significantly associated with the development of humoral immunity to ESO but not necessarily with survival in EOC patients, most likely as a result of immunologic tolerance. Although a relationship between the HLA-A*01 subtype and survival was seen, the underlying mechanism(s) will need to be determined. This study supports innovative vaccination strategies targeting HLA class I and II ESO epitopes, potentiating a broad immunologic response.

324 Dual mTOR inhibition demonstrates antiproliferative and chemosensitizing effects in chemoresistant high-grade papillary serous ovarian cancer
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Objective: To establish the effect of small-molecule mTOR inhibitors on the tumorigenesis of high-grade papillary serous ovarian cancer (OVCA) and to compare the effect of mTOR complex 1 inhibition (mTORCi1) vs. dual mTOR complex 1 and 2 inhibition (mTORCi1+2) with and without carboplatin (CPP) in an in vitro model of OVCA.

Methods: Clonogenic assays of NIH-OVCA3 were performed. Treatment conditions included increasing doses of RAD001 (mTORCi1), PP242 (mTORCi1+2), carboplatin (CPP; DNA damaging agent), and the combination of PP242+CPP. Colonies were stained with crystal violet and analyzed using ImageJ64. Cell lysate immunoblots using commercial antibodies probed for key proteins in the mTOR (S6 and p-S6, BP1 and p-BP1, mTOR and p-mTOR, Akt and p-Akt) and DNA repair pathways (CHK1 and p-CHK1, CHK2 and p-CHK2, ATM and p-ATM, ATR and p-ATR, p-BRCA1 and others). Colony counts (counts) and average colony diameter (ACD) were compared by ANOVA, with results expressed as mean ± systematic error. Post hoc analyses allowed pair-wise comparisons.

Results: One-way ANOVA was significant across treatment arms (F =17.718, P<0.002). PP242-treated cells had a significantly smaller ACD compared to CTL cells (30.5±3.5 vs. 131±23.5) and CPP-treated cells (115±15.1) (Tukey standard deviation [SD] P=0.004 and 0.009). Addition of CPP to PP242-treated cells further decreased the ACD (27±4) compared to CTL or compared to CPP alone (Tukey SD P<0.003 and 0.008). Counts in CPP+PP242-treated cells were decreased vs. CTL (56±9 vs. 129±27) (Tukey SD P=.02). RAD001 (20 nM-5 μM) did not alter counts or ACD when compared to CPP or CTL. Immunoblots of cells treated with PP242 and high-dose RAD001 revealed characteristic inhibition of the mTOR pathway (decreased p-mTOR, p-S6, and p-BP1), which was not observed with CPP. Furthermore, PP242 effectively reduced p-Akt (due to mTOR complex 2 inhibition) compared to RAD001 and CPP. Total CHK1 and p-CHK1 were reduced in cells treated with PP242 but not in cells treated with RAD001 or CPP alone.

Conclusions: mTOR regulates cap-dependent mRNA translation (CDT), which is upregulated in OVCA. mRNAs with long 5’ untranslated regions, such as CHK1 and other survival mRNAs, have a greater requirement for CDT and are highly sensitive to mTORCi1+2. We showed that PP242 has compelling antiproliferative and chemosensitizing effects in OVCA and is superior to RAD001. Inhibition of CHK1 by dual mTOR inhibitors has not yet been investigated in the clinical setting but is likely to be an effective target in control of advanced disease.

325 Chemokine receptors enhance T-cell vaccine cell homing to ovarian cancer
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Objective: Chemokines and their receptors are regulators of tumor immune response and T-cell homing. Our aim was to determine the chemokine receptor expression and homing ability of costimulated autologous T-cells of patients participating in our phase I/II T-cell vaccine trial.

Methods: Five patients with recurrent ovarian cancer, who received prime-boost vaccination with autologous DC vaccine in a prior clinical trial, were enrolled in a phase I/II clinical trial to determine the dose-limiting toxicities and immune and clinical effects of vaccine-primed, ex vivo CD3/CD28 costimulated peripheral blood autologous T-cells. Expanded T-cells were prepared according to study protocol. The initial apheresis and final vaccine T-cells were classified by CD45, CD3, CD4, and CD8 expression. Focusing on chemokines most commonly expressed in ovarian cancer, we determined the expression of their respective chemokine receptors by flow cytometry. To assess the functionality of the receptors, chemotaxis assays were carried out on the T-cell in the presence of chemokines.

Results: FACS analysis found a significantly higher CD4/CD8 ratio in the final vaccine product compared to the matching apheresis samples. The 3 most commonly expressed chemokine receptors on both the apheresis and the final vaccine product were CCR10, CXCR3, and CXCR4. CCR10 expression was slightly lower in the T-cell vaccine, while CXCR3 and CXCR4 were significantly upregulated during the expansion and stimulation. Chemotaxis assay found increased migration in the presence of the ligands of all 3 of these receptors (CCL28, CXCL10, CXCL12). CCL28 had the lowest effect on migration, followed by CXCL10, while migration was highest in the presence of CXCL12. Vaccine T-cells showed 2-fold and 4-fold increases in chemotaxis with CXCL12.
and CXCL12, respectively, compared to the apheresis product. This increase was consistent with CXCR3 and CXCR4 upregulation in these cells. Blocking antibodies reversed the promigratory effect of chemokines.

**Conclusions:** Ex vivo expanded tumor-specific cytotoxic T cells have shown promising results for the treatment of minimal residual disease and micrometastases. Our data demonstrated that ex vivo expanded autologous T-cells have upregulated CXCR3 and CXCR4 receptors and enhanced migration in the presence of their ligands, CXCL10 and CXCL12. Since these chemokines are also highly expressed in many ovarian tumors, they confer the improved ability of autologous T-cell vaccine for engraftment to ovarian cancer.

**Objective:** Recent evidence suggests that the human omentum functions as a niche promoting ovarian cancer metastasis. To better understand this phenomenon, we examined the ability of ovarian cancer cells isolated from distinct anatomic sites to create multicellular aggregates known as spheroids, which are thought to play a critical role in promoting metastasis and a pluripotent phenotype.

**Methods:** We have undertaken a series of experiments with the goal of better understanding the role of omentum in ovarian cancer by testing whether the omental microenvironment promotes spheroid formation and/or induces a pluripotent phenotype. Tissue removed from patients at the time of surgery was analyzed regarding spheroid number, size, function, and pluripotency.

**Results:** We found that ovarian cancer cells recovered from omental implants expressed higher levels of pluripotency-associated cell surface marker CD133 and created larger numbers of more rapidly growing spheroids that express significantly higher levels of CD133 than ovarian cancer cells recovered from the tubo-ovarian complex. Although CD133+ or CD44+ ovarian cancer cells were equally capable of creating large spheroids, spheroids self-assembled from the CD133+ subpopulation ovarian cancer cells were significantly more tumorigenic in vivo than CD44+, CD133−, or CD44−, or unsorted cells. Furthermore, we found that individual spheroids self-assembled from CD133+ ovarian cancer cells migrated to both the ovary and omentum of SCID mice, whereas spheroids self-assembled from CD44+ cells induced tumor only at the site of their injection. Similarly, subcutaneously injected CD133+ ovarian cancer cells in mice migrated to create tumor xenografts localized to fat-bearing intraperitoneal sites. Targeting knockdown of CD133 expression in A2780 cells inhibited not only the ability of this established ovarian cancer cell line to assemble into well-organized spheroids but also the ability to induce tumor implants in vivo.

**Conclusions:** These novel observations demonstrate that omental implants are enriched for CD133 and promote ovarian cancer metastasis and proliferation, which is intimately linked to the expression of this pluripotency-associated cell surface marker and to its ability to promote spheroid self-assembly in a CD133-dependent manner. These results establish novel paradigms for understanding the potential role for ovarian cancer stem cells in the most lethal aspects of this disease.

**Objective:** Aldehyde dehydrogenase (ALDH) enzymatic activity identifies ovarian cancer stem cells (CSCs). We sought to investigate the antineoplastic activity of the ALDH inhibitor disulfiram on bulk ovarian cancer cells and CD133+ cancer stem cell populations.

**Methods:** Ovarian cancer cell (OCC) lines, human ovarian surface epithelial cells (HOSEs), and mesenchymal stem cells (MSCs) were treated with increasing concentrations of disulfiram and/or cisplatin in vitro. Cell viability was assessed using the MTT assay, and cells were FACS analyzed for ovarian CSCs or the induction of apoptosis. The effect of disulfiram on tumor sphere formation, a property of CSCs, was examined using both cell lines and primary ovarian tumor ascites cells. Finally, bulk A2780 tumor cells or CD133+ tumor cell xenografts were initiated in mice and the mice were treated daily for 21 days with disulfiram.

**Results:** Disulfiram demonstrated antineoplastic activity against multiple cell lines, including both the platinum-sensitive and the platinum-resistant cells (A2780 cells; IC50 1.5 uM). Disulfiram’s activity was comparable to that of cisplatin (IC50 of about 1.5 and 4.5 uM, respectively, for A2780 cells) (Fig 1A). Disulfiram had a significant therapeutic index, selectively killing OCCs without a significant effect on HOSEs or MSCs (IC50 of ~15 and >30 uM, respectively) (Fig 1B). Analysis of Annexin-V induction demonstrated that disulfiram appeared to induce apoptotic cell death (Fig 1C). Interestingly, higher doses of disulfiram appeared to demonstrate a modest (2-4 times) selective depletion of CD133+ CSC. Consistent with this, disulfiram inhibited sphere formation of both SKOV3 primary and patient ascites cancer cells. In vivo therapeutic studies are ongoing.

**Conclusions:** Disulfiram, a less toxic drug compared to traditional chemotherapeutics, is active against ovarian cancer cells in biologically relevant drug concentrations. Disulfiram’s antineoplastic activity is at least in part, due to induction of apoptosis. Disulfiram may preferentially target ovarian cancer stem cells and, thus, may represent a novel therapeutic agent for the study of ovarian cancer therapy.

**Fig1:** In A&B, A2780DK, human ovarian surface epithelial cells (HOSE) and mesenchymal stem cells (MSC) were plated on 96-well plates at a seeding density of 7,500 cells/well. The following day, cells were treated with different concentrations of disulfiram (DSF) or cisplatin (Cis) for 3 days then cell viability was assessed using the MTT assay. The relative sensitivity of A2780DK to DSF & Cis is shown. (Fig 1A) as well as the relative sensitivity of the different cell lines to disulfiram (Fig 1B). In Fig 1C A2780DK cells were plated (250,000 cells/plate) in 60 mm plates and the following day treated with DSF (7.5 µM) for 3 days. Controls received vehicle only. Cells were then harvested, counted and FACSanalyzed. As shown here, the proportion of Annexin V positive cells increased with DSF treatment (Fig1C) consistent with apoptosis induction.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

329 Characterizing the activity of MK2206 in ovarian cancer and defining the molecular determinants of response
N. Bou Zgheib1, D. Marchion, Y. Xiong, E. Al Sawah, I. Ramirez-Diaz, P. Judson Lancaster, J. Gonzalez Bosquet, R. Wenham, S. Apte, J. Lancaster
H. Lee Moffitt Cancer Center, Tampa, FL

Objective: AKT, also known as protein kinase B (PKB), is a serine/threonine protein kinase that influences cell proliferation, apoptosis, transcription, and cell migration. When phosphorylated, AKT promotes cell survival and influences the response of human cancers to chemotherapy. We sought to: 1) determine the influence of AKT on survival from ovarian cancer (OVCA); 2) assess activity of a novel AKT kinase inhibitor, MK2206; and 3) explore the molecular determinants of MK2206 response.

Methods: Phospho-AKT expression values and Affymetrix U133a gene expression data were downloaded from The Cancer Genome Atlas (TCGA). Pearson correlation was used to determine associations between overall survival from OVCA (n=402) and response to therapy (complete response [CR], n=230 vs. incomplete response [IR], n=97). OVCA cells (n=18) were treated with MK2206 (1 mcM) and subjected to Affymetrix HuRSTA expression analysis. The genes associated with MK2206-sensitivity were subjected to pathway analysis using GeneGo Metacore software. Numeric values representing the expression of each pathway, as determined using the principal component analysis, were evaluated for associations with survival in a series of clinogenomic datasets: 1) Moffitt (MCC) (U133Plus, n=142); 2) Total Cancer Care (TCC) (HuRSTA, n=57); 3) The Cancer Genome Atlas (TCGA) (U133A, n=497); 4) MD Anderson (MDA) (U133Plus, n=53); and 5) Australian (AUS, n=220).

Results: Phospho-AKT[serine473] expression correlated with both overall survival from OVCA (P<0.05) and response to platinum-based therapy (P<0.004). In vitro MK2206-sensitivity was associated with expression of 69 probesets (P<0.001), with representation in 11 signaling pathways (P<0.05). Two of these pathways were significantly associated with survival from OVCA in more than 1 survival dataset: transcription_receptor-mediated HIF regulation (HIF) (AUS, P=0.04; MCC, P<0.001), and transcription_role of VDR in regulation of genes involved in osteoporosis (VDR) (AUS, P=0.03; MCC, P<0.001).

Conclusions: These data indicate that AKT signaling may be an important determinant of OVCA chemoresponse and overall survival and suggest a clinical utility to AKT inhibition. Our data provide insights into the molecular basis for MK2206 activity against OVCA cells and identify pathways associated with MK2206 sensitivity and clinical outcome.

330 Gene expression levels in archived FFPE ovarian carcinoma samples: Comparison of qPCR with tissue microarray in a 9-core pathway predictive treatment model in serous ovarian carcinoma
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1Medical College of Wisconsin, Milwaukee, WI, 2University of Wisconsin, Madison, WI

Objective: We have developed a statistical model based on gene expression within 9 core cancer pathways using The Cancer Genome Atlas (TCGA) microarray dataset that predicts clinical response to cytotoxic chemotherapies at the time of progression of serous ovarian carcinoma. We assessed the applicability of our microarray signatures to gene expression in quantitative polymerase chain reaction (qPCR) with patient-matched snap frozen and formalin-fixed, paraffin-embedded (FFPE) tissue samples. Successful results will enable large-scale validation from FFPE archival tissue with abundant clinical information and follow-up.

Methods: We evaluated the predictive and prognostic value of our core pathway-based model in the TCGA and 2 independent gene expression sets. Using biomarker validation techniques, we connected response of specific drugs to specific pathways. We then selected advanced-stage, grade 3 snap-frozen serous ovarian tissue samples and matched FFPE archival samples. All specimens were reviewed pathologically for >75% viable tumor. A 91-gene expression TaqMan qPCR was developed to compare the matched snap-frozen and FFPE samples through correlation analysis.

Results: There was a direct relationship between the number of perturbed core cancer pathways and reduction of time-to-recurrence. Stratifying time-to-progression by treatment yielded significant interactions with the pathway model. Snap-frozen qPCR expression aligned with expression levels seen in Affymetrix microarray in snap-frozen tissue. After adjusting for outliers, FFPE and snap-frozen samples demonstrated a highly significant level of correlation of expression (r=0.90 matches, r=0.79 mismatches; P<0.0003).

Conclusions: Using expression data from the TCGA, we have developed a set of time-to-event associated biomarkers that model known biological pathways. These models identify biologically important genomic aberrations and provide pathway-based patient-specific assessments of risk. We have further developed a pathway-based gene expression model predictive of response to commonly used chemotherapeutic agents. Expression in snap-frozen and matched FFPE samples showed a high level of correlation. Feasibility of validation in FFPE samples is confirmed.

331 Pathways involved in doxorubicin sensitivity in vitro correlate with overall survival from ovarian cancer
N. Bou Zgheib, Y. Xiong, D. Marchion, X. Stickles, E. Al Sawah, P. Judson Lancaster, J. Gonzalez Bosquet, R. Wenham, S. Apte, J. Lancaster
H. Lee Moffitt Cancer Center, Tampa, FL

Objective: Doxorubicin is commonly used for the treatment of recurrent ovarian cancer (OVCA). While the efficacy of doxorubicin as second-line therapy for patients with relapsed OVCA has been proven, the majority of patients ultimately succumb to the disease due to multidrug resistance. In this study, the molecular basis of doxorubicin resistance was explored in OVCA cells and correlated with overall survival from OVCA.

Methods: Ovarian cancer cells (n=31) were analyzed for doxorubicin sensitivity using CT-Blue cell viability assays and, in parallel, subjected to Affymetrix HuRSTA gene expression analysis. Pearson’s correlation test was performed on expression data and doxorubicin IC50 values. Genes found associated with doxorubicin resistance (P<0.001) were subjected to GeneGo Metacore analysis to identify significant pathway representations. The influence of pathway expression, as summed by the principal component analysis (PCA), on overall survival from OVCA was evaluated in a series of clinogenomic datasets: 1) Moffitt (MCC), n=142; 2) Total Cancer Care (TCC), n=57; 3) The Cancer Genome Atlas (TCGA), n=497; 4) MD Anderson (MDA), n=53; and 5) Australian (AUS), n=220.

Results: Doxorubicin sensitivity was associated with the expression of 152 unique genes (P<0.001), with significant representation of 3 pathways (FDR<0.05): 1) Cytoskeleton remodeling_Regulation of actin cytoskeleton by Rho GTPases (Rho, P=3.76E-06); 2) Immune response_CCR3 signaling in eosinophils (CCCR3, P=3E-05); and 3) Transforming growth factor-beta-mediated regulation of cell proliferation (TGF, P=5.04E-04). Pathway expression for Rho, CCR3, and TGF, as defined by the PCA, correlated with doxorubicin IC50. Using median cut-off, pathway expression for CCCR3 (P=0.02, P=0.032) and TGF (P=0.005, P=0.0038) correlated with overall survival from OVCA in two datasets (AUS, n=220; MCC, n=142, respectively). Furthermore, when stratified according to their surgical status, OVCA patients (AUS, n=220) with high CCCR3 (P=0.03) or low TGF (P=0.002) expression and suboptimal
Ovulation induction with gonadotropins accelerates tumor growth and (r=0.82, P<0.001). A multivariate analysis, only pSTAT3 expression (HR 2.614, 95% CI 1.264-5.407) was an independent predictor of survival. B-cell clustering did not enter the final model, possibly due to a high positive correlation with pStat3 expression (r=0.82, P<0.001).

**Conclusions:** Increased B-cell infiltration and pSTAT3 expression in omental tissue is associated with poorer survival. Our data adds to a limited body of evidence linking B-cell infiltration with clinical outcome in ovarian cancer and adds a possible mechanism for this observation (i.e., STAT3-mediated immune recruitment).

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**Objective:** Ovulation induction, a component of in vitro fertilization, has been linked to an increased risk of ovarian cancer. The mechanism underlying this association has not been established. We hypothesize that that high levels of estrogen produced in response to exogenous gonadotropin administration promotes malignant transformation in the disrupted ovarian epithelium during repetitive ovulation cycles. We used a murine model of serous cancer to investigate the effects of gonadotropin or estradiol administration on intraperitoneal (IP) tumor growth and dissemination as well as on markers of an antitumor immune response.

**Methods:** Mice were divided into 4 treatment groups following IP tumor inoculation: 1) control injections of saline, 2) weekly gonadotropins, 3) weekly gonadotropins plus aromatase inhibitor, and 4) estradiol only. Animals were euthanized upon reaching a weight of 30 g, and ascites volume and cumulative tumor weight were recorded. Vascular endothelial growth factor (VEGF) levels in ascites supernatant were quantified with enzyme-linked immunosorbent assay. Estrogen-receptor alpha and beta (ERα, ERβ) expression was quantified with reverse transcriptase polymerase chain reaction. Tumor-infiltrating T-cell populations were scored using immunohistochemistry and characterized with flow cytometry.

**Results:** Tumor weight and ascites volume were higher in all treatment groups compared to controls (P<0.038, P<0.007). VEGF concentrations were also higher in treatment groups, peaking in mice treated with estradiol alone (P=0.012). The mean number of tumor-infiltrating T cells was similar in all groups, but a higher proportion of suppressive FoxP3+ T cells were seen in controls. ERα expression did not differ among groups, but ERβ was significantly lower in animals treated with estradiol.

**Conclusions:** Both ovulation induction with gonadotropins and treatment with estradiol alone markedly accelerated tumor growth in this model. Increased tumor burden was associated with higher levels of VEGF, but this did not correlate with an increased infiltration of suppressive T cells. Further studies are required to distinguish the contributions of supraphysiologic hormone levels and ovulatory injury on tumor development, although our results suggest that exogenous gonadotropin exposure alters both angiogenic signaling and leukocyte trafficking in the peritoneal tumor environment.

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**Objective:** The HIV protease inhibitor ritonavir induces cell cycle arrest and apoptosis in the A2780 ovarian cancer cell line in vitro and in vivo.

**Methods:** Mice were divided into 4 treatment groups following IP tumor inoculation: 1) control injections of saline, 2) weekly gonadotropins, 3) weekly gonadotropins plus aromatase inhibitor, and 4) estradiol only. Animals were euthanized upon reaching a weight of 30 g, and ascites volume and cumulative tumor weight were recorded. Vascular endothelial growth factor (VEGF) levels in ascites supernatant were quantified with enzyme-linked immunosorbent assay. Estrogen-receptor alpha and beta (ERα, ERβ) expression was quantified with reverse transcriptase polymerase chain reaction. Tumor-infiltrating T-cell populations were scored using immunohistochemistry and characterized with flow cytometry.

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tumors showed larger areas of necrosis and activated caspase-3 staining together with TUNEL, indicating higher numbers of cells undergoing apoptosis. Consistent with this observation, western immunoblot revealed increased levels of cleaved poly ADP (adenosine diphosphate) -ribose polymerase (PARP) in ritonavir-treated xenografts.

**Conclusions:** Drug repositioning is an approach to expedite the long and exceedingly costly process associated with de novo drug discovery; usually by drawing on a compound's established safety and pharmacokinetic profile. Our study supported the idea of ritonavir as a potential candidate for repurposing from HIV to ovarian cancer. Additional in vivo studies will be needed to evaluate the efficacy in different cell lines and disease settings.

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**Palliative Care**

**335 The effect of religiosity on death anxiety and end-of-life care discussions among gynecologic oncology patients**

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**Objective:** To assess the relationship between religiosity and death anxiety and to examine a novel End-of-Life Care Discussion Scale (EOLCDS) among gynecologic cancer patients.

**Methods:** Hoge’s Intrinsic Religiosity Scale, Templer’s Death Anxiety Scale (DAS), and a 10-item EOLCDS were distributed anonymously to patients presenting to the gynecologic oncology clinic. All patients 18 years and older with a diagnosis of gynecologic cancer were eligible. Descriptive statistics were run on demographic variables. Bivariate correlations were run to examine the associations between death anxiety, religiosity, and openness to end-of-life-care discussions.

**Results:** Four hundred one surveys were distributed from February 2012 to June 2012. The response rate was 32.2% (n=129). The median age was 55 years (range, 20–84 years). The majority were Caucasian (72.9%). Cancers represented were as follows: ovarian (40.4%), uterine (19.4%), and cervical (18.6%). Thirty-five percent had advanced (stage III-IV) disease and 32.6% were currently receiving treatment, with chemotherapy being the most common treatment (61.9% of those receiving treatment). Most patients were self-reported Christians (85.3%). Higher scores on the EOLCDS were associated with lower death anxiety scores (r = -0.215, P < 0.05 [2-tailed]). Higher Hoge’s intrinsic scores (less religiosity) were positively associated with higher death anxiety scores (r = 0.288, P < 0.05 [2-tailed]). Religiosity was not significantly associated with the EOLCDS.

Advanced cancer stage correlated with lower Hoge’s intrinsic scores (more religiosity) (r = -0.288, P < 0.05 [2-tailed]). No significant relationship existed between cancer stage and score on the EOLCDS or DAS. Among patients who stated they practice religion (n=82), there was a stronger relationship between intrinsic religiosity and the DAS. In this subset of patients, r increased from 0.215 (P < 0.05 [2-tailed]) to 0.388 (P < 0.01 [2-tailed]), demonstrating that the relationship between religiosity and death anxiety was stronger among religious individuals.

**Conclusions:** Among gynecologic cancer patients, low levels of religiosity were associated with higher levels of death anxiety. Religiosity was not associated with the EOLCDS. Openness to end-of-life care discussions, as measured by the EOLCDS, was associated with less death anxiety. Patients may use religiosity to decrease death anxiety. The EOLCDS may be a useful clinical tool to evaluate patients' level of death anxiety and readiness to discuss end-of-life care.

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**336 The prevalence and impact of invasive procedures towards the end of life on patients referred to hospice care**


University of North Carolina at Chapel Hill, Chapel Hill, NC

**Objective:** To determine the prevalence of inpatient invasive procedures performed in patients who were referred to hospice and evaluate their impact on end-of-life (EOL) treatments and outcomes.

**Methods:** A retrospective cohort analysis of gynecologic oncology patients who were discharged from the hospital to hospice care from January 2009 to June 2012, comparing those who had invasive procedures (PRO) to those who did not (NOPRO), was conducted. PRO included laparotomy, G-tube placement, para/thoracentesis, radiology-guided biopsies and drains, port placements, and embolizations. Patients enrolled in hospice before admission were excluded. Clinical data included disease site and stage, clinical course of admission, hospice type chosen, treatment with palliative chemotherapy or radiation, hospital readmissions, and number and type of invasive procedures performed. Demographic data included age, race, and dates of death.

**Results:** Eighty-nine patients were identified. Median age was 63 years (range, 30 – 88 years); 61/89 (68.5%) were Caucasian and 23/89 (25.8%) were African American. Cancer types included: 41 (46%) patients with ovarian, 23 (29%) with uterine, 19 (21.3%) with cervical, and 6 (6.7%) with other cancers. Demographics did not differ between the 2 groups. Sixty-two percent (57/89) of patients had invasive procedures (PRO) within 4 weeks of hospice, while 35.9% (32/89) did not. There was no difference in PRO and NOPRO patient groups with respect to palliative chemotherapy (91% vs. 83%, P=0.48) or radiation treatments (8.7% vs. 16.1%, P=0.31), palliative care consultation (75% vs. 59%, P=0.22), the proportion of patients requiring inpatient hospice care (22% vs. 21%, P=0.87), or hospital readmissions (10.5% vs. 9.3%, P=1.00). Overall survival was not significantly different between the groups (56 days vs. 54 days, P=0.71).

**Conclusions:** The relationship between PRO and NOPRO during EOL care did not adversely affect palliative treatment delivery, hospital readmission rate, and home vs. inpatient hospice decision. We did not identify a survival difference with regard to use of invasive procedures. Caution should continue to be exercised when determining the need for performing invasive procedures in the palliative setting. Future research exploring invasive procedures and quality of life will be vital to our ability to accurately counsel and care for our patients during this difficult stage in their medical treatment.

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**337 A novel approach to palliative care and end-of-life decision-making: A patient-centered website to promote health care decision-making**

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**Objective:** Palliative care traditionally is delivered late in the course of disease, failing to alter quality of cancer care. For patients and families, barriers to optimal end-of-life care include deficient communication with family and providers, fears about being sick, and poorly defined and informed treatment goals. Our objective was to develop and evaluate an online interactive tool promoting decision-making about palliative and end-of-life care for ovarian cancer patients and their caregivers.

**Methods:** Cancer experts and ovarian cancer patients/caregivers joined in a design event to identify key issues for a website. Based on chronic care and decision-support models, a multidisciplinary team developed, tested (think aloud protocol), and refined a prototype intervention website over 18 months.
Components include: 1) information about ovarian cancer, palliative care, emotional health, and decision-making tailored to patients’ stage of disease and informational style; 2) social media (blog and journaling sites); and 3) resource tools such as self-monitoring, coping/communicating, and decision-making aids. The control website contains PDFs of information distributed as part of usual care. Specifically there is a fillable PDF. In a single university-based oncology clinic, 100 women with stage III/IV ovarian cancer and their caregivers are being equally randomized to the intervention or control website. Subjects are asked to access their web-system 3 times/week for 60 days. Evaluation surveys are completed at baseline and 60 days post-baseline. Primary outcomes include completion of an advance healthcare directive and decisions regarding palliative care. Additional measures include distress, support, attitudes, ovarian cancer knowledge, informational style, decisional conflict, health literacy, and website use, including time spent on the website, topics read, goals, and questions. Comparisons will be made between those assigned to the intervention or control websites.

Results: Usability testing revealed high website interest and satisfaction and identified key technical challenges, such as ways to provide feedback, emphasize important information, and limit remembrance between screens. Study completion is anticipated by 1/2013. Initial results will be discussed.

Conclusions: Results will be used to design a mobile application to include a clinic interface.

338 Palliative surgical procedures in the last 6 months of life: Effect on quality care measures
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Objective: To investigate the effect of palliative interventions on hospitalizations near the end of life (EOL) and to evaluate the impact of palliative interventions on EOL quality measures

Methods: A retrospective study of women with progressive or recurrent ovarian cancer from 2000-2008 who were hospitalized in the last 6 months of life was conducted at a single academic institution. Exclusion criterion: incomplete clinical information in the last 6 months of life. Palliative interventions related to the following clinical events were included: ascites, pleural effusion, bowel obstruction, obstructive uropathy. Outcomes: hospitalizations near the EOL and conformance to EOL quality measures. The National Quality Forum’s EOL quality measures were defined as: chemotherapy in the last 14 days of life, >1 hospitalization in the last 30 days, >1 emergency department visit in the last 30 days of life, dying in an acute care setting (intensive care unit), and admitted to hospice for >3 days. Wilcoxon signed-rank test and Fisher’s exact test compared outcomes between patients who underwent palliative procedures and those who did not.

Results: One hundred thirty-two patients met inclusion criteria. Ninety-four patients had at least 1 palliative procedure and 38 had no procedures performed. Frequency of clinical events and interventions was: (1) ascites (n=31): paracentesis 25/31, intraperitoneal drain 24/31; (2) pleural effusions (n=31): thoracentesis 16/31, pleural drain 11/31, chest tube 11/31, pleurodesis 9/31, video-assisted thoracoscopic surgery 2/31; (3) bowel obstruction (n=64): open gastrostomy 14/64, ostomy 13/64, resection/reanastomosis 4/64, lysis of adhesions 2/64, percutaneous gastrostomy 18/64; (4) obstructive uropathy (n=5): percutaneous nephrostomy 5/5. Patients who underwent palliative interventions had a higher average number of hospitalizations in the last 6 (2.38 vs. 1.71, P=0.008) and 3 (1.78 vs. 1.34, P=0.01) months of life. There was no difference in the number of hospital days in the last 30 days of life based on performance of palliative surgical procedures (11.3 vs. 9.4, P=0.28). Conformance with EOL quality measures was not statistically different between groups (Table).

339 The impact of outpatient hospice discussions on subsequent inpatient hospitalization in gynecologic oncology patients
University of North Carolina School of Medicine, Chapel Hill, NC

Objective: Hospice referrals are often made in the outpatient setting, but in gynecologic oncology, there is a subset of patients who will be discharged to hospice care from an acute inpatient hospitalization. The goal of this study was to determine the effect of prior outpatient exposure to hospice discussion on the subsequent inpatient course and end-of-life care among patients ultimately discharged to hospice.

Methods: Medical records of gynecologic oncology patients who were discharged from the hospital to hospice care (January 2009 – June 2012) were reviewed under an institutional review board-approved protocol. Patients with enrollment to hospice prior to admission were excluded. Demographic, clinical, and insurance data were abstracted. Hospice discussions were identified by abstraction of last outpatient clinical encounter before index admission. The Kaplan-Meier method and log-rank test was used to estimate overall survival and test for significant differences, and Wilcoxon test overall survival curves were generated.

Results: Eighty-nine inpatient hospitalizations resulted in discharge to hospice care. Forty-one women had ovarian cancer (46%), 23 uterine (29%), 19 cervical (21.3%), and 6 other (6.7%) cancers. Eighty-three patients (93%) were seen as outpatients before admission; 18% (15/83) were exposed to a documented hospice discussion during their last outpatient encounter (HD) while 82% (68/83) were not (NHD). Median time from last outpatient encounter was 18 days (range, 0-371 days). The NHD patients had a longer inpatient length of stay (median 7 days vs. 4 days, P=0.008) and were less likely to receive palliative care consultations (65% vs. 93%, P=0.0326) than the HD patients. Median overall survival (OS) for HD patients was 33 days (95% CI 22– 61) compared to 60 days (95% CI 49 – 84) for NHD patients (HR 2.2, 95% CI 1.17 – 4.15, P=0.0326). No differences found based on race, ethnicity, or insurance status.

Conclusions: HD patients had significantly shorter median OS after their final inpatient admission (Figure), implying that gynecologic oncologists were accurate in counseling these patients about end-of-life issues. Even among a subset of sick patients requiring hospital admission, those exposed to outpatient hospice discussions had shorter length of stay and increased utilization of palliative care resources. These benefits, crucial to quality of end-of-life care, suggest a need to broaden the scope of patients with whom timely hospice care discussions are held.

| Table. Association between palliative interventions and conformance with end of life quality indicators |
|----------------------------------|------------------|------------------|------------------|
| EOL quality measures            | Palliative interventions | No palliative interventions | P |
| Chemotherapy within last 14 days (n=11) | 8                | 3                | 0.61 |
| >1 hospitalization in the last 30 days (n=20) | 13               | 5                | 0.06 |
| Dying in acute setting (n=15) | 10               | 5                | 0.44 |
| Not admitted to hospice (n=8) | 49               | 11               | 0.84 |

Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology
Objective: Escalating costs require constant reassessment of health care programs. This study characterized the utilization of medical services by gynecologic cancer patients at an urban academic center at the end of life.

Methods: After institutional review board approval, we identified all gynecologic oncology patients registered at our institution who died between December 2006 and February 2012. Health care utilization measures per month included number of hospital days (HD), outpatient visits (OPV), blood draws (BD), radiology studies (Rad), chemotherapy infusions (Chemo), and invasive procedures (IP). Mixed effect linear regression models were used to test for time effect in the last year of life (STATA v9.0).

Results: Among the 116 patients with median follow-up of 1.4 years from first encounter to death, median age at diagnosis was 55 years (range, 27-85 years); 63% were Hispanic; 60% were primarily Spanish-speaking; 65% had stage III-IV disease; and 42%, 29%, and 22% had cervical, uterine, and ovarian cancers, respectively. Thirty-four percent of patients died in hospice, 27% in the hospital, 19% at home, and 11% at a skilled nursing facility. Median time from do not resuscitate (DNR)/do not intubate (DNI) documentation to death was 9 days; 66% of patients had no DNR/DNI documentation. Median time from last therapeutic intervention to death was 55 days. A significant time effect for all 6 utilization measures was seen during the study period (P <0.001) (Figure). Mean HD increased 6-fold, BD increased 3-fold, Rad increased 4-fold, and IP increased 3.5-fold. Conversely, OPV decreased 1.6-fold and Chemo decreased 3-fold. Trend changes were most dramatic during the last 2 months of life. Duration between patients’ first encounter and death was significantly associated with HD (P=0.01), BD (P<0.001), Rad (P=0.03), OPV (P=0.041), OPV (P<0.001), and Chemo (P=0.015). Of note, patients with continuous care for ≥1 year used fewer medical resources. Utilization was not significantly associated with ages at diagnosis and death, race, primary language, stage, tumor site, or follow-up time.

Conclusions: This is the first report quantifying the health care utilization of gynecologic cancer patients in a large, publicly funded hospital during their last year of life. The marked changes in use of diagnostic and treatment interventions in the last 2 months of life highlight the need to develop cost-effective, evidence-based metrics for delivering comprehensive cancer care. Importantly, our data support continuity of care as a significant determinant of inpatient and outpatient resource utilization.

At the end of life: Optimizing quality of care for women dying of cervical cancer

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Objective: End-of-life care is a vital component of gynecologic oncology, and appropriate hospice referral and associated symptom management are known to increase both quality and quantity of life. The objective of this study was to examine the use of palliative care services as well as markers for quality of life (QOL) at the end of life among women dying of cervical cancer and compare those dying in the hospital (IH) to those dying outside of the hospital (OH).

Methods: Women dying of cervical cancer from 2000 through 2009 at a single institution were identified, and demographics, end-of-life QOL indicators, palliative care interactions, and final hospitalization details were abstracted. Markers for QOL at the end of life that were examined included: hospitalizations in the last 6 months of life, intensive care unit (ICU) stay near death, and chemotherapy administration near the end of life.

Results: Eighty-six women with cervical cancer died from their disease during the study time period. The mean age at the time of death was 55 years (range, 12-90 years). The majority were white (80%), and insurance status varied, with 37% insured, 13% Medicaid, 19% Medicare, 17% uninsured, and 14% with an unknown insurance status. A total of 19 cervical cancer patients died IH and 7 died in the ICU. This represents 25% of all gynecologic oncology patients who died IH from 2000 through 2009. When women dying IH were compared to those dying OH, there was no difference in age, race, or insurance status. Cervical cancer patients dying IH had more hospitalizations during the last 6 months of life (2.8 vs. 1.4, P<0.005) and a greater proportion had an ICU stay near death (42% vs. 6%, P<0.0001). The time from last chemotherapy administration to death was shorter in cervical cancer patients dying IH versus OH (195 days vs. 80 days, P=0.01). There was no difference in the use of inpatient palliative care services.

Conclusions: Cervical cancer patients dying IH are more likely to have poor QOL indicators at the end of life. The similarity in the use of inpatient palliative care services suggests that end-of-life preparation may begin earlier and in the outpatient setting for women dying OH. Addressing end-of-life care earlier in a woman’s disease course may decrease in-hospital mortality and improve QOL for patients.
Beyond the dark side of the moon: Evaluating the quality of web-based information at the end of life

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Objective: To determine the quality of websites and search engines that gynecologic oncology patients encounter during a web search about palliative care, hospice, end-of-life care, and symptom management.

Methods: Four search engines (Google, Yahoo, Bing, Ask) were queried for search terms: “palliative care” (PC), “hospice” (HOS), “end of life care” (EOL), and “cancer symptom management” (SM). The websites on the first page of each search engine were used for analysis. Websites were characterized as nonprofit (NP), government (GOV), university-related (UNI), commercial (COM), or reference (REF). Paid ads were not evaluated. Websites were evaluated using DISCERN, a 16-question validated instrument to assess quality based on aims, relevance, references, treatment options, and overall impression.

Results: A total of 142 total websites were identified; 64 were paid and 78 were websites based on the search terms. Six websites were not accessible, leaving 72 for evaluation. Of these 72 websites, 23 (31.9%) were characterized as NP, 9 (12.5%) were GOV, 10 (13.9%) were UNI, 16 (22.2%) were COM, and 14 (19.4%) were REF sites. From all 4 search engines, PC had the highest number of unique web pages, followed by EOL (51.1%), HOS (47.9%), and SM (37.3%) with 1.4% being REF. Of all 72 websites, 14 (19.4%) were NP, 9 (12.5%) were UNI, 15 (20.8%) were COM, and 14 (19.4%) were REF sites. All search engines had a similar proportion of website types. There was no significant difference in DISCERN scores across search engines. Google had the highest mean score (58.7), followed by Yahoo (54.8), Bing (52.2), and SM (39.5) (P = 0.056.) With regard to website type, there was a significant difference in DISCERN scores, with REF sites having the highest mean score (67.9), followed by GOV (61.9), UNI (53.5), NP (49.4), and COM (28.4) (P < 0.001). There were significantly higher mean DISCERN scores with the search engines Ask (58.9, P < 0.001) and Google (55.3, P = 0.02) compared to Yahoo (52.4) and Bing (49.5). There was no correlation between individual search engine ranking and DISCERN score.

Conclusions: When patients and families search the internet for information regarding end-of-life care, the majority of websites encountered are of average to poor quality. Clinicians need to educate patients so they can obtain appropriate information. Reference and government sites have higher-quality information than other sites and patients should be encouraged to use these. Ask and Google result in significantly higher-quality websites and should be recommended as search engines. There is a trend toward better information with using “end-of-life care” as the search term.

Table. Distribution of Individual Website DISCERN Scores Based on Search Terms

<table>
<thead>
<tr>
<th>Search Terms</th>
<th>No. of Websites</th>
<th>Excellent (Score &gt;67)</th>
<th>Average (Score 44-67)</th>
<th>Poor (Score &lt;44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palliative Care</td>
<td>17</td>
<td>5</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Hospice</td>
<td>22</td>
<td>7</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>End-of-Life Care</td>
<td>22</td>
<td>3</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Cancer Symptom Management</td>
<td>20</td>
<td>3</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
<td>20</td>
<td>23</td>
<td>29</td>
</tr>
</tbody>
</table>

Public Health

Free testosterone is driver of cancer aggressiveness: Evidence from US population studies

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Objective: It has been reported that males tend to have higher cancer and mortality rates compared to females. Recently, more emphasis has been focused on a general gender difference underlying cancer rate and mortality. A higher male mortality rate was attributed to a higher male cancer incidence. However, the pathogenesis of higher male incidence of cancer remains unclear. In this study, we focused on survival to determine if there is a gender effect in cancer prognosis that could affect the future of treatment.

Methods: The last available Surveillance, Epidemiology and End Results (SEER) database was used to access survival data of the United States population. Around 1.2 millions of cases were included in the analysis. Cox and Kaplan-Meier method tested the impact of gender on survival across age and calculated the by-gender HR of dying from cancer 5 years following diagnosis. The distribution of HR across age was then compared with the distribution of 130 variables assessed in another large United States population study (National Health and Nutrition Examination Survey [NHANES] III). Kolmogorov-Smirnov test assessed the homology.

Results: Cancer survival was lower in males than in females in the age range 17 to 61 years. The risk of death from cancer in males was about 30% higher than that of females at the same age. The effect was more evident in African-Americans, in solid tumors, and in patients with metastatic disease. Interestingly, when compared to the 130 variables assessed in the NHANES III study, HR exactly matched the distribution of free testosterone, whereas none of the other 129 parameters investigated exhibited a similar homology.

Conclusions: Our findings suggest that male sex hormones are responsible for aggressive cancer in patients younger than 61 years. Therefore, antiandrogen therapies may be tested to reduce cancer mortality in male patients developing cancer before 61 years of age.
345 Occupational exposures and ovarian cancer: A national population-based cohort study

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Objective: Ovarian cancer risk is modified by genetic and reproductive factors. Studies have also demonstrated associations between occupational exposures and ovarian cancer. This study sought to determine whether ovarian cancer risk was associated with employment status, major occupational class, and/or specific occupations in a national population-based cohort study with data on both occupations and reproductive history.

Methods: The Canadian Census Mortality & Cancer Cohort was created by Statistics Canada through a linkage between the 1991 long-form Census, Canadian Cancer Database, Canadian Mortality Database, and Tax Summary Files. Women were grouped according to the 1991 Standard Occupational Classification (SOC) system into major occupational groupings and according to occupations/exposures suspected to be at increased risk of ovarian cancer. Women aged ≤74 years who were working as of 1991 were followed for cancer incidence until 2003. HR and 95% CI were determined using Cox proportional hazards modeling.

Results: There were 1,283,900 women in the linked cohort, 942,700 of whom were employed at the time of the 1991 census. Significant predictors of ovarian cancer incidence included age (HR 0.57, 95% CI 0.51 - 0.63 if age <40 years) and parity (HR 0.64, 95% CI 0.58 – 0.70 if ≥2 live births). When adjusted for age, women in religious occupations appeared to be at higher risk (HR 2.03, 95% CI 1.27 – 3.26). However, when parity was included as an adjustment factor, this risk was modified (HR 1.52, 95% CI 0.94 – 2.45). With the addition of parity, the age-adjusted risk for teachers was reduced from HR 1.17 (95% CI 0.94 – 1.43) to HR 1.12 (95% CI 0.94 – 1.33). When all covariates were included, the risk was nullified (HR 1.04, 95% CI 0.86 – 1.26). Overall, when age, parity, income, education, and province of residence were controlled for, employment status, major occupational groupings, and specific occupations were not associated with risk of ovarian cancer.

Conclusions: Reproductive factors play a major role in ovarian cancer risk, and reproductive factors can be independently related to occupation. When reproductive factors were considered, no significant association between occupational exposures and ovarian cancer was evident. Inclusion of reproductive factors in research on ovarian cancer may modify risk estimates and reduce bias. This can be a challenge when many population-based surveys do not include information on past pregnancies, live births, or genetic risk factors.

346 Comparison of the environmental impact of commonly used surgical approaches to hysterectomy

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Objective: The Da Vinci Robotic Surgical System is the focus of ongoing research to assess its clinical utility and costs (Intuitive Surgical, Sunnyvale, CA). The impact of these procedures on the environment, however, has not been assessed. With hospitals consuming 9% of United States energy and contributing 6,600 tons of waste to landfills each day, we sought to investigate the sustainability of this new, technology-driven surgical modality.

Methods: After obtaining institutional review board approval, we retrospectively reviewed 50 consecutive patients (pts) undergoing a staging procedure for endometrial cancer in each of the following 3 methods: robotic-assisted laparoscopic hysterectomy (RA-TLH), total laparoscopic hysterectomy (TLH), and total abdominal hysterectomy (TAH) for a total of 150 pts. Intraoperative data and demographic information were recorded, including body mass index (BMI), uterine weight, age, and prior surgical history. The energy consumption and solid waste produced were quantified and their resulting carbon emission equivalents were calculated to determine the “carbon footprint” of each. Continuous variables were analyzed using student’s t-tests, and variation in BMI and uterine weights for the groups were controlled for using ANOVA methodology.

Results: RA-TLH had the largest carbon footprint at 40.3 kg CO2/pt (P<0.01). TLH also generated more solid waste (14.3 kg/pt) than TAH (11.2 kg/pt) or RA-TLH (8.3 kg/pt). TAH had the shortest operative time (243 minutes), followed by RA-TLH at 375 minutes and TLH at 409 minutes (P<0.01).

Conclusions: The increased carbon footprint of RA-TLH over conventional laparoscopy and laparotomy for hysterectomy is a result of both increased waste production and energy usage. This increased environmental impact necessitates further research into the development of sustainable health care technology and techniques.

347 Regional variation in the incidence of gynecologic malignancies (GM) in the US

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Objective: To describe regional variation in the incidence of GM.

Methods: A total of 212,541 women in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) dataset diagnosed with invasive GM from 2000 through 2009 were identified in 16 geographically determined registries. Average annual age-adjusted incidence rates per 100,000 women (IR) of uterine, cervical, ovarian, and vagina/vulva/other malignancies were calculated. Correlation of IR of the primary tumor sites within regions was evaluated with Pearson’s r.

Results: The national incidence rate (NIR) of GM for all registries combined was 49.1 (95% CI 48.9-49.3). The highest IR (57.2; 95% CI 56.5-57.8) was in New Jersey (NJ); the lowest IR was in Louisiana (LA) (42.8; 95% CI 41.9-43.6). In 6 registries, the IR of GM was significantly higher than the NIR, and in 8 registries, the IR was significantly lower. To avoid overstating variability in the less common tumors, rates were standardized by expression of regional IR as a percent of the NIR. We found significant regional variation in the incidence of GM. The standardized IR of all primary gynecologic tumors combined ranged from 87% (LA) to 116% (NJ). Substantial regional variation was found in each of the primary tumor sites. The range of standardized IR was 72% to 126% for uterine, 67% to 126% for cervical, 83% to 111% for ovarian, and 76% to 124% for vagina/vulva/other tumors. Standardized IR of ovarian malignancy was moderately correlated with uterine and vaginal/vulva/other tumors (r=0.4 for each); rates of cervical cancer were essentially uncorrelated with any other primary site (range of r = -0.3 to 0.3).

Conclusions: A component of any regional variation in resource utilization, and expense for gynecologic cancer care can be attributed to the observed variation in incidence rates. Precise understanding of this variability can assist in optimizing clinician workforce, as well as allocation of funding for prevention, early detection, treatment, and other scarce resources.
348

Using social media as a research platform for rare gynecologic tumors
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Objective: To perform a cross-sectional epidemiologic and quality-of-life survey of patients with neuroendocrine tumors of the cervix using the social media network Facebook.

Methods: An established support group of patients with neuroendocrine tumors of the cervix was identified on the social media network Facebook. Members of the group were asked to voluntarily complete an online institutional review board-approved survey composed of 106 questions evaluating clinical presentation, treatment, recurrence, and quality-of-life endpoints.

Results: The survey was available for 31 days. In that time, 57 women with small cell or large cell cervical cancer responded. Respondents hailed from 24 countries including the United States (79%), the United Kingdom, (5%), Australia (5%), Norway (4%), Canada (2%), Hong Kong (2%), and New Zealand (2%). United States patients came from 26 states, with no state representing more than 9% of the sample. Mean age of respondents was 38.5 years (range, 24-67 years). Respondents received clinical care at 51 different clinical centers, with more than 9% of the sample. Mean age of respondents was 38.5 years (range, 24-67 years). Respondents received clinical care at 51 different clinical centers, with more than 9% of the sample.

Conclusions: The social media network Facebook provides an efficient and timely method to conduct such studies.

349

Pretreatment oncology reproductive counseling improves quality of life and satisfaction with health care in survivors of gynecologic cancers
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Objective: To determine the relationship between reproductive health counseling and quality of life in gynecologic cancer survivors.

Methods: A written and electronic survey was sent to women with ovarian, uterine, cervical, vulvar, and vaginal cancers diagnosed from 1993 through 2007 who were between the ages of 18 and 40 years at time of diagnosis. Survey questions explored the relationship between 10 reproductive health issues (including effect on menses, ability to have a baby, treatment-related early menopause) and posttreatment quality of life. Quality-of-life measures included the Decision Regret Score, Satisfaction with Life Scale, World Health Organization QoL, and Reproductive Concerns Scale. Linear regression was used to assess this relationship.

Results: A total of 237 surveys have been returned to date. Of these, 197 reported undergoing treatment with potential to affect fertility. Fifty percent reported receiving some counseling on posttreatment fertility issues. Those who received counseling reported improved quality-of-life scores (16.8 vs.16, P<0.05) and less regret (9.3 vs.12, P<0.01) compared to those who were not counseled. The more reproductive health issues discussed, the lower the regret score (P<0.01) and the more satisfied patients were with their cancer and fertility care (P<0.01). However, increased number of issues addressed had no significant effect on global life satisfaction (P=0.44).

Conclusions: Pretreatment reproductive outcome counseling from the gynecologic oncology team improved quality of life in women with gynecologic cancer. These data suggest that the more reproductive health issues a gynecologic oncologist can address before cancer treatment, the better a patient's posttreatment quality of life and the higher her satisfaction with her health care afterwards.

350

Lower-limb drainage mapping for lymphedema risk reduction after pelvic lymphadenectomy for endometrial cancer
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Hôpital Européen Georges-Pompidou, Paris, France

Objective: To evaluate the feasibility of identifying the lower-limb drainage nodes (LLDNs) during pelvic lymphadenectomy for endometrial cancer to describe lower-limb drainage and to assess the diagnostic value of the mapping technique.

Methods: Pilot prospective study of patients with endometrial cancer requiring pelvic lymphadenectomy. A radioisotope was injected into both feet the day before surgery. LLDNs were identified using preoperative lymphoscintigraphy (LS) and intraoperative isotopic detection, then removed before complete pelvic lymphadenectomy. LLDNs and pelvic lymphadenectomy specimens underwent separate histologic analysis.

Results: Of the 12 patients with early-stage endometrial cancer, 10 underwent preoperative LS, which consistently identified inguinal, femoral, and pelvic LLDNs. The intraoperative detection rate was 83% (10/12). The 2 patients without intraoperatively detected LLDNs had LS-detected LLDNs. Median number of hot nodes per patient was 5 (range, 3-7) on the right and 3 (range, 2-6) on the left. Of 107 LLDNs, 106 were in the external iliac area, including 38 in the lateral group and 45 in the intermediate and medial groups. No patient had node metastases. No early complication related to the technique occurred.

Conclusions: Our mapping technique appears feasible, safe, and associated with a high LLDN identification rate. LS mapping may allow the preservation of LLDNs, thereby decreasing the risk of lower-limb lymphedema and improving quality of life.

Quality of Life

349

Pretreatment oncology reproductive counseling improves quality of life and satisfaction with health care in survivors of gynecologic cancers
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Objective: Counseling about reproductive health outcomes has been shown to improve quality of life in nongynecologic cancer patients. We sought to determine the relationship between reproductive health counseling and quality of life in gynecologic cancer survivors.

Methods: A written and electronic survey was sent to women with ovarian, uterine, cervical, vulvar, and vaginal cancers diagnosed from 1993 through 2007 who were between the ages of 18 and 40 years at time of diagnosis. Survey questions explored the relationship between 10 reproductive health issues (including effect on menses, ability to have a baby, treatment-related early menopause) and posttreatment quality of life. Quality-of-life measures included the Decision Regret Score, Satisfaction with Life Scale, World Health Organization QoL, and Reproductive Concerns Scale. Linear regression was used to assess this relationship.

Results: A total of 237 surveys have been returned to date. Of these, 197 reported undergoing treatment with potential to affect fertility. Fifty percent reported receiving some counseling on posttreatment fertility issues. Those who received counseling reported improved quality-of-life scores (16.8 vs.16, P<0.05) and less regret (9.3 vs.12, P<0.01) compared to those who were not counseled. The more reproductive health issues discussed, the lower the regret score (P<0.01) and the more satisfied patients were with their cancer and fertility care (P<0.01). However, increased number of issues addressed had no significant effect on global life satisfaction (P=0.44).

Conclusions: Pretreatment reproductive outcome counseling from the gynecologic oncology team improved quality of life in women with gynecologic cancer. These data suggest that the more reproductive health issues a gynecologic oncologist can address before cancer treatment, the better a patient's posttreatment quality of life and the higher her satisfaction with her health care afterwards.

351

Pilot study of the PARO therapeutic robot demonstrates decreased pain, fatigue, and anxiety among patients with recurrent ovarian carcinoma
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1University of California Irvine Medical Center, Orange, CA, 2University of Tokyo, Tokyo, Japan

Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology
Objective: Because recurrent ovarian cancer (ROC) is rarely curable, quality of life (QOL) is a priority among patients receiving chemotherapy. Animal-assisted therapy has been shown in other diseases to improve QOL but its applications in ROC are limited. The PARO therapeutic robot is a harp seal designed to interact with patients through 5 unique sensors that respond to touch, light, sound, temperature, and posture. Clinical trials in Alzheimer’s disease have reported improved QOL and cognitive function. We sought to prospectively assess the impact of PARO on QOL among patients with ROC.

Methods: A nonrandomized pilot study was designed to evaluate 9 QOL parameters using a 100-point visual analog scale immediately prior to and following completion of chemotherapy. Beginning with cycle 2, patients were allocated to interaction with PARO and completed pre- and postinfusion QOL questionnaires. Paired t-tests were used to evaluate changes in QOL parameters between cycle 1 (without PARO) and 2 (with PARO). If a QOL signal was detected, a second stage was planned.

Results: From June through August of 2012, a total of 20 patients were enrolled, of whom 12 were evaluable at time of first analysis. The median age was 67 years (range, 49-71 years), 67% were white, and 92% had ROC. Baseline QOL scores did not differ significantly among patients. There was a total of 48 hours of interaction with PARO (Figure). When compared to cycle 1, the PARO-containing sessions were associated with significantly greater improvement in pain ($P=0.04$), fatigue ($P=0.034$), and anxiety ($P=0.036$) (Table). PARO was also associated with superior health-related QOL when taking into account all 9 QOL variables ($P=0.03$) (Table). Ninety-two percent of patients reported they enjoyed their interaction with PARO and desired to use it again.

Conclusions: This constitutes the first report of a clinical trial in oncology using the PARO therapeutic robot. PARO significantly improved QOL in ROC in all parameters studied. Cohort expansion with randomization and adoption of the ovarian cancer-specific modified FACT-O instrument is underway. Potential applications to address chemobrain among ovarian cancer patients are implicit.

Table. QoL Results Reported as Mean ± Standard Deviation

<table>
<thead>
<tr>
<th>QOL Parameter</th>
<th>Post - Pre VAS Score Without PARO</th>
<th>Post - Pre VAS Score With PARO</th>
<th>Difference Without PARO - With PARO</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>8.9±7.1</td>
<td>-6.4±9.7</td>
<td>15.3±16.3</td>
<td>0.040</td>
</tr>
<tr>
<td>Fatigue</td>
<td>18±23.7</td>
<td>-5.7±20.8</td>
<td>23.7±27.8</td>
<td>0.034</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2.5±19.6</td>
<td>-15.2±12.9</td>
<td>17.7±21</td>
<td>0.036</td>
</tr>
<tr>
<td>Average QOL</td>
<td>4.5±8.5</td>
<td>-9.4±12.1</td>
<td>13.9±15.9</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Results will be used to develop a mobile application intervention.

An interactive website for patients with ovarian cancer and their caregivers - can we improve quality of life?

M. Geller, S. Petzel, R. Vogel, M. McClellan, J. Jacko, J. Cragg, M. Gerber, D. Chan, F. Sainfort, University of Minnesota, Minneapolis, MN

Objective: Health internet sites increasingly are used by patients to access information and resources to augment traditional care. Current websites for patients with ovarian cancer rely on excessive text-based information with little evaluation and have few resources tailored to patient/caregivers’ needs or to promote interactive communication. Our objective was to improve quality-of-life (QOL) outcomes for women with ovarian cancer and their caregivers using an online system we created that is applicable across the disease trajectory.

Methods: Clinical and research experts met with 22 ovarian cancer patients and caregivers in an all-day design event to identify key issues for the proposed system. Based on chronic care and decision-support models, a web-based prototype system was developed, tested, and refined to serve as the intervention. Core content components are: 1) Learning Library-information about ovarian cancer, palliative care, emotional health, and decision-making tailored to patients’ treatment stage and informational style; 2) Discussion Forum using social media technology; and 3) Resource tools, including self-monitoring, coping/communication, journaling, and decision-making tools. Based on health education/behavioral research, guidelines established to promote consistency in content design recommended incorporating: 1) health literacy, 2) maximal interaction and practice, 3) video to engage users/provide credible role models, 4) goal setting, 5) user control of amount of information accessed, and 6) user support and reinforcement (Figure). The control website contains PDFs of information distributed in the clinic as part of usual care. Patient and caregiver websites are accessible to partners/providers by user consent. In a university-based cancer clinic, 100 women with stage III/IV ovarian cancer and their caregivers were randomized to an intervention or control website. Subjects are asked to use their respective web-based system 3 times/week for 60 days. A survey at baseline and 60-days post-baseline include QOL measures, health literacy, and demographics. Website use is tracked. Comparisons are being made between those assigned to the intervention vs. control websites.

Results: Website usability testing revealed high interest and satisfaction with the site. Study completion is expected by January 2013. Initial results, design challenges, and user issues will be discussed.

Conclusions: Results will be used to develop a mobile application intervention.
Abstracts presented for the 44th Annual Meeting of the Society of Gynecologic Oncology

353
Pilot study evaluating the integration of psychological assessment among women undergoing care for gynecologic malignancies
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Objective: To assess depression, anxiety, and support among women diagnosed with gynecologic malignancies during different phases of their disease.

Methods: Women 18 years and older who presented with a diagnosis of gynecologic cancer were prospectively evaluated in this study. Each participant, after informed consent was obtained, completed a series of self-administered surveys, including functional assessment of cancer (FACT-G), patient health questionnaire (PHQ), brief scale for anxiety (GAD), and general information questions. Descriptive statistics were assessed on demographic variables. Bivariate correlations were also assessed to examine associations between disease status, anxiety, depression, and patient support.

Women with high scores were referred to the psychiatric department for a more comprehensive assessment.

Results: A total of 152 patients were enrolled in the study. The median age was 56.5 years (range, 21-85 years). The majority of participants were in remission (44.4%), diagnosed with ovarian cancer (33.6%), and had stage I/II disease (36.0%). Approximately 11.8% of participants had a GAD score of 10 or more, 7.2% had a PHQ score of 10 or more, and 76.5% reported having family support. No difference was observed among different stages of disease and high GAD (P=0.70), high PHQ (P=0.26), and family support (P=0.38). There was a significant difference among high PHQ and type of cancer among women with ovarian cancer presenting with a high PHQ (P=0.01). No difference was seen for high GAD and type of cancer (P=0.34). No difference was seen among high GAD score (P=0.06) and high PHQ score (P=0.33) and stage of disease. High GAD score (P=0.03) and high PHQ score (P=0.00) was seen among women with no family support.

Conclusions: Psychological conditions among women with gynecologic malignancies seemed to be influenced by family support and type of cancer rather than phase of disease. Integration of a psychological assessment program should be considered in a comprehensive cancer program.

354
Idiographic assessment of quality of life of women with high risk gynecological malignancies
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Objective: Women with high-risk gynecologic malignancies experience significant psychosocial and physical symptoms that may affect quality of life (QOL). Traditional instruments for assessment, including the EORTC Quality of Life Questionnaire, have been validated in gynecologic malignancies. However, we hypothesize that significant domains of symptom burden are underestimated by these methodologies. Idiographic assessment of quality of life uses patient-generated domains of symptom burden. The goal of this pilot study was to evaluate the feasibility of a novel assessment instrument for quality of life, “idiographic assessment,” and compare assessed symptom burden to results from traditional assessment tools.

Methods: Twenty-seven patients with gynecologic malignancies and estimated survival of <35% at 5 years were consecutively identified at our outpatient gynecologic oncology clinic and asked to complete a QOL survey that included traditional and idiographic measures. Data from 25 evaluable surveys compared results from traditional and idiographic measures.

Results: Ninety-two percent of eligible patients agreed to answer the study survey. Symptom burden assessed from the EORTC QLQ-C30 was low. The most troublesome symptoms were pain (10 [38%]), fatigue (10 [38%]), and interference with social activities (11 [42%]). The idiographic survey produced 204 goal statements. A total of 144 (71%) of goal statements were not yet attained by patient report, and 59 (29%) of patients were not satisfied with their progress toward achieving goals. Forty-six percent of goal statements were reported as difficult to achieve by patients, help was needed for 45%, and more help was asked for with 30%. Symptoms provoked by goal attainment included pain (84 [41%]) and fatigue (98 [60%]). Twenty-one domains of goal attainment were identified. The most common domains were cancer treatment, independence and interpersonal relationships.

Conclusions: Idiographic survey is feasible in an ethnically, racially, and socioeconomically diverse population of women with high-risk gynecologic malignancies. Idiographic survey may provide a measurement of symptom burden that more accurately reflects issues that affect patient quality of life than that provided by traditional assessment tools.

355
Self-reported physical activity among gynecologic oncology patients in an outpatient setting: A pilot survey
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Objective: Studies have shown that physical activity (PA) programs can improve a cancer survivor’s quality of life and enhance recovery. However, health care providers may not know how to assess their patients’ levels of daily PA. As such, promoting PA remains challenging. The purpose of this study was to assess daily PA among patients with a self-reported assessment of activity level.

Methods: After obtaining institutional review board exemption, patients were asked to complete a modified MOSPA survey, which is a 13-item tool that asks questions regarding PA levels, intensity, frequency, and type. Fisher’s exact test was used to evaluate tests of general association. The nonparametric Jonckheere-Terpstra method was used to test for ordered differences among the ordinal responses to survey questions. We hypothesized that responses would vary by age.

Results: Two hundred seventeen women completed the survey of whom 28 (13%) were in treatment, 169 (78%) had completed therapy, and 20 (9%) did not specify and were excluded. There was no significant difference in PA levels between the women in active treatment (14%) and those who completed their therapy (9%) (P=0.72). Fifty percent of women reported light PA, and 41% of patients reported vigorous PA. Older patients (median 58 years) were less likely to believe that they could engage in vigorous PA than younger patient (median 51 years; P <0.0001). Of the 28 women in active treatment, 50% reported performing light PA and 36% vigorous PA. Of the 28 women in active treatment, 50% reported performing light PA and 36% vigorous PA. The majority of women answered that they can walk, 39% do aerobic exercise, 26% do yoga, 31% can dance, and 57% can stretch. However, more older women did walking for exercise (P <0.001), while younger women engaged in aerobic exercise (P <0.001) or dancing (P <0.002). Women who reported access to the internet were significantly younger (P=0.002), as were those who used Facebook (P <0.0001).

Conclusions: Among patients in a gynecologic oncology clinic, age was associated with belief about the level and type of exercise. One-third of women who said that they did not need more exercise reported only light exercise. This is a group we need to further investigate. If we use the internet for intervention strategies, we will likely miss the more elderly patients, thus suggesting that a mixed mode approach in development of interventions should be considered.

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S137
Reintegration of cervical cancer survivors: A survey of women’s health providers

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Objective: There is an expanding body of literature surrounding cancer survivorship and the role of cancer survivor care plans, but limited data specifically related to cervical cancer survivors (CCS) and the perspectives of women’s health providers (WHP) in caring for this group of survivors.

Methods: WHP were identified in the referral base for an academically affiliated public teaching hospital. A self-administered questionnaire was developed to assess: 1) provider opinions surrounding reintegration of CCS back into WHP care, 2) perceived barriers to providing care to this patient population, and 3) acceptability of a survivor care plan (SCP) similar to the one released by the Society of Gynecologic Oncology in September 2012.

Results: A total of 33 WHP from 5 practice sites agreed to participate, with 29 completed surveys returned for a response rate of 87.9%. Nineteen respondents declared a specialty: 36.8% represented family medicine (FM) and 63.2% obstetrics-gynecology (OB/GYN). Ninety-three percent of providers reported being willing to provide surveillance care to CCS at low risk for recurrence (100% FM, 91.7% OB/GYN), but only 34.5% reported being willing to provide surveillance care for high-risk CCS following a 2-year surveillance period with a specialist (42.9% FM, 25% OB/GYN). Among all providers, 93.1% agreed that it was important for CCS to reintegrate out of subspecialist care back into generalist care. Identified barriers perceived by community WHP included: limited communication with specialists, lack of education and support resources for patients, lack of continuing education for providers, and time constraints. Ninety-three percent of providers felt the SCP would allow them to feel more comfortable in caring for CCS, reporting the most useful aspect of the SCP being surveillance recommendations.

Conclusions: WHP in our survey overwhelmingly agreed that reintegration into generalist care was important for CCS. Our data demonstrated a high level of willingness on the part of WHP to reassume care for patients deemed at low risk for recurrence. They were largely unwilling to reassume care for high-risk patients, even after initial surveillance with a specialist, with OB/GYNs being the least willing. The SCP was well received among all participating providers and may improve WHP comfort in reassuming care for CCS.

Sexual function in older cancer survivors

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Objective: To compare the sexual function of older cancer survivors with other older adults.

Methods: Secondary analysis of the National Social Life, Health, and Aging Project (NSHAP) was performed to examine sexual function in older cancer survivors. The NSHAP survey was conducted to investigate sexuality of older adults (ages 57 to 85 years) in the United States. We compared older cancer survivors to other older adults, with gender-specific analyses. Outcomes included sexual partnership, activity, frequency, attitudes and beliefs, and problems. Our statistical analysis (SAS 9.2, SAS Institute, Inc.) achieved 89.9% power to detect a difference of 10% sexual activity within the last 12 months (assuming a prevalence of 45%) with a significance level of 0.05.

Results: A total of 1,550 women and 1,455 men were included. One hundred ninety-eight (6.5%) women were cancer survivors. Mean age was slightly higher in cancer survivors (70.2 vs. 68.2 years, P=0.005). The most common cancer was breast cancer (38.6%), followed by ovary/uterus/cervix (32.4%). Female cancer survivors were less likely to have a current sexual partner (50 vs. 62.6%, P=0.004). Female cancer survivors were less likely to report sexual activity the last 12 months compared with other women (P=0.03). No differences were seen between the groups in attitudes or types of activity. Among those with a current partner, female survivors were more likely to report lack of interest (P=0.04). One hundred eighty (6.0%) men were cancer survivors. Mean age (69.4 vs. 67.3 years, P=0.0008) was slightly higher in cancer survivors compared with other men. The most common cancers were prostate (47.1%) and colorectal cancer (16.2%). The percentage of men with a current sexual partner was similar between male cancer survivors and other men. The only difference in types of sexual activity were that male survivors were less likely to report vaginal coitus (P=0.001) and masturbation (P=0.05). Survivors were less likely to report sexual activity the past year compared with other men (P=0.04). Male survivors tended to be less likely to believe sex was essential to maintaining a relationship (P=0.06). Cancer survivors were more likely to report lack of interest/pleasure, erectile problems, pain, and anxiety (P <0.05).

Conclusions: We found sexual activity to be similar among genders regardless of cancer survivor status, although sexual frequency was decreased and lack of interest more common in cancer survivors. These findings suggest that sexual activity is an important quality-of-life issue to be addressed with cancer survivors regardless of gender or type of cancer.

Improvement in quality of life after robotic surgery results in patient satisfaction

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Objective: There are well-described benefits to minimally invasive surgery, including shorter hospital stay and recovery period and decreased blood loss. The role of robotic surgery in gynecologic oncology has become increasingly prominent, but limited data are available on quality of life (QOL) after robotic surgery.

Methods: In this prospective, institutional review board-approved study, women scheduled for robotic surgery for a gynecologic indication completed validated QOL measures at baseline, 6 weeks postoperative (6wk), and 4 months postoperative (4mo). Functional status (SF-12), symptom severity and interference (MD Anderson Symptom Inventory, MDASI), sexual function (FSFI), and satisfaction with decision-making (SWD) were assessed at relevant time points. SPSS version 19 was used to analyze the data. Differences between groups were evaluated using the Mann Whitney test.

Results: Between 05/08 and 02/12, 406 women underwent robotic surgery and 286 (70%) completed the QOL measures. Median age was 55.2 years (range, 25.7-85.1 years). Thirteen percent were Hispanic, 75% were white, and 7% were black. Indications for surgery included cervical cancer/dysplasia (17%), adnexal mass (15%), endometrial cancer/hyperplasia (52%), and other (3%). While physical functioning scores declined from baseline to 6wk (51.5 to 41.6, P<0.001), they improved at 4mo (53.3). Mental functioning scores improved over time: baseline (48.7), 6wk (52.8), and 4mo (55.4, P<0.001). Symptom severity decreased over time: baseline (14), 6wks (11), and 4mo (8, P=0.04). Symptom interference significantly improved: baseline (6), 6wks (5), and 4mo (1, P<0.001). At 4mo, all symptoms resolved, with the exception of fatigue, which had decreased significantly compared to baseline levels (score = 1, P<0.001). Sexual function (FSFI) improved significantly from baseline (8.4) to 4mo (20.2, P<0.001). Patients were extremely satisfied with their decision to have robotic surgery at 6wk (SWD=30/30) and at 4mo (SWD=30). These findings remained consistent by procedure and by age.

Conclusions: In this prospective study, general health and symptom burden returned to or improved beyond baseline levels within 6 weeks of robotic surgery. Sexual function improved significantly at 4 months to levels surpassing baseline scores. As a result, women were highly satisfied with their decision to undergo robotic surgery.
Objective: To evaluate the short-term impact of acupuncture and massage on symptoms and well-being in gynecologic cancer patients and to assess the long-term impact of acupuncture and massage on health-related quality of life (QOL).

Methods: Between May 2009 and June 2012, gynecologic oncology patients were enrolled in this pilot study for treatments with either acupuncture or massage. Treatments were provided at no cost under a philanthropic grant from Abra Prentice Wilkins. Patients self-selected 5 sessions of acupuncture, massage, or combination of both. The participants completed assessments at baseline and end of study based on 4 FACT surveys and the Brief Pain Inventory. The Edmonton Symptom Assessment Scale was completed immediately before and after each of the 5 treatments. Massage and acupuncture were administered during chemotherapy in the outpatient infusion suite, inpatient unit, or at the integrative medicine center. Statistical analysis included chi-square and t-test.

Results: A total of 124 patients were enrolled, 32 patients completed all 5 sessions, 31 died before completion, and 63 completed between 1 and 4 treatments. Among the patients who completed the study, the average age was 53 years, the majority (59%) had ovarian cancer, 18% had endometrial cancer, and most patients (93%) were on active treatment (chemotherapy or radiation) at the time of enrollment. At the time of the data analysis, approximately 30% of the enrolled patients had died. Among the 126 massage and 68 acupuncture treatments, patients reported statistically significant (P<0.05) decreases in symptoms and improvement in sense of well-being and appetite following individual treatments. Analysis for those who completed all 5 treatments and who were alive showed statistically significant higher functional well-being between the baseline and end of study (P=0.011). Those patients who died had comparatively lower emotional, functional well-being, and global QOL scores. Furthermore, there were no significant changes in QOL or symptoms between baseline and end of study for the deceased patients. There were no significant differences in QOL or symptoms between massage and acupuncture.

Conclusions: Gynecologic oncology patients reported significant symptom relief across a wide spectrum of symptoms after individual treatments. Those patients who were alive at the end of 5 treatments expressed significant improvement in functional well-being over the study period.

360
Physician preferences for involvement in survivorship care: Are benign gynecologists ready?
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Objective: With estimates for the number of cancer survivors approaching nearly 20 million by the year 2022, establishing plans for the continued care of this population is crucial. As resources become more limited, involving benign gynecologists in the care of cancer survivors is increasingly important. Our objective was to investigate benign gynecologist willingness and comfort in evaluating and managing gynecologic cancer survivors.

Methods: A prospective survey was launched to benign gynecologists who were current members of the American Medical Association. An email was sent to 10,000 physicians at random with a link to an online survey. Demographic and practice information was collected, and respondents were asked about their comfort in implementing American College of Obstetrics and Gynecology (ACOG) screening guidelines, evaluating specific issues in a patient previously treated for a gynecologic malignancy, and managing potential medical and surgical complications. Analyses were performed with summary statistics.

Results: A total of 121 physicians completed the questionnaire. Of these, 74 (61.2%) were female, 51 (42.2%) were older than 50 years of age, 79 (66.4%) were in private practice, and 75 (55%) had been out of residency for >15 years. Greater than 80% of respondents reported being very comfortable implementing ACOG screening guidelines for osteoporosis, breast cancer, and colorectal cancer. Of the potential comorbidities of cancer treatment, gynecologists were least comfortable evaluating patients for lymphedema (61.9%), bowel obstruction (38.9%), and bowel incontinence (38.1%). Physicians reported being least comfortable with managing lymphedema (78.4%), renal dysfunction (76.1%), and bowel incontinence (71.7%). A large proportion was also uncomfortable managing diabetes (56.3%), hypertension (54.5%), and infertility (39.8%). Thirty-seven (33.3%) gynecologists reported being comfortable assuming primary responsibility for cancer survivors only at 5 years posttreatment; 6 (5.4%) were not willing to care for a cancer survivor at any time. All 6 reported being uncomfortable managing rectal bleeding, osteoporosis, lymphedema, and renal dysfunction.

Conclusions: There is variability among gynecologists with regard to level of willingness and comfort in treating cancer survivors. These data warrant further investigation with a larger survey but suggest that an organized multidisciplinary approach is probably best to optimize care for these women.

Rare Tumors
361
Presentation and management of borderline ovarian tumors: Should mucinous tumors be managed differently?
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Objective: Relatively little data exist on optimal surgical staging for mucinous borderline ovarian tumors. Surgical staging is not without complications; thus, a better understanding of the optimal staging for mucinous borderline ovarian tumors is needed.

Methods: A historic cohort study was completed looking at all cases of borderline ovarian tumors at a single institution between 1976 and 2005. Cases of borderline ovarian tumor were confirmed by pathology report. Multiple variables were examined, including procedure performed, residual disease after surgery, surgical stage, histologic type, presence of microinvasion, site of primary disease, date of recurrence, whether or not adjuvant chemotherapy was given, and whether or not there was death secondary to disease.

Results: Of 146 identified cases of borderline ovarian tumor, 50 were of the mucinous type. Of these, 1 case (2%) was noted to have an appendix positive for mucinous borderline tumor, and this case was complicated by pseudomyxoma peritonei. One case (2%) was noted to have a single pelvic lymph node positive for mucinous borderline tumor with no other sites of disease. There were 2 cases (4%) of recurrence, 1 of which was stage IC with pseudomyxoma peritonei and no residual disease that recurred in the large intestine and pelvis and had associated pseudomyxoma peritonei 3 years after initial diagnosis. The other recurrence was unstaged; the patient underwent a right salpingo-oophorectomy and had recurrence in the pelvis 2 years later. After undergoing adjuvant chemotherapy, the patient had no further recurrences. Only 1 other patient received chemotherapy for a total of 4% of all patients. There were no (0%) deaths secondary to disease. Mean follow-up was 73.5±72.1 months.

Conclusions: Conventionally, ovarian cancer is staged by completing a hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection, and omentectomy. In cases of mucinous cancer, an appendectomy is also performed. Based on our data, there is a low risk of either appendiceal or lymph node involvement and a low risk of recurrence. However, there is a significant risk of complications when lymphadenectomy and appendectomy are performed. Thus, it may not be necessary to complete an appendectomy or lymph node dissection in cases of mucinous borderline...
ovarian cancer. On the contrary, in a patient presenting with pseudomyxoma peritonei, completion of a full surgical staging may be advisable.

362

Glassy cell carcinoma of the cervix: A systematic review and meta-analysis
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Objective: To report the incidence, clinical features, and survival of patients with glassy cell carcinoma of the cervix (GCCC).

Methods: A retrospective chart review was performed at 2 academic centers from 1990 through 2011 and combined with a PubMed database search to retrieve all English published abstracts and papers from 1976 through 2011 regarding GCCC. Patient demographics, stage, treatment, and follow-up data were obtained. Descriptive statistics and Kaplan-Meier plots for overall survival (OS) were used for analysis.

Results: A total of 40 studies (24 case series and 16 case reports) of 279 patients and 13 patients from our chart review were included for a total of 292 patients. The incidence at our institutions was 1.6% of all cervical cancers in the study period, which was comparable to the incidence reported in the literature (0.2% to 9.3%). Overall, the average age at the time of diagnosis was 46.9 years, the majority of patients were white (64.9%) and had early-stage disease (50.3% stage I, 29.1% stage II). The overall recurrence rate across all stages was 22% and 5-year OS was 54.8%. The stage-by-stage survival for GCCC was lower in the early stages when compared to published 5-year survival rates for cervical cancer (Table). The median OS from all combined cases with follow-up data (n=148) was 25.0 months (mo) (95% CI 8.4-41.6). This was not significantly different from the OS of our institutional cohort (P=0.39). There was a significant difference in survival by stage (P<0.01). The median OS for stage I was not reached. The mean OS for stage I (n=61) was 233.9 mo (95% CI 182.7-285.1). Median OS for stage II (n=54) was 25.0 mo (95% CI 10.7-39.3), for stage III (n=24) was 18.0 mo (95% CI 7.1-28.9), and stage IV (n=7) was 3.0 mo (95% CI 1.7-4.3) (Figure). There was no significant difference in OS by race (P=0.66). There appeared to be a survival benefit in early stages when treated with surgery and/or chemotherapy as primary treatment (P<0.01).

Conclusions: GCCC is a rare subgroup with historically poor prognosis and limited response to treatment. Given the rarity of this disease and lack of prospective studies to determine the appropriate management, a variety of treatment options have been explored with this patient population. This meta-analysis found median OS to be 25 months, with decreased survival in more advanced disease and more favorable results when early-stage disease was treated with surgery and/or chemotherapy.

Table. Survival Rates, Treatment, and Recurrence

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of Patients</th>
<th>Percentage</th>
<th>5-year Survival GCCC</th>
<th>5-year Survival All Cervical Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>147</td>
<td>50.3%</td>
<td>73.5%</td>
<td>80% to 93%</td>
</tr>
<tr>
<td>II</td>
<td>85</td>
<td>29.1%</td>
<td>48.1%</td>
<td>58% to 63%</td>
</tr>
<tr>
<td>III</td>
<td>38</td>
<td>13.0%</td>
<td>37.3%</td>
<td>32% to 35%</td>
</tr>
<tr>
<td>IV</td>
<td>9</td>
<td>3.1%</td>
<td>0%</td>
<td>13% to 16%</td>
</tr>
<tr>
<td>Unstaged</td>
<td>13</td>
<td>4.5%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Stage I (n=118)</th>
<th>Stage II (n=64)</th>
<th>Stage III (n=26)</th>
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</thead>
<tbody>
<tr>
<td>Surgery alone</td>
<td>52 (44.1%)</td>
<td>3 (4.7%)</td>
<td>0%</td>
</tr>
<tr>
<td>RT alone</td>
<td>10 (8.5%)</td>
<td>30 (46.9%)</td>
<td>14 (53.8%)</td>
</tr>
<tr>
<td>Chemo alone</td>
<td>0 (0%)</td>
<td>2 (3.2%)</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>Surgery + RT</td>
<td>38 (32.2%)</td>
<td>12 (18.8%)</td>
<td>3 (11.5%)</td>
</tr>
<tr>
<td>Surgery + Chemo</td>
<td>2 (1.7%)</td>
<td>3 (4.7%)</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>RT + Chemo</td>
<td>2 (1.7%)</td>
<td>1 (1.6%)</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>Surgery + RT + Chemo</td>
<td>14 (11.9%)</td>
<td>13 (20.3%)</td>
<td>3 (11.5%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Stage 1</th>
<th>Stage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery alone</td>
<td>17/52 (32.7%)</td>
<td>1/13 (7.7%)</td>
</tr>
<tr>
<td>RT alone</td>
<td>1/10 (10.0%)</td>
<td>1/50 (2.0%)</td>
</tr>
<tr>
<td>Chemo alone</td>
<td>0/0 (0%)</td>
<td>0/2 (0%)</td>
</tr>
<tr>
<td>Surgery + RT</td>
<td>2/19 (11.0%)</td>
<td>1/4 (25.0%)</td>
</tr>
<tr>
<td>Surgery + Chemo</td>
<td>0/2 (0%)</td>
<td>0/3 (0%)</td>
</tr>
<tr>
<td>RT + Chemo</td>
<td>1/2 (50.0%)</td>
<td>0/1 (0%)</td>
</tr>
<tr>
<td>Surgery + RT + Chemo</td>
<td>3/14 (21.4%)</td>
<td>0/13 (0%)</td>
</tr>
</tbody>
</table>

RT=radiation therapy, Chemo=chemotherapy
363
The impact of obesity and adjuvant chemotherapy regimens on women with ovarian granulosa cell tumors
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Objective: To determine the effect of obesity and the efficacy of 2 adjuvant chemotherapy regimens on progression-free survival (PFS) in ovarian granulosa cell tumors (GCTs).

Methods: A multi-institution retrospective analysis of patients diagnosed with GCTs between 1995 and 2010 was conducted. Demographics included age, race, and body mass index (BMI). Clinical data included stage, adjuvant treatment, and PFS. HRs for recurrence were estimated by univariate and multivariate Cox regression models.

Results: A total of 201 women were identified, with a median age of 47 years (range, 37-58) and a median BMI of 29 (range 24-35). One hundred nine (57%) were Caucasian, 68 (36%) were African American, and 13 (7%) were other. The majority of women had stage I disease (86%), 20 (10%) had stage II/III disease, and 8 (4%) were unstaged. Median follow-up time was 41 months (range, 0.2-350 months). There were no differences in BMI, age, and race among the groups. In univariate analysis, BMI ≥30 was associated with worse PFS (HR 1.74, 95% CI 1.03, 2.92). Forty-one (20%) patients received adjuvant chemotherapy. The median number of cycles of chemotherapy was 6 (range, 3-6) for paclitaxel/carboplatin (PC) and for bleomycin/etoposide/cisplatin (BEP) (range, 3-6); other chemotherapy regimens had a median of 3 cycles (range, 1-12). Only 1 out of 14 (7%) patients who received PC had recurrent disease compared with 10 of 16 (63%) patients who received BEP and 6 of 11 (55%) patients who received other chemotherapy regimens (HR 4.5, 95% CI 0.55-36.99, P=0.16) (Figure).

Conclusions: This large study analyzed PFS in women with GCTs who received different chemotherapy regimens. Obesity is a modifiable risk factor that was associated with worse PFS. Therefore, studies evaluating weight reduction programs in GCT patients should be conducted to determine if this intervention will improve survival outcomes. Women treated with PC had fewer recurrences than those treated with BEP. PC has a more favorable therapeutic index than BEP. These encouraging results for PC await confirmation from the ongoing prospective non-inferiority trial comparing PC to BEP in women with ovarian sex-cord tumors.

364
Sentinel lymph nodes and vulvovaginal melanoma: Comparison of sentinel lymph node protocols
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The University of Texas, MD Anderson Cancer Center, Houston, TX

Objective: The optimal sentinel lymph node (SLN) protocol in vulvovaginal melanoma (VVM) is yet to be determined. This study presents a single-institution experience with 2 different SLN protocols in cases of vulvovaginal melanoma.

Methods: From 1995 to 2012, 30 pts with VVM underwent SLN biopsy. Patient (pt) age, follow-up, tumor size, tumor thickness, presence/absence of lymphovascular invasion, number/status of SLN and non-SLN, and size of SLN metastases were recorded. Ultrastaging (US) was performed on 26 pts with negative SLN on the initial hematoxylin and eosin (H&E) slide: H&E level only, 3 pts; 1 H&E level (at 4-16 μ) with immunohistochemistry (IHC), 17 pts; superficial level (at 4-16 μ) plus 4 additional H&E levels (250 μ) with IHC, 6 pts; not performed, 2 early pts. To determine whether wide interval (WI) H&E levels (250 μ) plus IHC was superior to 1 H&E level plus IHC, 4 additional WI at 250 μ were cut in all cases without WI. IHC with a PanMel stain was performed in cases lacking IHC.

Results: The median pt age was 62 years (range, 17-85 years), with a median 29 months (range, 5-149 months) follow-up available for 27 pts: alive, 11 pts; alive with disease, 2 pts; dead of disease, 13 pts; dead of unknown cause, 1 pt (Table). Median tumor size was 1.6 cm (range, 0.55 to 5.0 cm) and median thickness was 2.0 mm (range, 0.43-12.0 mm). A total of 110 SLN were identified (1-11 SLN/pt). Ten pts (30%) had 15 positive (+) SLN. Initial H&E section detected 6 (+) SLN; US detected 9 (+) SLN; 1 (+) SLN was seen on the second WI H&E slide. Metastasis size ranged from 2 cells to 14.0 mm. In 4/15 (27%) SLN, metastases were detected by IHC only. Seventeen pts had non-SLN identified, and 2 pts had (+) non-SLN. There were no false-negative SLN.
Conclusions: An US protocol of 1 H&E level and IHC improved detection of (+) SLN over 1 H&E slide (routine processing) alone (6/110 [5.45%] vs. 14/110 [12.72%]). Additional WI H&E levels further increased detection of (+) SLN (15/110 [13.63%]). Additional studies are required to determine whether the modest gain in (+) SLN detection of more comprehensive SLN protocols justifies increased time, labor, and cost with respect to patient outcome.

Table. Clinicopathologic Features of Patients

<table>
<thead>
<tr>
<th>Feature</th>
<th>Positive SLN (n=10)</th>
<th>Negative SLN (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (yr)</td>
<td>56.5</td>
<td>65.5</td>
</tr>
<tr>
<td>Follow-up</td>
<td>6/10 pts DOD</td>
<td>7/20 pts DOD</td>
</tr>
<tr>
<td>Tumor thickness (mean, mm)</td>
<td>3.25±3.35</td>
<td>3.17±3.17</td>
</tr>
<tr>
<td>Lymphovascular invasion present</td>
<td>5/10</td>
<td>10/20</td>
</tr>
</tbody>
</table>

SLN=sentinel lymph node, DOD=dead of disease

365 Molecular alterations of PIK3CA in uterine malignant mesodermal mixed tumors and clear cell carcinomas
S. Bashir1, J. Gaofeng2, A. Joshi2, A. Yang2, A. Yemelyanova2, T. Caputo1, K. Holcomb1, L. Ellenson2, D. Gupta1
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Objective: Uterine clear cell carcinoma (UCC) and uterine malignant mesodermal mixed tumor (UMMMT), also known as uterine carcinosarcoma, are rare but clinically aggressive histologic variants of endometrial carcinoma. The molecular alterations in the oncogenic PI3K-alpha pathway have not been studied in detail in these subtypes. In prior studies, 80% of PIK3CA mutations were found in exons 9 and 20 and the remaining 20% were found in exons 1-7. Our objective was to analyze UCC and UMMMT cases for mutations in PIK3CA in exons 1-9 and 20.

Methods: DNA was microdissected from formalin-fixed, paraffin-embedded hysterectomy specimens of 18 UCC and 20 UMMMT cases. The UMMMT’s carcinomatous components and sarcomatous components were separately microdissected. Exons 1-9 and 20 were amplified using exon-specific primers for PIK3CA. All polymerase chain reaction products were sequenced and potential mutations were verified.

Results: Three mutations located at nucleotides 1017, 1035, and 1041 (resulting in amino acid changes L339I, N345S, and N347K, respectively) in PIK3CA exon 4 were identified in 3/18 (16.7%) cases of UCC. In addition, a previously reported polymorphism in exon 6 was identified. The A-to-G polymorphism in exon 6 at nucleotide 1173 resulting in I391M change was present in 8/18 (44.4%) cases. A C-to-T transition was detected in exon 20 in tumor and normal tissue of 1 case. The alteration did not affect the amino acid sequence. Twenty UMMMT cases were successfully amplified for exons 1, 5, 6, 9, and 20 of PIK3CA. A mutation was found in exon 20 in a carcinomatous component in 1/20 (5%) UMMMT cases. This mutation was located at nucleotide 3141, resulting in H1047R change, which is a hot spot published in endometrial and gastric cancers. A deletion was found in exon 6 in the carcinomatous components of 2/20 (10%) UMMMT cases. This novel mutation is located at c.1227 and is a single base-pair deletion (delT). The same A-to-G polymorphism found in exon 6 of UCCs was found in 5/20 (25%) of UMMMT cases in tumor and corresponding normal tissue.

Conclusions: We evaluated UCC and UMMMT for molecular alterations in PIK3CA and found that a significant percentage contained mutations. This suggests that the oncogenic properties of PIK3CA contribute to the carcinogenesis of these histologic subtypes of endometrial carcinoma, which may lead to the development of tailored therapy targeting the PI3K/AKT pathway in these aggressive tumors.

366 Uterine leiomyosarcomas have reproducible molecular subtypes that correlate with survival
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1Memorial Sloan-Kettering Cancer Center, New York, NY, 2Fox Chase Cancer Center, Philadelphia, PA

Objective: Few molecular studies have been performed in uterine leiomyosarcoma (LMS). We have previously reported that gene expression profiling of LMS suggests that cell cycle genes play a key role in sarcomagenesis. Here we tested the hypothesis that reproducible molecular subtypes exist within uterine LMS.

Methods: A discovery set of fresh-frozen tissues included 23 LMS samples. RNA was hybridized to U133A 2.0 microarrays. Unsupervised hierarchical clustering was performed using standard statistical methods. The NanoString nCounter gene expression system was used on 44 independent archival samples to externally validate molecular subtypes. Standard statistical methods were used for survival analysis, and all tests were 2-sided.

Results: Unsupervised clustering identified clear segregation of LMS into 2 clades with 251 genes differentially expressed at P<0.001. External validation of the existence of 2 LMS clades was performed using a separate subset of 73 differentially expressed genes in the independent set of 44 LMS samples. The 73-gene subset was able to cluster the original 23 LMS samples reproducibly into the 2 clades and was used to assign group membership to the 44 external validation samples. When the 24 primary surgical specimens with a median follow-up of 68 months were analyzed for clinical outcome, the molecular subtypes were significantly associated with progression-free survival (clade 1: 4.0 months vs. clade 2: 26.0 months, P=0.02, HR 0.33) and overall survival (clade 1: 18.2 months vs. clade 2: 77.2 months, P=0.04, HR 0.33) (Figure). On bivariate analysis of primary specimens incorporating stage and clade, clade remained independently associated with progression-free survival (P=0.02, HR 0.29).

Conclusions: Two reproducible molecular subtypes for uterine LMS were identified from gene expression profiles using a 73-gene signature. This molecular fingerprint was associated with clinical outcome. These data can provide a novel endpoint to phase II or III clinical trials and expand our understanding of molecular pharmacology in this disease.
367
Uterine adenosarcoma: A closer look at a rare disease
The University of Texas, MD Anderson Cancer Center, Houston, TX

Objective: Uterine adenosarcoma (AS) is a rare disease and standard therapy remains elusive. We aimed to review treatment and outcomes for patients diagnosed with uterine AS with high-risk features, including heterologous elements and sarcomatous overgrowth (SO).

Methods: We performed a retrospective review of patients diagnosed with uterine AS at a single institution from July 1982 to December 2011. All patients underwent hysterectomy with or without bilateral salpingo-oophorectomy or staging lymphadenectomy. Demographics, clinicopathologic data, and adjuvant treatment data were obtained from patient records. Univariate and multivariate analysis was performed to identify predictors associated with poor progression-free survival (PFS) and disease-specific survival (DSS).

Results: We identified 100 patients with uterine AS. A total of 74 patients met inclusion criteria. Median age was 54 years (range, 15-84 years), and median follow-up was 55.5 months (range, 3.3 to 241.1 months). In the entire cohort, 31 patients (42%) were diagnosed with SO and 15 patients (20%) were diagnosed with heterologous elements. Twenty-four patients (32%) underwent lymphadenectomy, and only 1 lymph node was positive for disease. Forty-six patients (62%) had disease limited to the uterus, 14 (30%) with SO. Among patients with stage I disease, those with SO were more likely to receive adjuvant therapy (43% vs. 16%, P=0.07). Thirty-five patients (47%) received chemotherapy. On univariate analysis, age, heterologous elements and/or SO and advanced stage were identified as poor prognostic factors for worse PFS, although only the presence of SO (HR 3.41, 95% CI 1.86-6.25, P<0.001) persisted on multivariate analysis for PFS. Similarly, on univariate analysis for DSS, heterologous elements and/or SO and advanced stage were identified as prognostic factors for worse DSS, although only the presence of SO (HR 7.4, 95% CI 2.75-19.9, P<0.001) persisted on multivariate analysis as a prognostic factor for worse DSS. There was no difference in recurrence rates for patients with SO who received adjuvant therapy vs. those who received no additional treatment (75% vs. 79%, P=NS), regardless of stage of disease.

Conclusions: Presence of SO in patients diagnosed with uterine AS is a poor prognostic factor and is associated with worse PFS and DSS, regardless of adjuvant therapy. Lymphadenectomy appears to add little benefit to determine prognosis or adjuvant therapy.

368
Vulvar melanoma: An institutional experience
Memorial Sloan-Kettering Cancer Center, New York, NY

Objective: Melanoma of the female genital tract is a rare tumor type with a poor prognosis. We sought to describe the management of vulvar and vaginal melanoma at a single referral center.

Methods: We identified all patients presenting to our institution for management of primary and recurrent vulvar or vaginal melanoma from 2000 to 2012. Demographics and clinicopathologic data were abstracted from the medical record, along with treatment and survival outcomes. The 2002 American Joint Committee on Cancer classification system for melanoma was used to determine stage.

Results: Sixty-one cases were identified; 30 (49%) were vulvar and 31 (51%) vaginal. Eleven cases (18%) were multifocal at diagnosis. Median age was 64 years (range, 27-88 years). Presenting symptoms were as follows: vaginal bleeding, 23 (37.7%); incidental lesion, 17 (27.9%); palpable mass, 8 (13.1%); and pruritus, 7 (11.5%). Forty-nine patients (80.3%) underwent surgical resection. Median depth of invasion was 3 mm (range, 0-18 mm). Fifty percent of lesions had documented ulceration. An evaluation of lymph nodes was performed in 34 (55.7%) cases, of which sentinel lymph nodes were obtained in 23 (37.7%). Positive lymph nodes were identified in 8 (13.1%) cases. Stage was as follows: in situ, 4 (6.6%); stage I, 8 (13.1%); stage II, 28 (45.9%); stage III, 11 (18.0%); and stage unspecified, 10 (16.4%). In 26 cases (42.6%), chemotherapy was administered, while radiation therapy was used in 22 (36.1%), and 14 (23%) received both modalities. Seventeen patients (27.9%) received targeted treatment, including imatinib (n=5) and sunitinib (n=4). Local recurrence occurred in 14 cases and distant recurrence in 20 cases. Twenty-eight patients (45.9%) died of disease, while 6 (9.8%) died of another cause, 8 (13.1%) were alive with disease, and 19 (31.1%) had no evidence of disease. Median follow-up was 32 months (range, 3-144 months). Median disease-specific survival for all patients was 73 months (95% CI: 28.0-118.0). However, in patients with vaginal melanoma, median disease-specific survival was 29 months (95% CI: 13.6-44.4). Median survival was not reached in the vulvar group.

Conclusions: Surgical excision remains the mainstay of treatment for localized vulvovaginal melanoma, while primary radiation is reserved for patients with unresectable disease. Cytotoxic chemotherapy options remain limited, but the impact of new targeted agents is yet to be determined. Patients with vaginal melanoma did significantly worse than those with primary vulvar disease.

369
Institutional review of primary lymphoma of the female genital tract: A 32-year experience
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1Yale New Haven Hospital, New Haven, CT, 2Yale University School of Medicine, New Haven, CT

Objective: Primary lymphomas affecting the female reproductive system are exceedingly rare, with most literature revealing a poor prognosis for patients. Our objective was to report our experience of this rare gynecologic malignancy at our institution.

Methods: A retrospective chart review was performed on patients diagnosed with non-Hodgkin lymphoma (NHL) of Müllerian organs from 1980 to 2012. Histologic classification and staging were determined according to the Working Formulation and the Ann Arbor systems, respectively.

Results: Thirty-two patients (31 primary disease, 1 recurrent) were diagnosed with NHL of Müllerian organs and were followed for a median of 68 months (range, 0.3-360 months). Median age of diagnosis was 43.5 years (range, 19-87 years), with 78% (25) of patients diagnosed at stage IV. Presenting symptoms included abdominal discomfort/bloating (8/32), abnormal vaginal bleeding (5/32), nausea/vomiting (1/32), oliguria (1/32), lower extremity swelling (2/32), and constitutional symptoms (5/32). Seven patients were asymptomatic and 6 were identified incidentally during surgery or radiographically. One was diagnosed on routine first-trimester prenatal ultrasonography, while 3 were incidental findings on Papanicolaou smear. Location of the disease included: ovary (7), uterus (3), vagina/cervix (9), pelvic mass encompassing multiple Müllerian organs (7), isolated pelvic lymph nodes (3), and/or multiple sites (5). Four cases were concomitant with endometrial cancer diagnosis, 2 of which were uterine carcinosarcomas. Diffuse lymphoma and a B-cell phenotype (14/24) was the most common histologic type, with 4 cases of follicular lymphomas, 5 high-grade Burkitt lymphomas, and 1 mantle cell lymphoma. Twenty-four patients underwent surgical debulking. Twenty-four patients received combination chemotherapy, with concomitant radiation therapy in 7 and stem cell transplant in 3. Eight patients did not receive chemotherapy. Four patients incurred 1 central nervous system, 1 pulmonary, 1 bone, 1 manubrium). Overall median survival from diagnosis of lymphoma was 60.5 months (range, 0.3-355 months), with a 78% 1-year survival, 63% 2-year survival, and a 53% 5-year survival.

Conclusions: Our report is the largest single-institution experience of primary lymphomas of Müllerian organs and shows a significantly more favorable prognosis than previous studies. With early diagnosis and appropriate therapy, radical gynecologic surgery can be avoided, and these cancers can be managed successfully with prolonged overall and disease-free survival.
Objective: To evaluate the importance of robotic-assisted surgery and its impact on the physical strain of laparoscopic surgery.

Methods: Surveys on minimally invasive surgery (MIS) were sent to Society of Gynecologic Oncology members and anonymous responses were collected. The survey included 6 validated questions on surgeon strain and discomfort.

Results: A total of 406 (31.7%) practitioners responded to the survey. More than half (57.8%) of respondents indicated that they have physical discomfort or symptoms that would attribute to performing MIS surgery. Of those who reported physical discomfort, 70.5% specified stiffness as the most common symptom, followed by fatigue (61.3%), pain (58.3%), and numbness (32.3%). Approximately 34% of respondents reported a history of treatment for these ailments. When respondents were asked when they experienced the symptoms or discomforts, 54.0% revealed that the symptoms occurred while performing MIS surgery, immediately after, but not persistently, while 21.6% stated that their symptoms persisted after surgery. Over three-fourths (77.6%) attempted to minimize these injuries or conditions by changing natural position, while 26.2% ignored any injury or condition, and 20.5% changed instruments. Almost two-thirds (66.0%) of practitioners identified display monitor location as 1 of the operating room factors that minimized their physical symptoms. 47.0% identified operating room table set-up, and 44.0% cited instrument design. Of the respondents who cited other ways of minimizing physical strain, 47.9% associated with MIS warrants further investigation.

Objective: To evaluate the feasibility and efficacy of robotic–assisted management of recurrent disease in gynecologic oncology.

Methods: Retrospective chart review of cases managed with either robotic-assisted or abdominal surgery by a single surgeon (2008–2012). Cases included those presenting with pelvic mass, initial staging, or debulking after neoadjuvant chemotherapy. Patient characteristics and outcomes were compared using chi-squared or 2-tailed student's t-tests.

Results: Overall, 63 patients underwent a robotic approach and 26 patients underwent an abdominal approach. Patient characteristics were similar for age (59.8 vs. 55.7 years, P=0.1371), uterine weight (81 vs. 114 g, P=0.0508), and body mass index (27 vs. 28, P=0.4805). The prior abdominal surgery rate was higher in the abdominal group (76% vs. 96%, P=0.0257). Operative time was longer (139 vs. 95 min, P=0.0009), and major complication rates were similar (16% vs. 23%, P=0.4209). Lymph node dissection (13 vs. 11 nodes, P=0.2310) and omentectomy (92% vs. 96%, P=0.4840) were performed when indicated. The neoadjuvant chemotherapy rate was higher in the robotic group (52% vs. 15%, P=0.0013). There was no residual disease in 68% of robotic and 50% of abdominal patients (P=0.105) (Table). For the subgroup of stage II-IV patients, there was no residual disease in 24/43 (56%) of robotic vs. 8/20 (40%) of abdominal patients (P=0.2425). Follow-up was longer for the abdominal group (15 vs. 24 months, P=0.0096), although an equivalent percentage of patients had at least 1 year of follow-up (36/63 [57%] vs. 20/26 [77%], P=0.0789). At 1 year, the survival rate was 78% for robotic patients and 79% for abdominal patients (P=0.8251). P

Objective: Data to support the role of robotic-assisted surgery for recurrent disease are scant, and minimally invasive surgery in this setting is generally not performed. The aim of this study was to assess the feasibility and surgical outcomes of robotic-assisted surgery in the management of isolated recurrences in gynecologic oncology.

Methods: The institutional review board at each participating center approved this retrospective multi-institutional study. Eligible patients included those with a confirmed gynecologic malignancy (ovary, corpus, cervix, vulva, vagina) and diagnosed with probable recurrence after completion of initial therapies and planned-for surgical cytoreduction using the robotic platform. Clinical and pathologic data were abstracted from the medical records. Isolated recurrence was defined as recurrent disease in 1 anatomic region but may have included multiple tumors in that region. Optimal resection was defined as no individual visible residual tumor >1 cm in size. Appropriate statistical tests were performed using SPSS statistical software program (SPSS 20.0 Inc., Chicago, IL).

Results: A total of 74 patients were identified: 48 (64.9%) ovarian, 18 (24.3%) corpus, 6 (8.1%) cervical, 1 (1.4%) vulvar, and 1 (1.4%) vaginal cancer. The median age was 58 years (range, 20-82 years). The median body mass index was 26 (range, 19-51). Fifty-seven (77%) patients had an isolated recurrence, with 17 patients (23%) having multiple-region recurrence. Conversion to laparotomy was necessary in 13 (17.6%) cases. In cases not requiring conversion to laparotomy, the median operative time, estimated blood loss, and length of stay were 175 minute, 50 mL, and 1 day, respectively. Fifteen (15%) patients underwent an abdominal approach. Patient characteristics were similar for age (59.8 vs. 55.7 years, P=0.1371), uterine weight (81 vs. 114 g, P=0.0508), and body mass index (27 vs. 28, P=0.4805). The prior abdominal surgery rate was higher in the abdominal group (76% vs. 96%, P=0.0257). Operative time was longer (139 vs. 95 min, P=0.0009), and major complication rates were similar (16% vs. 23%, P=0.4209). Lymph node dissection (13 vs. 11 nodes, P=0.2310) and omentectomy (92% vs. 96%, P=0.4840) were performed when indicated. The neoadjuvant chemotherapy rate was higher in the robotic group (52% vs. 15%, P=0.0013). There was no residual disease in 68% of robotic and 50% of abdominal patients (P=0.105) (Table). For the subgroup of stage II-IV patients, there was no residual disease in 24/43 (56%) of robotic vs. 8/20 (40%) of abdominal patients (P=0.2425). Follow-up was longer for the abdominal group (15 vs. 24 months, P=0.0096), although an equivalent percentage of patients had at least 1 year of follow-up (36/63 [57%] vs. 20/26 [77%], P=0.0789). At 1 year, the survival rate was 78% for robotic patients and 79% for abdominal patients (P=0.8251).
year, the survival (93% vs. 85%, \( P=0.0888 \)) and no evidence of disease (NED) (67% vs. 50%, \( P=0.2211 \)) rates were equivalent. These rates were also equivalent for stage II-IV patients at 1 year (survival: 92% vs. 88%, \( P=0.6357 \) and NED: 68% vs. 56%, \( P=0.4461 \)).

**Conclusions:** The use of a robotic approach in the management of epithelial ovarian cancer, including for patients treated with neoadjuvant chemotherapy, is feasible and effective. Debulking rates were similar to an abdominal approach in ovarian cancer, including for patients treated with neoadjuvant chemotherapy, 68% vs. 56%, \( P=0.6357 \) and NED: for stage II-IV patients at 1 year (survival: 92% vs. 88%, \( P=0.0888 \) and NED: for stage II-IV patients at 1 year (survival: 92% vs. 88%, \( P=0.0888 \) and NED: 68% vs. 56%, \( P=0.4461 \)).

### Table. Pathology and Survival

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Robotic n=65</th>
<th>Abdominal n=26</th>
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<tbody>
<tr>
<td>Pathologic State, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>20 (31.8)</td>
<td>6 (23.1)</td>
<td>0.658*</td>
</tr>
<tr>
<td>II</td>
<td>5 (7.9)</td>
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</tr>
<tr>
<td>III</td>
<td>30 (47.6)</td>
<td>18 (61.5)</td>
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<tr>
<td>IV</td>
<td>7 (11.1)</td>
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<tr>
<td>Missing</td>
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<td>Residual Disease, n (%)</td>
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<tr>
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<td>2 (3.2)</td>
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<td>4 (6.3)</td>
<td>6 (23.0)</td>
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<tr>
<td>Residual Disease for Stage II-IV Patients, n (%)</td>
<td>43 Patients</td>
<td>20 Patients</td>
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<tr>
<td>Overall Survival</td>
<td>61/63 (96.8)</td>
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</tbody>
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*Chi-squared contingency table

NED=no evidence of disease

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### 373

**Robotic surgery for the management of ovarian cancer**

**T. Evans**1, T. Randall1, L. Wilkinson-Ryan2

1University of Pennsylvania Health Systems, Pennsylvania Hospital, Philadelphia, PA, 2University of Pennsylvania Medical Center, Philadelphia, PA

**Objective:** To determine the feasibility of using robotic surgery in the treatment of epithelial ovarian and fallopian tube cancer.

**Methods:** Thirty patients with a preoperative diagnosis of epithelial ovarian/fallopian tube cancer who were scheduled to undergo robotic surgical management between 04/2011 and 08/2012 were reviewed. Major intraoperative and postoperative complications; operative characteristics, including operative time, blood loss, and additional procedures; transfusion rate; length of hospitalization; length of follow-up; patient demographics; and ability to optimally debulk and obtain periaortic and pelvic lymph nodes for staging were reviewed.

**Results:** A total of 28 cases were included in the final analysis. Of the 30 procedures, 2 were aborted due to tumor burden and were not included in the final analysis. Two patients had a final surgical pathology of papillary serous adenocarcinoma of the endometrium. There were 19 debulking procedures and 9 staging procedures. There were no major intraoperative complications. No procedures were converted to laparotomy. There were 3 postoperative complications: atrial fibrillation on postoperative day 1 (1), small bowel obstruction requiring intravenous hydration and bowel rest with a nasogastric tube (1), and need for registered respiratory therapist on postoperative day 1 for somnolence on narcotics for pain control that resolved with administration of naloxone (1). The mean operative time was 227 minutes. The mean estimated blood loss was 74 mL, the mean hemoglobin change was 2.07 g/dL, and the mean hospital stay was 2 days. No gross residual or <1 cm residual tumor was seen in 94.7% of patients, 21.4% of patients had neoadjuvant chemotherapy, 64.3% of cases had stage III cancer, and 3.6% had stage IV disease.

**Conclusions:** Robotic surgery may be feasible for the management of selected women with epithelial ovarian cancer. The presence of advanced-stage disease does not appear to be an absolute contraindication to minimally invasive surgery. Even in the setting of radical debulking surgery, minimally invasive surgery may decrease morbidity.

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### 374

**Low incidence of port-site metastasis after robotic-assisted surgery for endometrial cancer staging**

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1Berkshire OB/GYN Associates PC, Pittsfield, MA, 2Women’s Cancer Care Associates, Albany, NY

**Objective:** To evaluate the incidence and characteristics of patients with port-site metastasis following robotic-assisted surgery for gynecologic malignancies.

**Methods:** This was a retrospective study of patients who underwent robotic-assisted total laparoscopic hysterectomy and surgical staging at a single institution. After institutional review board approval was obtained, patients with endometrial carcinoma undergoing robotic-assisted hysterectomy were identified through ICD-9-CM codes from November 2006 through November 2011. A review of medical records was performed, and data collected included diagnosis, histology, tumor extension, procedure, complications, and postsurgical intervention. At the time of procedure, hysterectomy specimens were retrieved vaginally and lymph nodes were placed in an EndoCatch bag and retrieved through the assistant port. All cases were discussed at tumor board and recommendations were made based on staging, pathology, and patients conditions. Port-site metastasis was differentiated between isolated and not isolated. All metastases were confirmed with biopsy and treated with chemotherapy and radiotherapy, as indicated.

**Results:** A total of 452 patients with endometrial carcinoma were identified who had undergone robotic hysterectomy and node sampling. The incidence of port-site metastasis after robotic-assisted surgery for treatment of endometrial cancer was 0.8% in our patient population. The 4 patients with port-site metastasis are described in the Table. Two cases were reported as isolated metastasis and 2 as not isolated at the port-site. Peritoneal washing was positive in 1 patient (patient 3); lymph vascular space invasion was presented in patients 1, 2 and 3. No intraoperative complications were reported.

**Conclusions:** The incidence of port-site metastasis is low after robotic-assisted surgery for treatment of endometrial cancer (0.8%). There is no clear risk factor for development of port-site metastasis or easily identifiable prevention.
Trends in surgical training among gynecologic oncology fellows before and after the introduction of robotic surgery

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1The Cleveland Clinic Foundation, Cleveland, OH, 2Case Western Reserve University School of Medicine, Cleveland, OH

Objective: To describe trends in gynecologic oncology surgical training at 1 institution and assess the impact of robotic surgery on fellows’ open, laparoscopic, and robotic case mix.

Methods: Fellows’ case logs were retrieved and reviewed with institutional review board approval. Total case volume was calculated using clinical and research fellows’ logs. Cases performed by clinical fellows during each year were divided by the number of clinical fellows each year to determine case volume per clinical fellow year (CFY). Cases were grouped by approach and indication, allowing tabulation of proportional case volumes. Significance of proportional variance over time was tested with linear-by-linear chi square. Trends were described by the best fit line with |r| >0.45 and P <0.05.

Results: Between 1999 and 2010, 15 fellows completed 22 CFYs of training. A total of 5,202 surgical episodes resulting in 13,804 distinct procedures per CFY. The mix of benign and oncologic cases was stable, averaging 42% and 58% annually (standard deviation [SD]=3.6, P=0.67). Among oncology cases, endometrial, ovarian, and cervix cancers were the most common indications (45%, 31%, and 11% of fellows’ case mix [SD=4.6, 4.9, and 2.6]), without significant variability (P=0.71). Advanced surgical volume (Panel A) was stable except for urologic cases, declining an average 5% annually, (P=0.02). Adnexal mass, preinvasive disease, and risk-reducing surgery were the most prevalent indications for benign surgery (40%, 27%, and 9%). Surgery for risk reduction and adnexal mass grew 14% and 3% annually per CFY (P=0.02 and 0.02). Upon introduction of robotics in 2006, proportional robotic volume grew an average 5 percentage points annually, accounting for 21% of fellows’ volume by 2009. After the introduction of robotics, open volume decreased 6.5 points annually (P=0.02) (84% of fellows’ volume in 2006, 58% in 2009). After a brief contraction, proportional laparoscopic volume grew 2 points annually (P=0.02), eclipsing pre-robotics proportions by 2009 (14% vs. 21%, 1999 vs. 2009) (Panel B). Procedure-specific volume trended similarly (Panel C). The proportional volume of robotic hysterectomies increased at the expense of open and vaginal hysterectomies, while proportional laparoscopic volume increased.

Conclusions: Introduction of robotics has not compromised fellows’ exposure to laparoscopic cases. With the exception of urologic cases, advanced procedure volume was stable during the study period.

Table. Characteristics of Patients With Port-Site Metastasis

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>Body Mass Index</th>
<th>Positive Lymph Nodes</th>
<th>Histology</th>
<th>Stage</th>
<th>Grades</th>
<th>Adjuvant Therapy</th>
<th>Time of Port Metastasis in Days</th>
<th>Number of Port Involved</th>
<th>Other Metastasis sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>39.5</td>
<td>0</td>
<td>Endometriod</td>
<td>IA</td>
<td>3</td>
<td>Vaginal brachytherapy</td>
<td>275</td>
<td>1</td>
<td>Vaginal cuff</td>
</tr>
<tr>
<td>2</td>
<td>85</td>
<td>28</td>
<td>0</td>
<td>Endometriod</td>
<td>IIIA</td>
<td>2</td>
<td>Refused treatment</td>
<td>184</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>49.3</td>
<td>0</td>
<td>Endometriod</td>
<td>IIIA</td>
<td>1</td>
<td>Observation</td>
<td>3125</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>40</td>
<td>0</td>
<td>Endometriod</td>
<td>IC</td>
<td>2</td>
<td>WPRT</td>
<td>579</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

375
Feasibility of robotic extraperitoneal para-aortic lymphadenectomy for gynecologic cancer

A. Bats, C. Bensaid, A. Achouri, L. Makke, C. Nos, F. Lecuru
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Objective: As the most recent evolution of minimally invasive techniques, robotic technology has increased in surgical procedures for gynecologic oncology. Robotic extraperitoneal para-aortic lymphadenectomy has never been reported. The aims of our study were to describe the technique, the feasibility, and results of robotic extraperitoneal para-aortic lymphadenectomy.
Methods: Eight patients undergoing robotic extraperitoneal para-aortic lymphadenectomy using the Da Vinci system were evaluated retrospectively: 4 with cervical cancer and 4 with endometrial cancer. Extraperitoneal para-aortic lymphadenectomy was performed using a similar surgical technique as previously described by laparoscopy. The procedure was carried out using 4 port sites: 1 for the camera, 1 each for the no. 1 and no. 3 arms of the Da Vinci robot system, and 1 for the assistant.

Results: The operation was completed in all but 1 patient. Beyond para-aortic lymphadenectomy, 3 patients with endometrial cancer had transperitoneal bilateral pelvic lymphadenectomy and hysterectomy, and 1 patient with advanced cervical cancer had anterior pelvicectomy. The median age of patients was 61 years (range, 52-66 years) and body mass index was 25.7 (range, 21.6-28.5). The median operating time was 270 min (range, 195-302 min). The median number of para-aortic lymph nodes removed reached 17 (range, 13-20), the median decrease in hemoglobin was 1.1 g/dL (range, 0.7-1.9 g/dL), and median hospital stay was 5 days (range, 4-7). There was 1 intraoperative complication (bilateral pneumothorax) and 1 postoperative complication (desaturation).

Conclusions: Robotic-assisted extraperitoneal para-aortic lymphadenectomy via the Da Vinci system appears feasible and safe.

378  
Advancing robotic sentinel lymph node detection with indocyanine green (ICG) fluorescence: Optimal concentration for discrimination of the sentinel node

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Objective: To determine the optimal dose of ICG to accurately distinguish the sentinel node from surrounding tissue.

Methods: The study was performed on healthy female pigs weighing 40-60 kg. After induction of anesthesia, all pigs underwent exploratory laparotomy, dissection of the bladder, and a colpotomy to reveal the cervical os. Using a 21-gauge needle, 0.5 mL of normal saline was injected at the 3 o’clock and 9 o’clock positions as a control. Four concentrations of ICG were constituted for doses of 1,000 mcg, 500 mcg, 250 mcg, and 175 mcg per 0.5 mL. ICG was then injected at the 3 o’clock and 9 o’clock positions on the cervix. The SPY camera (Novadaq Technologies Inc.) was used to track ICG into the sentinel node and to quantify the intensity of light emitted. SPY technology uses an intensity scale from 1 to 256, which was used to determine the difference in intensity between the sentinel node and surrounding tissues. This difference was calculated at the time the sentinel node was first identified and when the sentinel node reached maximum intensity. The average intensity in the surrounding tissues was calculated by taking the average intensity in 4 surrounding quadrants adjacent to the node.

Results: A sentinel node was identified at all doses except for the 175 mcg dose, at which ICG stayed in the cervix and vasculature only (Table and Figure). For the 1,000 mcg dose, the sentinel node was only delineated once maximum intensity was reached. At that time, the difference in intensity between the surrounding tissue and the node was 119 (251 vs. 132). For both the 500-mcg and 250-mcg doses, the sentinel node was identified before reaching maximum intensity. At that time, the difference was 172 (191 vs. 19) for the 500-mcg dose and 84 (124 vs. 40) for the 250-mcg dose. At maximum intensity, the difference between the surrounding tissue and the node was 207 (251 vs. 44) for the 500-mcg dose and 159 (251 vs. 92) for the 250-mcg dose.

Conclusions: For sentinel lymph node detection, the dose of ICG is related to the ability to discriminate the sentinel node from the surrounding tissue. ICG dose of 250-500 mcg successfully identify a sentinel lymph node with more distinction from the surrounding tissues.

Table. Discrimination of the Sentinel Node

<table>
<thead>
<tr>
<th>Sentinel Node First Recognized</th>
<th>Sentinel Node at Maximum Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sentinel Node</td>
<td>Surrounding Tissues</td>
</tr>
<tr>
<td>1,000 mcg</td>
<td>251</td>
</tr>
<tr>
<td>500 mcg</td>
<td>191</td>
</tr>
<tr>
<td>250 mcg</td>
<td>124</td>
</tr>
<tr>
<td>175 mcg</td>
<td>0</td>
</tr>
</tbody>
</table>
Is robotic hysterectomy really less painful than traditional laparoscopy?

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Objective: To compare narcotic use (as a surrogate for postoperative pain) in patients who had a total robotic hysterectomy (TRH) compared to those with total laparoscopic hysterectomy (TLH) for endometrial cancer.

Methods: All cases of TRH for the treatment of endometrial cancer (EC) from 1/08 until 7/12 were reviewed with institutional review board approval. These were matched with TLHs for age, body mass index (BMI), type of procedure, and the use of intravenous nonsteroidal anti-inflammatory drugs (NSAIDs). Exclusion criteria included cases that were converted to open hysterectomy and patients with pre-existing chronic pain. The cumulative dose of narcotics, including intraoperative doses, were calculated for each patient during the first 6, 12, 18, and 24 hours and converted to fentanyl equivalents for comparison.

Results: There were 100 TLHs and 63 TRHs, with no difference in age, BMI, or use of NSAIDs. Statistically significant differences were noted between the estimated blood loss and operative time of the 2 groups (\(P=0.007\) and \(P=0.01\), respectively). The mean fentanyl use at 24 hours for TLH was 484 mcg compared to 511 mcg (\(P=0.38\)). The mean values at the first 6, 12, 18, and 24 hours were all lower for TLH than TRH, but the values did not reach statistical significance (Figure). There was no significant difference in narcotic use with respect to BMI, operative time, number of ports, and type of cuff closure.

Conclusions: Patients undergoing TRH for EC used on average more narcotic analogues at 6, 12, 18, and 24 hours from the time of incision. However, the difference was not statistically significant. There was no evidence that the TRH is any less painful than TLH. Although claims by the robotic manufacturer have suggested that this device decreases pain, there is no objective evidence to support this conclusion.

<table>
<thead>
<tr>
<th>Time</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 hrs</td>
<td>0.36</td>
</tr>
<tr>
<td>12 hrs</td>
<td>0.33</td>
</tr>
<tr>
<td>18 hrs</td>
<td>0.33</td>
</tr>
<tr>
<td>24 hrs</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Learning curve associated with becoming proficient in completing a robotic-assisted total laparoscopic hysterectomy: A single-institution gynecologic oncology fellowship experience

Memorial Sloan-Kettering Cancer Center, New York, NY

Objective: To describe the learning curve associated with training fellows in completing robotic-assisted total laparoscopic hysterectomies.

Methods: All patients scheduled to undergo a robotic procedure from 5/15/07–5/22/12 were identified. Various intraoperative time points were captured per our ongoing quality assessment. Fellow participation per procedure was also documented. For the current analysis, we focused on the learning curve of fellows for the time to complete a hysterectomy (from initiation of developing the retroperitoneal space to completion of the colpotomy). All cases were performed jointly and under the direct supervision of attending faculty. The dual-console platform was used for all cases starting in 2009. Appropriate statistical tests were used.

Results: Of the 1,754 planned robotic cases, 1,626 were completed robotically and 128 were converted to laparotomy. Fifty-seven fellows, including gynecologic, urologic, and surgical fellows, participated in 99.5% of the cases. A total of 1,035 hysterectomies (including 56 radical hysterectomies) were performed. During this time period, 11 gynecologic oncology fellows completed at least 1 robotic-assisted total laparoscopic hysterectomy. Fifty-four hysterectomies were performed from 5/15/07–7/6/08; none were completed by a fellow. From 7/7/08–5/21/12, 981 hysterectomies were completed robotically, 256 of these (26.1%) by the 11 fellows. The rate of hysterectomy completion per fellow increased from 2.1% in 2008 to 42.4% by the end of 2011. Prior to completing a hysterectomy, the median number of hysterectomies in which a fellow participated to some degree on the console was 16 (range, 11–40). Median amount of time for a fellow to complete a hysterectomy decreased from 60 minutes in 2009 (\(n=27\) cases) to 31 minutes in 2011 (\(n=147\) cases). Based on the recorded completion times in which the 11 fellows completed a hysterectomy, it required ~33 cases per fellow to be able to perform the hysterectomy in 30 minutes or less.

Conclusions: These data suggest that the learning curve associated with hysterectomy requires completion of ~30 cases by the fellow after an initial median experience of 16 cases. Our data suggest that a minimum of 50 total cases is required during fellowship to achieve proficiency performing a robotic hysterectomy. The dual-console platform greatly enhanced fellow training.

Incidence of port-site hernias and/or dehiscence in robotic-assisted procedures in gynecologic oncology patients

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Objective: The incidence of port-site hernias and/or dehiscence using bladeless trocars is approximately 0.5% to 1%. Robotic surgery requires the use of additional port sites with increased manipulation of instruments, raising the concern for higher rates of port-site complications. We sought to characterize the incidence of port-site complications in patients who did not undergo routine fascial closure of robotic port sites.

Methods: We performed a retrospective review of patients undergoing robotically assisted (RA) procedures for evaluation of a suspected gynecologic malignancy between 1/2006 and 12/2011. Five ports were routinely used: 2 12-mm blades and 2 or 3 8-mm robotic trocars. Fascial closure was not performed. With the exception of cases requiring removal of the specimen through the port site, the decision to close the fascia was at the discretion of the surgeon. Abstred data included patient demographics, body mass index (BMI), procedures performed, and final diagnosis.
Results: Data from 842 procedures were included in analysis. The mean age was 55.6 years and the majority of patients were white (77.3%). The mean BMI was 33.6 (range, 16.5-80). RA-total laparoscopic hysterectomy (RA-TLH) ± unilateral or bilateral salpingo-oophorectomy (USO/BSO) ± lymph node dissection (LND) accounted for the majority of procedures (n=771 [91.6%]). Over half of all cases (58.6%) had confirmed malignancy on final pathology, the most common being endometrial cancer (47.5%). We examined the 35 patients undergoing BSO ± omentectomy ± LND who required removal of their specimen through the port site. Fascial closure was performed in 54.3% of cases, and the most common site of specimen removal was the 12-mm accessory port (74.3%). There were no port-site hernias or dehiscence in this group. Overall, only 1 patient (0.1%) who underwent a RA procedure was found to have a port-site dehiscence. This patient underwent a RA-TLH/BSO/LND for stage IIIA endometrial adenocarcinoma and had a port-site dehiscence of the 8-mm trocar site, which was repaired at the bedside in clinic. No port-site hernias were noted.

Conclusions: Port-site hernias and dehiscences are rare in RA gynecologic oncology procedures. When bladeless dilating trocars are used, routine closure of even the 12-mm port site is unnecessary, even in cases requiring removal of the specimen through the trocar sites.

382 Surgical complications associated with robotic, laparoscopic, and open approaches in endometrial cancer: A study of 6,560 patients
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1UCSF Comprehensive Cancer Center, San Francisco, CA, 2The University of Memphis, Memphis, TN

Objective: To determine the proportion of serious surgical complications associated with robotic (RS) vs. laparoscopic (LS) vs. open surgery (OS) for endometrial cancer.

Methods: Data were obtained from the United States National Inpatient Survey in 2010. Serious complications such as hemorrhage requiring a blood transfusion, urinary tract injury, and gastrointestinal injury were extracted. Chi-squared, t-test, ANOVA, and multivariate models were used for statistical analyses.

Results: Of 6,560 patients, the median age was 62 years (range, 22 to 99 years). Seventy-six percent of patients were White, 10% Black, 8% Hispanic, and 4% Asian. Seventy-eight percent of patients had their surgeries performed from teaching vs. nonteaching hospital, 91% in private vs. public hospitals, 94% in urban vs. rural areas, and 72% were from higher-volume (>20 cases/year) hospitals. The overall rate of serious adverse events (AE) associated with surgical care was 4%, 8%, and 13% for RS, LS, and OS. AE were associated with a greater average length of stay (3 vs. 6 days, P<0.01) and median total charges ($47,782 vs. $32,927, P<0.01). On subset analysis, 1%, 2%, and 1% had urinary injuries (P=0.02) in RS, LS, OS, respectively, while all surgical techniques had <1% gastrointestinal injuries. The percentages of patients who required blood transfusions postoperatively were 4%, 5%, and 12% of RS, LS, and OS, respectively (P=0.03).

Conclusions: In a large nationwide study on endometrial cancer, the incidence of overall serious AEs associated with surgery was <4%. RS was associated with lower rates of hemorrhage compared to LS and OS.

383 Does robotic hysterectomy increase the incidence of lymphovascular space invasion in endometrial cancer?
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Wayne State University, Detroit, MI

Objective: Lymphovascular space invasion (LVSİ) is an independent risk factor for nodal disease and poor outcomes in endometrial cancer. Uterine manipulators are a useful adjunct for robotic-assisted laparoscopic hysterectomy (RALH), but some surgeons avoid their use for fear of altering pathology or interpretation of LVSİ. The aim of the study was to compare the incidence of LVSİ in FIGO stages IA, IB, and II endometrial cancer operated by laparotomy (TAH) vs. RALH.

Methods: We retrospectively compared clinicopathologic data and tumor pathology from patients with endometrial cancer undergoing TAH vs. RALH.

Results: A total of 365 endometrial cancer cases (223 TAH, 142 RALH) with stages IA (115), IB (180), and II (70) were reviewed. Histology types were endometrioid (68%), serous (9%), carcinosarcoma (5%), and others (18%). No significant difference was seen in the age, grade, histology, and myometrial invasion between TAH and RALH groups. LVSİ was identified in 161 cases (44%), including 48 stage IA (41%), 77 IB (42%), and 36 stage II (52%). The RALH group had a statistically significantly higher LVSİ for stage IA (P=0.013) but not stage IB (P=0.65) or II (P=0.28) compared to the TAH group.

Conclusions: RALH cases that used a uterine manipulator showed a significantly higher LVSİ rate in stage IA but not in stage IB or II disease. The clinical and prognostic implications of these findings are being evaluated. Further studies are recommended to review RALH conducted with no manipulator or other types of uterine manipulators.

384 A health care economic analysis of robotic surgery for endometrial cancer: A nationwide study of 420 hospitals
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1Stanford University Medical Center, Stanford, CA, 2The University of Memphis, Memphis, TN, 3UCSF Comprehensive Cancer Center, San Francisco, CA

Objective: To determine the hospital charges and associated trends of robotic surgery (RS) in the United States.

Methods: All endometrial cancer patients who underwent surgery were identified from the National Inpatient Sample. Demographic, clinical, and hospital charges were analyzed using Chi-squared and multivariate analyses.

Results: Of 420 hospitals, the overall median hospital charge associated with robotic surgery (RS) was $35,248, which was comparable to laparoscopic (LS) $33,302 and open surgery (OS) $33,487 (P=0.12). The variations in robotic hospital charges based on west, northeast, midwest, south were $39,143, $29,688, $35,241, and $43,301, respectively (P<0.01), with corresponding utilization of 23%, 26%, 26%, and 25% (P=0.11). The charges for RS were significantly lower charges associated with RS at $35,173 compared to RS at $34,248 to $33,955 (P<0.01). In a subset analysis limited to hospitals with RS programs, we found that the median charge of RS was $35,248 compared to $35,530 for LS and $35,558 for OS. Additionally, higher-volume hospitals (>20 surgeries/year) had lower charges associated with RS at $35,002 compared to $36,754 in lower-volume hospitals.

Conclusions: In this nationwide analysis of endometrial cancer patients, the overall charges associated with robotic surgery was comparable to those for laparoscopic and open surgery. Further, robotic surgery charges decreased over this short period and was lower in higher-volume hospitals.
Objective: Surgeon strain has been evaluated to some degree in gynecologic oncologists who perform laparoscopic surgery but has not been evaluated in those who perform robotic surgery. This study sought to identify ergonomic stressors associated with using the Da Vinci® robotic system.

Methods: After obtaining institutional review board exemption, robotic surgeons at a tertiary care center were observed and videotaped while operating. A human factors engineer experienced with health-care ergonomics analyzed the videotapes and provided ergonomic evaluations of the surgeons. An initial ergonomic assessment was performed using the Rapid Upper Limb Assessment (RULA) tool, an ergonomic assessment and prioritization method for determining posture, force, and frequency concerns with focus on the upper limbs, neck, and trunk. A more detailed subjective and objective analysis followed using the Strain Index (SI) tool.

Results: A total of 17 hours of video were analyzed and descriptive data based on RULA/SI analysis were determined (Table). Cycle time was the length of a surgeon’s uninterrupted activity on the console during each video segment. Number of exertions was defined as the number of arm extensions and changes in wrist posture while operating. Ergonomic evaluation of surgeon activity resulted in mean RULA score of 6.46 (range, 6–7), indicating an immediate need for further investigation. The mean SI grand score was 24.34 (range, 10.12–40.5), indicating that current use of the surgical robot is hazardous and should be modified.

Conclusions: The data indicated ergonomics deficits at a high-volume robotics center, which are hazardous to surgeons and require urgent intervention. A training strategy is being developed to address these ergonomic issues and ergonomic training deficiencies.

Table. Job Variables

<table>
<thead>
<tr>
<th>Average cycle time in seconds (range)</th>
<th>Average Number of exertions per cycle (range)</th>
<th>% of the cycle when arm is not rested</th>
<th>Average RULA scores</th>
<th>Average SI Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,029 (108–3,001)</td>
<td>452 (57–1,453)</td>
<td>37% (8%–74%)</td>
<td>6.46 (6–7)</td>
<td>24.34 (10.12–40.5)</td>
</tr>
</tbody>
</table>

386

Hospital characteristics associated with the utilization of robotic surgery in endometrial cancer

C. Jones1, C. Jones1, K. Blansit1, J. Ram1, R. Brooks1, S. Ueda1, L. Chen1, D. Kapp1, X. Yu1, J. Chan1
1UCSF Comprehensive Cancer Center, San Francisco, CA, 2Georgetown University, Washington, DC, 3Stanford University Medical Center, Stanford, CA, 4The University of Memphis, Memphis, TN

Objective: To determine the association between hospital characteristics and utilization of robotic surgery (RS) in a nationwide study.

Methods: Data were obtained from the United States National Inpatient Survey in 2010. Hospital characteristics, including division of United States, location, volume, teaching status, and ownership, were extracted. Chi-square, t-test, ANOVA, and multivariate models were used for statistical analysis.

Results: Of 420 hospitals that reported surgeries for endometrial cancer, the average number of cases per year was 16 (range, 1–274). The proportion of hospitals in the south, west, and southeast were 31%, 22% and 20%, respectively. Seventy-seven percent of hospitals were in urban locations, 77% were considered higher-volume (>20 surgeries/year) hospitals, 44% were teaching hospitals, and 80% were reported as privately owned. The overall utilization of RS was 24% compared to 12% for laparoscopic (LS) and 63% for open surgery (OS). Utilization of RS was higher in urban vs. rural (27% vs. 5%, P<0.01), teaching vs. nonteaching (28% vs. 24%, P=0.02), and private vs. public hospitals (29% vs. 10%, P<0.01). The mean length of stay (LOS) for RS was 3.8 days in public hospitals, 2.4 days in for-profit, and 1.4 in nonprofit (P<0.01). There was no difference in RS LOS among low- and high-volume hospitals (P=0.39), differing hospital locations (P=0.25), and teaching status (P=0.29). With respect to hospital charges, RS had the highest charge in private, for-profit hospitals ($55,540 compared with private nonprofit ($41,578) and public hospitals ($38,720). RS was associated with higher charges at teaching hospitals ($45,288) than non-teaching hospitals ($32,709) (P<0.01).

Conclusions: In this nationwide analysis, the utilization of robotic surgery was higher in the midwest and in urban, teaching, and private hospitals. Further, the charges for robotic surgery were higher in private and teaching centers.

387

Comparison of vaginal cuff closure outcomes in patients having robotic-assisted total laparoscopic hysterectomy: V-Loc vs. Vicryl

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Objective: To determine if the use of V-Loc suture for vaginal cuff closure following robotic-assisted total laparoscopic hysterectomy decreased the incidence of vaginal cuff dehiscence compared to Vicryl suture.

Methods: All patients who had completed robotic-assisted laparoscopic hysterectomy from 6/1/2008 to 12/31/2011 were identified through the institution’s database. Those patients who underwent vaginal closure with 2-0 V-Loc (unidirectional barbed suture) were retrospectively compared to the cohort that underwent vaginal cuff closure with 0-Vicryl (synthetic braided suture). Exclusion criteria included use of suture material other than 0-Vicryl or 2-0 V-Loc. The primary outcome measure was vaginal cuff dehiscence. Fisher’s exact test was used for data analysis.

Results: Seven hundred thirty-two patients (328 in the 2-0 V-Loc group and 404 in the 0-Vicryl group) were analyzed. The incidence rate of vaginal cuff dehiscence among those with V-Loc suture was 0% (n=0/328), while it was 0.82% (n=6/404) among those with Vicryl suture (P=0.03568). There was no correlation identified between vaginal cuff dehiscence and type of uterine manipulator used, body mass index, smoking habits, uterine size, or estimated blood loss.

Conclusions: Dehiscence of the vaginal cuff after robotic-assisted total laparoscopic hysterectomy is a rare but important and serious complication in gynecologic surgery. The use of 2-0 V-Loc unidirectional suture to close the vaginal cuff following robotic-assisted laparoscopic hysterectomy may eliminate the problem of vaginal cuff dehiscence.

388

Port-site metastases after robotic surgery for gynecologic malignancy

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Objective: To evaluate the outcomes of patients diagnosed with port-site metastases after robotic surgery for gynecologic malignancies.

Methods: After institutional review board approval was obtained, a retrospective chart review was conducted evaluating all patients undergoing gynecologic robotic surgery between 6/2006 and 10/2011. Patient demographics, medical/surgical histories, histology, treatments, disease-free survival, and overall survival were collected.

Results: A total of 681 patients were identified, and 418 (61.4%) were diagnosed with a gynecologic malignancy for final pathology. Five (1.2%) patients had a recurrence in a laparoscopic port site. The mean age of patients with a port-site metastasis was 69.2 years compared to a 56.9 years for patients without a port-site metastasis (P=0.2). The average body mass index for patients diagnosed with port-site metastasis was 26.2 compared to 33.3 for all other patients (P=0.01). All patients with port-site metastasis had endometrioid histology. Three patients were diagnosed with stage IB cancer, 1 had stage IA, and 1 had stage IIB. One patient underwent adjuvant therapy following her primary surgery, completing 3 cycles of taxane and platinum-based chemotherapy followed
by whole pelvic radiation therapy and brachytherapy. The remaining patients received no adjuvant therapy. Port-site metastases were diagnosed in the right lateral port site in 2 patients, left lateral port in 1 patient, the midline camera port in 1 patient, and the accessory port in 1 patient. The disease-free survival was 6.2 months. Four patients (80%) had isolated recurrence and were treated with surgical resection followed by 6 cycles of taxane and platinum-based chemotherapy. The patient who previously completed adjuvant therapy was diagnosed with unresectable metastatic disease and was treated with doxorubicin and cisplatin. Four patients are alive with disease; 1 patient is dead of disease. The overall survival was 24.4 months (range, 14-29 months).

Conclusions: There is a low incidence of port-site metastases in patients undergoing robotic surgery for gynecologic malignancies. In patients with an isolated port-site recurrence, treatment with surgical resection followed by taxane and platinum-based therapy is a reasonable option.

389 Vaginal cuff complications decreased in total robotic vs. laparoscopic hysterectomy in cancer and noncancer patients: Bidirectional barbed vs. conventional suture

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Objective: The literature suggests that vaginal cuff dehiscence is highest with robotic procedures (1%-4%). The purpose of this study was to compare vaginal cuff complications among patients undergoing total robotic hysterectomy (TRH) vs. total laparoscopic hysterectomy (TLH) and the effect of bidirectional barbed suture used to close the vaginal cuff.

Methods: A retrospective cohort study was performed that included women undergoing TRH and TLH from 2007 to 2011. Age; weight; body mass index (BMI); surgical procedure; estimated blood loss (EBL); and vaginal cuff complications, including dehiscence, deep vein thrombosis (DVT), and pulmonary embolism (PE), were evaluated. Student t-test and chi-square test were used to determine statistical significance (P value < 0.05).

Results: A total of 437 patient charts were evaluated, with 243TRH and 194 TLH. There was statistically lower EBL (128 g vs. 179 g) and higher uterine weight (333 g vs. 184 g) among TRH. Overall vaginal cuff complications were less with TRH vs. TLH (1.83% vs. 2.74%, P=0.65) but not statistically significant. Vaginal cuff dehiscence was lower among TRH vs. TLH but not statistically significant (0.23% vs. 1.14%, P=0.42). Vaginal cuff complications were lower in cancer vs. noncancer patients but not statistically significant (0.68% vs. 2.74%, P=0.723). Bidirectional barbed sutures were used more often during TRH (46%) than TLH (0). Vaginal cuff complications among the TRH closed with bidirectional barbed sutures (0.41%) were 6 and 12 times less compared to TRH (2.47%) or TLH closed with conventional suture (6.18%), respectively.

Conclusions: In our study, vaginal cuff complications were lowest overall after robotic hysterectomy. This finding appears to be related to the use of a bidirectional barbed suture, which decreased the risk by 6 to 12 times when compared to conventional suture.

390 Circulating endothelial progenitor cells in gynecologic cancer

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Objective: Tumor growth and metastasis are closely related to abnormal angiogenesis and neovascularization. The mechanisms of tumor angiogenesis are not clear, but recent studies have shown that circulating endothelial progenitor cells (EPCs) play an important role in the tumor angiogenic reaction. The aim of this study was to compare the levels of circulating EPCs between gynecologic cancer patients and healthy subjects and to test the hypothesis that the cancer treatment such as tumor debulking surgery or computer-controlled radiation therapy (CCRT) would help in lowering the levels of EPCs.

Methods: Tumor growth and metastasis are closely related to abnormal angiogenesis and neo-vascularization. The mechanisms of tumor angiogenesis are not clear, but recent studies have shown that circulating endothelial progenitor cells (EPCs) play an important role in the tumor angiogenic reaction. The aim of this study was to compare the levels of circulating EPCs between gynecologic cancer patients and healthy subjects, and to test the hypothesis that the cancer treatment such as tumor debulking surgery or CCRT would help in lowering the levels of EPCs.

Results: Circulating EPCs in peripheral blood were significantly higher in the cancer group compared with those in control group (frequency in cervical cancer: 0.032±0.014% and 0.002±0.002%, P=0.004; number in cervical cancer: 542.7±773.3 and 20.9±22.3 cells; frequency in ovarian cancer: 0.012±0.002% and 0.003±0.002%, P=0.000035; number in ovarian cancer: 146.030±107.860 and 23.935±22.385 cells, P=0.01). Both CCRT and surgery were effective in lowering the circulating EPC levels in the cancer patient group (frequency in CCRT: 0.034±0.014% to 0.005±0.004%, P=0.016; number in CCRT: 633.732±976.425 to 84.560±40.755 cells; frequency in cervical cancer surgery: 0.0157±0.00033 to 0.005±0.001%, P=0.044; number in cervical cancer surgery: 360.675±173.653 to 56.086±23.247 cells, frequency in ovarian cancer surgery: 0.012±0.002% to 0.005±0.001%, P=0.0001; number in ovarian cancer surgery: 146.030±107.860 to 61.810±46.780 cells, P=0.005).

Conclusions: Circulating EPCs were significantly higher in the cancer group compared to the control group and had a declining tendency as treatment continued. EPCs might be surrogate markers in gynecologic malignant disease to monitor cancer treatment response.

391 An innovative in silico method to identify agents that target pathways of human cancer chemoresistance

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Objective: Few clinical or biologic events affect patient outcome more than the development of resistance to chemotherapy. Patients with chemoresistant disease have a poor prognosis and are subject to empirically driven treatment with multiple drugs. Here we apply an in silico method to identify new and existing agents that target pathways associated with human cancer resistance to a broad range of chemotherapeutics.

Methods: To identify molecular signaling pathways associated with resistance to multiple commonly used chemotherapeutic drugs, we studied Affymetrix HG-U133A expression data for 59 human cancer cell lines correlated with GSI sensitivity data for 41 chemotherapeutic agents (e.g., cisplatin, paclitaxel, doxorubicin). Pathways associated with resistance to >9 drugs were evaluated for associations with survival of 2,205 patients with ovarian, breast, lung, leukemia, brain, and colon cancers. Of these, pathways also associated with patient survival in >3 of 11 datasets were studied further to identify predicted novel, pathway-specific inhibitors. To do so, pathway expression was correlated with sensitivity of 48,000 agents in 59 cancer cell lines.

Results: Ten molecular signaling pathways (P<0.05) were associated with resistance to 9 or more commonly used chemotherapeutic drugs, and 6/9 pathways were associated with survival in >3 clinical datasets. These pathways include: androgen (breast, colon, ovarian cancer survival), EMT (breast, colon, ovarian survival), ERNOS (colon, ovarian cancer survival), histamine (breast, colon, ovarian cancer survival), TGF-WNT (ovarian, colon cancer, leukemia survival), and WNT2 (colon and ovarian cancer survival). Pearson’s correlation of pathway expression and cancer cell sensitivity to 48,000 agents identified...
agents predicted to target each of the androgen (n=213), EMT (n=180), eNOS (n=342), histamine (n=947), TGF-Wnt (n=446), and Wnt2 (n=42) pathways.

Conclusions: We have developed a novel in silico methodology to identify molecular signaling pathways that are commonly associated with resistance to standard chemotherapeutic agents and further to identify novel agents that may target those pathways, including new compounds and new uses for existing drugs that are currently the focus of ongoing in vitro analyses.

392

Identifying drug repurposing opportunities to target genes and molecular pathways associated with cancer cell proliferation


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Objective: Cancer is characterized by deregulated cell proliferation. Identifying genes and molecular pathways associated with this process will allow for development of targeted molecular therapy. We propose that in silico analysis of genomic and proliferation data could identify new and existing agents that target specific cancer molecular pathways.

Methods: Genes and molecular signaling pathways associated with human cancer cell proliferation were identified by Pearson’s correlation test of Affymetrix genomic expression data (U133Plus) and growth rates of the NCI60 cancer cell panel. Identified genes and signaling pathways (summarized by principal component analysis) were evaluated for association with overall patient survival in 2,205 cancers from 11 independent clinicoengenetic datasets using 3 statistical models: 1) Mantel-Cox, median PCA threshold, 2) Mantel-Cox, 25%-75% quartiles, and 3) Cox proportional hazard model test. Genes and pathways with expression associated with survival were analyzed against the NCI60 cell-drug screening database to identify agents predicted to have pathway- and gene-specific activity.

Results: We identified genes (n=83, false discovery rate [FDR]=0) correlated with human cancer cell proliferation rates and 49 represented molecular signaling pathways (FDR<0.05). At a pathway level, expression of 12/49 pathways was also associated with overall patient survival in ≥3 clinical datasets (P<0.05). Pearson’s correlation (P<0.0001) of pathway expression and cancer cell sensitivity to 48,000 agents identified agents predicted to target each of the A2A (n=2), EIF4F (n=16), EMT (n=36), HMGB1-RAGE (n=10), insulin-regulation (n=6), integrins (n=8), lipoxin (n=42), lipoxin-IL8 (n=22), PKA (n=42), Sp2-Sp3 (n=1), TGF-MAPK (n=26), and TGF-Wnt (n=81) pathways. At an individual gene level, 17/83 genes associated with proliferation (FDR=0) were associated with patient survival (>2 clinical datasets, P<0.05). We identified 5082 agents with in vitro activity that correlated with expression of these 17 genes (P<0.01).

Conclusions: A novel in silico analysis allows for the identification of genes and molecular signaling pathways associated with cancer cell proliferation. Furthermore, we identified existing agents that may be repurposed to target these genes and pathways and that are currently the focus of in vitro functional analyses.
KRAS mutation in endometrial and ovarian cancers: Preliminary data on association with phenotype and clinical outcome in primary disease

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Objective: Oncogenic KRAS mutations are known to activate RAS/RAF/MEK signaling, a pathway essential to tumorigenesis in solid malignancies. Previous studies of somatic mutations in solid tumors have demonstrated tropism of mutated tumors for specific organs at diagnosis and recurrence. We explored the impact of KRAS mutation on phenotype and clinical outcomes in patients with advanced endometrial and ovarian cancer.

Methods: Tumors from patients with endometrial, ovarian, primary peritoneal (PP), and fallopian tube (FT) cancer referred to a phase I clinic between October 2007 and August 2010 were analyzed for KRAS mutations. When possible, analysis for PIK3CA, NRAS, BRAF, CKIT, and EGFR mutations was performed. Demographic, clinical, and outcomes data were collected from the medical record. Time to progression (TTP) was defined as time from completion of primary treatment to time of progression.

Results: Ninety-two patients were tested for KRAS mutation. Of those, 33% (n=30) had endometrial, 64% (n=59) had ovarian/PP/FT, and 3% (n=3) had synchronous endometrial and ovarian cancer. Eleven (12%) patients had KRAS mutation (6 endometrial [54.5%], 4 ovarian [36.4%], and 1 synchronous [9.1%]). Patients with KRAS mutation were more likely to have a concurrent mutation in PIK3CA (54.5% vs. 10%, P=0.001). Compared to patients with KRAS wild type tumors, patients with KRAS mutations had significantly lower median TTP (1.5 vs. 6.5 months, P=0.04). KRAS mutation was associated with presence of pelvic lymph node metastasis (54.5% vs. 21.2%, P=0.02) and diaphragmatic disease in the primary setting (27.3% vs. 7.4%, P=0.07). Despite low numbers, KRAS mutation in the ovarian cancers trended toward increased recurrence in the spleen (50.0% vs. 8.7%, P=0.09). Among endometrial cancers, patients with KRAS mutation had a trend toward higher proportion of bone metastasis in the recurrent setting (33.3% vs 8.3%, P=0.13).

Conclusions: These preliminary data provide a foundation for analysis of the potential impact of KRAS mutation on primary disease presentation and outcome in endometrial and ovarian cancer. KRAS mutation is associated with poor prognostic features, including lymph node metastasis and diaphragmatic disease. Further, it appears that KRAS mutation is associated with worse TTP after primary therapy.

Table. Study Results

<table>
<thead>
<tr>
<th></th>
<th>&quot;SS&quot; Group (n=25)</th>
<th>&quot;R&quot; Group (n=79)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>56 (38-73)</td>
<td>60 (36-80)</td>
<td>NS</td>
</tr>
<tr>
<td>Median follow-up duration (months)</td>
<td>23.0 (4.0-45.5)</td>
<td>30.0 (5.5-64.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Median inhibition rate (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To carboplatin</td>
<td>80.0 (68.0-89.0)</td>
<td>50.6 (3.0-90.0)</td>
<td>NS</td>
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<tr>
<td>To paclitaxel</td>
<td>65.2 (51.0-90.0)</td>
<td>39.4 (2.0-84.0)</td>
<td>NS</td>
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<tr>
<td>Histology</td>
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<tr>
<td>PSA</td>
<td>10</td>
<td>40</td>
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<tr>
<td>PSC</td>
<td>9</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>6</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Drop rate of CA-125 level (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After 2nd cycle</td>
<td>80</td>
<td>74</td>
<td>NS</td>
</tr>
<tr>
<td>After 6th cycle</td>
<td>84</td>
<td>86</td>
<td>NS</td>
</tr>
<tr>
<td>CA-125&gt;10 after 6th cycle of chemotherapy</td>
<td>20 (80.0%)</td>
<td>56 (70.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Event of recurrence</td>
<td>7 (28.0%)</td>
<td>49 (62.0%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Event of death</td>
<td>4 (16.0%)</td>
<td>9 (11.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Median progression-free survival (months)</td>
<td>34.0 (24.9-38.6)</td>
<td>17.1 (23.1-34.0)</td>
<td>0.041</td>
</tr>
<tr>
<td>Median overall survival (months)</td>
<td>38.3</td>
<td>54.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Progression-free survival can be predicted in epithelial ovarian cancer patients by in vitro chemosensitivity testing using the histoculture drug response assay - A prospective observational study in a single institution

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Objective: To correlate clinical outcomes of advanced epithelial ovarian, fallopian tube, and primary peritoneal cancers with the results of chemosensitivity testing of paclitaxel and carboplatin using in vitro histoculture drug response assay (HDRA) to presume the course of disease and to evaluate the clinical value of the chemosensitivity test.

Methods: A total of 200 patients with FIGO stage III to IV were treated with combination chemotherapy of paclitaxel and carboplatin after primary cytoreductive surgery between 2007 and 2012 in a single institution. A piece of fresh tumor tissue from each patient was obtained for in vitro chemosensitivity test during the surgery. Of those, 104 patients were included in this study, excluding those who received neoadjuvant chemotherapy. To compare chemosensitivity with clinical courses, the patients who had higher-than-average inhibition rate of each drug were regarded as sensitive to the drug. In this way, 104 patients were divided into 2 groups: "SS" group of 25 patients, who were sensitive to both paclitaxel and carboplatin, and "R" group of remaining 79 patients.

Results: During 28 months of median follow-up duration (range, 2-66 months), 56 patients (53.8%) had recurred and 13 patients (12.5%) had died of disease (Table). The HDRA results of all patients were sensitive to cisplatin, topotecan, carboplatin, and paclitaxel, with inhibition rates of 54%, 52%, 50%, and 46%, respectively. The drop rate of CA-125 after the second cycle of chemotherapy was higher in "SS" group than in the "R" group (80% vs. 76%) but was not significant (P=0.31). Patients in the "SS" group had a greater tendency of having CA-125 below 10 after the sixth cycle of chemotherapy (80.0%) compared to those of the "R" group (70.8%) (P=0.37). The median recurrence rate was lower in "SS" group than "R" group (26.0% vs. 62.0%, P=0.03). The median progression-free survival (PFS) also was significantly higher in the "SS" group (34 months) than the "R" group (17 months) (P=0.041) (Figure). However, the median overall survival did not differ significantly (38.5 vs. 54.8 months, P=0.113). Median PFS for all 104 patients was 18.7 months, with an estimated 3-year survival of 85%.

Conclusions: Patients with tumors that appeared in vitro to be sensitive to both paclitaxel and carboplatin had significantly longer median PFS and lower recurrence rates. Therefore, the result of in vitro HDRA chemosensitivity testing was related to PFS and recurrence rate, which indicates the responsiveness of chemotherapy. The primary chemotherapy regimen could be individualized and the second regimen could be modulated.
Vulvar Cancer

396 Therapeutic choices and outcomes in vulvar cancer cases reported by the National Cancer Database Registry

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Objective: To explore data from the National Cancer Database Registry (NCDB) to identify the association of clinical factors with both treatment rendered and overall survival in patients with vulvar cancer.

Methods: Between 1998 and 2003, 11,303 patients with vulvar squamous cell carcinoma were registered with the NCDB. Patient characteristics evaluated were age, race, insurance, facility type, region, stage, income and education level, date of diagnosis, surgery performed, margin status, radiation dose, and location of radiation treatment. Overall survival was analyzed using the logrank test and the multivariable Cox regression.

Results: Of the patients included in the analysis, 42% (n=4791) were stage I, 25% (n=2781) were stage II, 23% (n=2582) were stage III, and 10% (n=1149) were stage IV. Advanced stage (III or IV) was significantly associated with older age, nonprivate insurance, northeast region of the country, and a lower case volume center. Stage was not associated with race, income or education level, facility type, or year of diagnosis (P=0.001). Early-stage disease was associated with a higher likelihood of clear surgical margins (P<0.0001). Radiation and/or chemotherapy were given (with or without surgery) to 64% of stage III and 73% of stage IV patients. In the advanced stages, radiation therapy was most likely to be given at the reporting facility (P<0.0001), although roughly 33% (n=1,221) of advanced-stage patients did not receive radiation therapy. Of the 1,105 patients with advanced-stage disease who received radiation therapy, 881 (80%) were reported to receive doses <5,040 cGy while 224 (20%) received doses ≥5,040 cGy. Overall 5-year survival by stage was 82.3%, 64.44%, 46.01%, and 24.11%, respectively for stages I-IV. Within the advanced stages, treatment at community cancer centers, age ≥60 years, and northeast region were all associated with a greater risk of death (P<0.05). Among stage III patients, sampling or biopsy of lymph nodes may be associated with decreased risk of death (P<0.05). This was not as evident among stage IV patients, although patients with negative surgical margins did have a decreased risk of death (P<0.05).

Conclusions: Being that vulvar cancer is a rare condition, these data will help to explain practice patterns and disease distribution in the United States. Certain pre-existing factors have been shown to be associated with therapeutic choices and outcomes in this disease.

397 Low yield of residual vulvar carcinoma and dysplasia upon re-excision for close or positive margins

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Objective: Close surgical margins are an adverse prognostic factor for women with vulvar cancer, but little is known about the yield of re-excision, especially when gross or pathologic margins are clear. We aimed to determine the utility of re-excision after a primary diagnosis of microinvasive or frank vulvar carcinoma by assessing the frequency of residual carcinoma found on re-excision specimens. Secondarily, we aimed to quantitate the wound breakdown and recurrence rates.

Methods: We reviewed 1,122 cases of vulvar intraepithelial neoplasia (VIN) or vulvar carcinoma treated at 2 regional university medical centers by gynecologic oncologists. Abstracted clinical data included patient’s age, disease stage, recurrence, and wound breakdown upon re-excision. Pathologic data included histology of the initial excisional and re-excisional specimens, depth of invasion of initial specimen, and status and histology of margins (positive vs. negative for dysplasia/carcinoma).

Results: We identified 87 evaluable patients. Of these, 84 (97%) had detailed pathology reports describing histology and margin status. Seventy-three patients had stage I disease, 4 had stage II, and 10 had stage III disease (FIGO 2009). Upon the initial excisional procedure, 33 of 84 patients (39%) had margins positive for microinvasive or invasive carcinoma, 27 patients had VIN-negative margins (32%), and 24 patients (28%) had negative margins (>1 mm). Upon re-excision, only 1/24 (4%) patients with negative margins, 2/27 (7%) patients with VIN-positive margins, and 11/33 (33%) patients with microinvasive or invasive carcinoma at margins were found to have carcinoma or microinvasive carcinoma in the re-excision specimens (P<0.0001, χ²=31) (Table). Greater depth of invasion (mm) in the initial excision sample was associated with worse histology upon re-excision (P=0.015, χ²=19). Nineteen of 83 (23%) evaluable patients were noted to have vulvar wound breakdown after re-excision. Twelve of 81 patients (15%) had recurrence of carcinoma (median follow-up time, 28 months).

Conclusions: The yield of microinvasive or invasive carcinoma at re-excision is low, with a relatively high wound breakdown rate. Re-excision should be considered for patients with margins positive for carcinoma, while women with VIN or close but clear margins may be followed. Depth of invasion of the initial excisional sample may also serve as a predictor of histology upon re-excision. Studies are underway to identify additional risk factors.

Table. Correlation between margin status of initial excision specimen and histology of re-excision specimen

<table>
<thead>
<tr>
<th>Initial excision margin status</th>
<th>microinvasive/invasive carcinoma [n=27]</th>
<th>VIN [n=0]</th>
</tr>
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<tbody>
<tr>
<td>negative [n=24]</td>
<td></td>
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</table>


Patterns of inguinal lymph node metastasis in patients with vulvar cancer

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Objective: The current standard evaluation of groin metastasis in vulvar squamous cell carcinoma (VSCC) is unilateral or bilateral lymphadenectomy. However, sentinel node detection has shown a safe treatment option for early-stage disease. Most recurrences are locoregional and related to inadequate surgical margins or groin lymph node metastasis. Our aim was to analyze the pattern of inguinal lymph node metastasis in VSCC in relation to the site of the primary lesion.

Methods: We analyzed a series of 210 individuals who underwent inguinal lymph node dissection for VSCC from January 1980 to June 2009. This cohort was divided in 3 subgroups by primary lesion location: unilateral, bilateral, and midline.

Results: One hundred forty-six patients underwent bilateral groin lymph node assessment and are the subject of our study. Of the 75 (51.3%) patients with positive groin lymph node involvement, 47 (62.7%) presented with unilateral and 28 (37.3%) with bilateral inguinal/femoral involvement. Of the 100 patients presenting with only unilateral vulvar lesions, 50 had inguinal/femoral involvement: 33 (66%) with ipsilateral-only nodal metastasis and 17 (34%) with bilateral lymph node metastasis. None of these patients with a unilateral vulvar lesion that was either ≤2 cm in biggest diameter or with invasion ≤5 mm had bilateral groin node involvement. No patient with a unilateral lesion present had contralateral metastasis without concomitant ipsilateral involvement.

Conclusions: Ipsilateral lymphadenectomy is suitable for patients with unilateral lesions, distant from the midline, and either negative ipsilateral nodes or positive ipsilateral nodes with lesions <2 cm.

Prognostic factors of recurrence in patients with advanced squamous cell carcinoma of the vulva treated with primary surgery and adjuvant radiotherapy: An institutional experience

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Objective: Squamous cell carcinoma (SCC) of the vulva is a rare gynecologic malignancy, which often occurs in the elderly population. The cornerstone of treatment in advanced SCC of the vulva is surgery, consisting predominately of wide radical local excision with bilateral inguinal/femoral lymphadenectomy. Postoperative radiotherapy represents the optimal adjuvant treatment in patients with fixed ulcerated inguinal lymph node metastases, extranodal extension, 2 or more positive lymph nodes, and pathologic margins of resection (<8 mm). The aim of this study was to evaluate the prognostic factors for disease-free survival (DFS) and overall survival (OS) in women with SCC of the vulva treated with primary surgery and adjuvant radiotherapy.

Methods: We retrospectively reviewed all patients with vulvar SCC who had been treated with primary surgery and adjuvant radiotherapy from January 1996 to December 2006. Demographic characteristics such as age and race, histologic features including stage, grade, lymphovascular space involvement, and lymph-node invasion were collected. Recurrence rates, DFS, and OS were also recorded. Multivariable logistic regression analysis was performed to examine which parameters were independently associated with prolonged survival. Kaplan-Meier survival estimates for events were graphed over the follow-up period.

Results: A total of 45 patients with mean age of 71.3 years (standard deviation=11.9 years) were enrolled in this study. The 5-year DFS rate was 34.4% (Figure). Multiple Cox regression analysis revealed age >64 years and number of positive lymph nodes as the only independent prognostic factors for high recurrence rates. Age >64 years was found to be associated with 2.47 times greater odds to present recurrence in a 5-year period (HR=2.47, 95% CI: 1.01-6.07, P=0.048), while patients with >4 positive lymph nodes in histology had 2.01 times greater likelihood for recurrence (HR=2.01, 95% CI: 1.00-4.05, P=0.049). The overall recurrence rate was 28.9% (15/45).

Conclusions: Older age and lymph node metastasis were the independent predictors of poor prognosis for patients with advanced SCC of the vulva treated with primary surgery and adjuvant radiotherapy.
Conclusions: In addition to being associated with fewer postoperative complications, vulvectomy and SLNB is the most cost-effective strategy for the management of patients with early-stage vulvar cancer.

401 Lymphatic mapping and sentinel lymph node dissection is cost-effective compared to complete lymphadenectomy in the management of early-stage vulvar cancer

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Objective: Sentinel lymphadenectomy (SLN) has been established as a feasible and reliable method of evaluating groin lymph nodes in women with vulvar cancer. The purpose of this study was to assess the cost and effectiveness of SLN dissection (SLND) compared with superficial inguinal-femoral lymphadenectomy (LND) for vulvar cancer.

Methods: A modified Markov decision model was generated to compare 2 surgical approaches for women with newly diagnosed, early-stage vulvar cancer: 1) modified radical vulvectomy + full LND or 2) modified radical vulvectomy + SLND. Published data were used to estimate survival outcomes, incidence of positive LN, adjuvant therapy, and incidence of lymphedema. Costs of surgery, radiation therapy, and treatment of lymphedema were estimated based on published data, Medicare Current Procedural Technology codes and the Physician Fee Schedule. We assumed 5% of the SLND group would receive full LND due to grossly positive nodes. The effect of lymphedema on quality of life (QOL) was assigned a utility score of 0.84 (1=perfect QOL and 0=death; unpublished data). Sensitivity analyses were performed on various factors in the model.

Results: SLND was less costly ($13,449 vs. $14,261) and more effective (4.16 quality-adjusted life years [QALYs] vs. 4.00 QALYs) than full LND, making SLND the strategy of choice. Sensitivity analysis revealed a robust model under several assumptions (Figure). When the cost of SLND was varied over a wide range, SLND remained cost-effective compared to LND. Variation in the cost of lymphedema treatment over its range did not change the model’s results. Unless the impact of lymphedema on QOL was essentially nil (utility score >0.975), SLND dominated LND. Assuming lymphedema had no effect on QOL, full LND was cost-effective compared to SLND, with an incremental cost-effectiveness ratio (ICER) of $23,706/QALY. SLN was the strategy of choice over LND when the rate of microscopically positive SLN was varied up to 45%.

Conclusions: SLND is a cost-effective strategy for the treatment of women with newly diagnosed vulvar cancer, mainly due to the impact of lymphedema on QOL.
Zajchowski, D., 308
Zand, B., 10, 11, 274, 307
Zanotti, K., 164, 280
Zhang, W., 332
Zhang, Y., 211
Zhong, M., 326
Zhou, C., 43, 212, 301
Zhou, Q., 172, 177, 178, 366
Zighelboim, I., 234
Ziogas, A., 45
Zong, Y., 43, 301
Zorn, K., 184, 243, 295, 315
Zou, J., 93
Zsiros, E., 25, 320, 325
Zujewski, J., 24