GYNECOLOGIC CANCER

Ovarian Cancer: Old Subtypes, New Approaches

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The Life and Times of Low-Grade Serous Carcinoma of the Ovary

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OVERVIEW

For the past several years, all women with epithelial ovarian cancer have been treated identically, whether in a clinical trial or off protocol. Over the past decade, we have come to appreciate the magnitude of the heterogeneity of ovarian cancer. The development of the binary grading system for serous carcinoma was a major advance, leading to separate clinical trials for patients with this subtype, originating from the Gynecologic Oncology Group’s Rare Tumor Committee. The mitogen-activated protein kinase (MAPK) pathway appears to play a prominent role in the pathogenesis of this subtype. Approximately 20% to 40% of low-grade serous carcinomas have a KRAS mutation, while BRAF mutations are rare—approximately 5%. In genomic profiling studies, these tumors appear to cluster with serous tumors of low malignant potential. Compared with high-grade serous carcinomas, low-grade serous carcinomas are also characterized by a low frequency of p53 mutations, greater expression of ER and PR, and greater expression of PAX2 and IGF-1. Primary treatment of low-grade serous carcinoma includes surgery plus platinum-based chemotherapy (either adjuvant or neoadjuvant). Clinical behavior is characterized by young age at diagnosis, relative chemoresistance, and prolonged overall survival. Current options for treatment of relapsed disease include secondary cytoreduction in selected patients, salvage chemotherapy, or hormone therapy. A recently completed trial of a MEK inhibitor for women with recurrent disease demonstrated promising activity. Future directions will include further investigations of the molecular biology and biomarker-driven clinical trials with targeted agent monotherapy and combinations.

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ver the past decade, it has become increasingly clear that ovarian cancer is not one but several distinct entities. Even today, the vast majority of ovarian cancer clinical trials include women with all histologic subtypes. Such is true in both the front-line and the recurrent settings. However, advances in our understanding of the heterogeneity of ovarian cancer have emerged on the basis of refinement of pathologic diagnostic criteria, molecular biology and genetic investigations, and reports of hypothesis-generating clinical studies.

Specifically, for low-grade serous carcinoma of the ovary, the confluence of two major factors—reports of the binary grading system for serous carcinoma1,2 and the establishment of the Gynecologic Oncology Group’s Rare Tumor Committee in 2005—has led to a widespread recognition of this histologic subtype and to the dawn of separate clinical trials for women diagnosed with this rare entity. The principle of separate clinical trials for major rare histologic subtypes of ovarian cancer—clear cell carcinoma, mucinous carcinoma, and low-grade serous carcinoma—was subsequently validated in two consensus conferences.3,4

Based on initial studies, it is estimated that approximately 10% of serous carcinomas are low-grade. Most are metastatic at diagnosis. Low-grade serous carcinoma may arise de novo or as a recurrence after a diagnosis of a serous tumor of low malignant potential with peritoneal implants.5–8 Of the serous tumors of low-malignant potential that recur, approximately 75% to 80% do so as a low-grade serous carcinoma.5,8 In addition, serous tumor of low malignant potential is found coexisting in approximately 60% of newly diagnosed low-grade serous carcinomas.1 Furthermore, comparison of newly diagnosed low-grade serous carcinoma and serous tumors of low malignant potential has indicated that the age at diagnosis, the overall survival time, and the progression-free survival (PFS) time of stages II–IV low-grade serous carcinoma of the ovary are similar to those of serous ovarian tumors of low malignant potential that recur as low-grade serous carcinoma (measured from the diagnosis of relapse).9 Thus, these two tumor types—serous tumor of low malignant potential and low-grade serous carcinoma—appear to exist on a continuum.

This article will discuss the unique features of low-grade serous carcinoma of the ovary in terms of its histologic characteristics, molecular biology, and clinical behavior.

PATHOLOGY OF LOW-GRADE SEROUS CARCINOMA OF THE OVARY

Although several studies have shown that histologic grade is an important prognostic factor in serous carcinoma of the
easy to learn and very reproducible. After 15 years of experience and refinement, the MD Anderson group initially reported their experience with a two-tier grading system based primarily on the evaluation of nuclear atypia with mitotic rate as a secondary feature. Within this system, tumors with mild to moderate nuclear atypia and a mitotic index of up to 12 mitoses per 10 high-power fields are classified as low-grade serous, while those tumors with marked nuclear atypia and a mitotic index of greater than 12 mitoses per 10 high-power fields are considered to be high-grade serous.

Seidman and colleagues evaluated the MD Anderson binary grading system for serous carcinoma, as well as another binary system developed at the Washington Hospital Center. In this study, the authors found that the MD Anderson grading system was more predictive of survival and concluded that it was more promising. In evaluating the interobserver and intraobserver variability among seven gynecologic pathologists and two general surgical pathologists using the MD Anderson grading system, Malpica and colleagues observed that the binary grading system for serous carcinoma is easy to learn and very reproducible.

Bodurka and colleagues recently reported the findings of a GOG ancillary study that further strengthened the fact that the MD Anderson binary grading system is more predictive of outcome than the grading system of the International Federation of Gynecology and Obstetrics (FIGO). The authors retrospectively reviewed data of 290 patients with stage III serous carcinoma of the ovary treated with surgery plus paclitaxel/carboplatin chemotherapy on GOG protocol 158. Tumors had previously been classified by using the FIGO three-tier system. A panel of six gynecologic pathologists performed a blinded review to reclassify these tumors by using the binary grading system. Of 241 cases, both systems demonstrated substantial agreement when combining FIGO grades 2 and 3. However, by using the binary system, patients with low-grade serous carcinoma had significantly longer progression-free survival than those with high-grade serous carcinoma. Furthermore, in multivariate analysis, there was no difference in clinical outcome in patients with grade 2 or 3 tumors using the FIGO system. The authors concluded that the binary grading system provides a more precise framework for predicting clinical outcomes in this patient cohort.

Vang and colleagues have also conducted studies that are supportive of the binary grading system for serous carcinoma. They found that subclassification of high-grade serous carcinoma of the ovary or peritoneum into grade 2 or grade 3 carcinomas using the FIGO grading system was not relevant. And Hannibal and associates, using the Danish Pathology Data Bank, evaluated 4,317 ovarian serous carcinomas. They also concluded that a binary grading system is a significant predictor of survival in ovarian serous carcinoma.

Thus, just over the past few years, the MD Anderson binary grading system for ovarian serous carcinoma has been embraced by expert gynecologic pathologists world-wide as an advance in the prediction of outcome. Concomitantly, as we learn more about the clinical behavior of low-grade serous carcinoma in contrast to its high-grade counterpart, treatment recommendations have begun to diverge, as discussed below.

**MOLECULAR BIOLOGY AND GENETICS OF LOW-GRADE SEROUS CARCINOMA OF THE OVARY**

Over the past decade, investigations of the molecular biology of low-grade serous carcinoma have not only strengthened evidence for the relationship between serous tumors of low malignant potential and low-grade serous carcinoma but also underscored the observation that the mitogen-activated protein kinase (MAPK) pathway plays a prominent role in its pathogenesis. In the initial report of the relationship with the MAPK pathway, Singer and colleagues analyzed 182 ovarian tumors, including 51 serous ovarian tumors of low malignant potential and 21 low-grade serous carcinomas (to use the authors’ term, “invasive micropapillary serous carcinoma”). KRAS mutations were reported in 33% of serous tumors of low malignant potential and in 35% of low-grade serous carcinomas, and BRAF mutations were found in 28% and 33%, respectively. Furthermore, BRAF and KRAS mutations were mutually exclusive, and no such mutations were found in high-grade serous carcinomas.

In a subsequent report, the MD Anderson research team analyzed 30 serous tumors of low malignant potential, 43 low-grade serous carcinomas, and 18 high-grade serous carcinomas. Although the authors observed a KRAS mutation frequency of 19% in the low-grade serous carcinomas, only one specimen (2%) harbored a BRAF mutation. In addition, they concluded that the low frequency of BRAF mutations in advanced stage low-grade serous carcinomas, which contrasted with previous reports, suggested that low-grade serous carcinomas are more likely derived from serous tumors of low malignant potential without BRAF mutation and that
advanced stage low-grade serous carcinoma patients with BRAF mutation have a better clinical outcome. A recent article, in which 56 serous tumors of low malignant potential and 19 low-grade serous carcinomas were analyzed, confirmed the MD Anderson findings. Although the BRAF mutation frequency was 45% in the serous tumors of low malignant potential, only a single case (5.3%) of low-grade serous carcinoma had a BRAF mutation. Furthermore, the findings suggested that the presence of a BRAFV600E mutation is associated with early-stage disease and improved prognosis in serous tumors of low malignant potential and low-grade serous carcinomas. Interestingly, none of the 22 patients who received chemotherapy had BRAF mutant tumors.

Genomic profiling studies have also indicated that low-grade serous carcinomas segregate from high-grade serous carcinomas but are similar to serous tumors of low malignant potential. Bonome and colleagues found that the majority of low-grade serous carcinomas clustered with serous tumors of low malignant potential. They also noted that pathways present in high-grade tumors—cell-cycle progression, cellular proliferation, and chromosomal instability—were absent in both low-grade serous types.

Several other studies have characterized the molecular biology and genetics of low-grade serous carcinoma. Compared with high-grade serous carcinomas, low-grade tumors have a much lower frequency of p53 mutations or p53 expression, greater expression ER and PR, greater expression of PAX2, overexpression of anterior gradient homolog 3 (AGR3), and overexpression of IGF-1.

**CLINICAL BEHAVIOR AND TREATMENT OF LOW-GRADE SEROUS CARCINOMA OF THE OVARY**

**Newly Diagnosed Low-Grade Serous Carcinoma**

**Primary surgery.** There is no evidence to date that indicates that the primary surgical management of low-grade serous carcinoma is different from that of ovarian cancer in general. Options include primary surgery—comprehensive surgical staging for apparent early-stage disease or maximum cytoreductive surgery for advanced-stage disease—or interval debulking surgery following neoadjuvant chemotherapy for select patients with apparent unresectable disease or significant comorbidities.

**Postoperative therapy.** Evidence to date suggests that low-grade serous carcinoma is relatively resistant to first-line chemotherapy on the basis of the metrics that we have available. In a review of 112 patients with newly diagnosed stage II-IV low-grade serous carcinoma of the ovary treated with primary surgery and platinum-based chemotherapy, it appeared that treatment was not as successful as expected on the basis of the high frequency of persistent disease at completion of therapy and low negative second-look rate. Of note as well, the median age of patients was only 43 years, and the median overall survival was 82 months. This relative chemoininsensitivity was also observed in a review of women who received neoadjuvant chemotherapy for advanced stage low-grade serous carcinoma. In this report, despite the fact that half of evaluable patients had a greater than 50% reduction in serum CA 125 levels after neoadjuvant chemotherapy, only one patient had an objective response by imaging assessment. One of the questions raised by these observations is whether our standard parameters for evaluation of response—serial imaging and CA 125—are adequate to determine outcome. Currently, although there are legitimate concerns about the efficacy of chemotherapy as standard first-line therapy, a potentially better alternative is not immediately evident.

**Recurrent Low-Grade Serous Carcinoma**

**Secondary surgery.** Secondary cytoreductive surgery may be indicated for selective patients with recurrent low-grade serous carcinoma—either following an original diagnosis of serous tumor of low malignant potential or advanced-stage low-grade serous carcinoma. Of course, as with all subtypes of ovarian cancer, supporting evidence for this subtype is retrospective. Based on current information, optimal candidates include those with platinum-sensitive disease and a limited number of recurrent sites (in contradistinction to patients with carcinomatosis).

Crispens and colleagues reported 35 patients with recurrent low-grade serous carcinoma after a diagnosis of serous tumor of low malignant potential who underwent 48 procedures. Patients who had suboptimal residual tumor were more likely to die of disease than those with optimal residual tumor. Likewise, Bristow and colleagues observed significantly better survival in patients who had optimal secondary surgical resection compared with those who did not.

**Chemotherapy.** Similar to observations in the first-line setting, recurrent low-grade serous carcinoma appears to be relatively chemoresistant. Of 58 patients who received a total of 108 separate salvage chemotherapy regimens, the overall response rate was 3.7%. However, stable disease was observed in 60% of patient-regimens. In addition, the median progression-free survival was about 7 months. Whether the high stable disease rate is more related to tumor biology or therapy remains unclear.

**Hormone therapy.** Gershenson and colleagues reported their experience with 64 women with recurrent low-grade serous carcinoma who received 89 separate hormone therapy regimens. The overall response rate was 9%, and the stable disease rate was 61%. The median progression-free survival was 7.4 months. Moreover, patients whose tumors were ER+/PR+ had a longer median time to progression (8.9 months) than those with ER+/PR- tumors (6.2 months). However, this difference approached but did not reach statistical significance. Hormonal agents that have demonstrated some degree of activity include the aromatase inhibitors, tamoxifen, and leuprolide acetate.
**TABLE 1. Studies of Systemic Treatment for Recurrent Low-Grade Serous Carcinoma**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Chemotherapy(^3)</th>
<th>Hormonal Therapy(^4)</th>
<th>Selumetinib(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. Patients</td>
<td>58</td>
<td>64</td>
<td>52</td>
</tr>
<tr>
<td>No. Regimens</td>
<td>108</td>
<td>89</td>
<td>52</td>
</tr>
<tr>
<td>CR (%)</td>
<td>1</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>PR (%)</td>
<td>2.8</td>
<td>2</td>
<td>13.5</td>
</tr>
<tr>
<td>SD (%)</td>
<td>60.2</td>
<td>62</td>
<td>65</td>
</tr>
<tr>
<td>% Median Clinical Benefit</td>
<td>64</td>
<td>71</td>
<td>80.5</td>
</tr>
<tr>
<td>Median PFS</td>
<td>7.3 mo.</td>
<td>7.4 mo.</td>
<td>11 mo.</td>
</tr>
<tr>
<td>% PFS &gt;6 mos.</td>
<td>58</td>
<td>61</td>
<td>63</td>
</tr>
</tbody>
</table>

**Abbreviations:** CR, complete remission; PFS, progression-free survival; PR, partial remission; SD, stable disease.

**Targeted therapy.** Based on the observations that low-grade serous carcinomas may be related to driver mutations in the MAPK pathway, agents that target this pathway are of great interest. In the initial study of this type, Farley and colleagues recently reported the results of a GOG phase II trial of selumetinib, a MEK 1/2 inhibitor, in 52 women with recurrent low-grade serous carcinoma.\(^3\) The response rate was 15%, and 65% of patients had stable disease. Median PFS was 11 months. Good quality formalin-fixed paraffin-embedded tissue was available in 34 patients and underwent mutational analysis. Two (6%) tumors had BRAF mutations, and 14 (41%) had KRAS mutations. However, there was no correlation between tumor response and mutational status. Table 1 compares the results of this GOG trial with historic information regarding treatment with chemotherapy or hormone therapy. Currently, an international randomized phase II/III study of another MEK inhibitor, trametinib, compared with standard therapy is under development for women with recurrent low-grade serous carcinoma. Embedded in this trial is a much more robust translational research component that will hopefully link outcome to mutational status. In addition, preclinical studies suggest that dual blockade of the MAPK and PI3K/AKT pathways may result in greater efficacy.

**CONCLUSION**

The study of low-grade serous carcinoma of the ovary has been greatly facilitated by development of a binary grading system. Consequently, a major advance over the past few years has been the initiation of separate clinical trials for this subtype. Chemotherapy has limited benefit against this tumor type but remains the standard for treatment of primary disease. In the recurrent setting, options include chemotherapy, hormone therapy, or targeted agents. Over the next several years, biomarker-driven clinical trials should increase our ability to achieve our goal of personalized cancer medicine.


Rare Epithelial Tumors Arising in or near the Ovary: A Review of the Risk Factors, Presentation, and Future Treatment Direction for Ovarian Clear Cell and Mucinous Carcinoma

Angela Jain, MD, and Michael V. Seiden, MD, PhD

OVERVIEW

Currently all advanced-stage epithelial ovarian cancers are treated with a total abdominal hysterectomy, bilateral oophorectomy, and complete tumor debulking surgery, followed by carboplatin and paclitaxel. This treatment recommendation is based on clinical trials that are mostly populated with women with high-grade serous carcinomas. Patients with mucinous or clear cell carcinomas of the ovary tend to present with earlier-stage disease, and may not require adjuvant chemotherapy; those with advanced-stage disease tend to have carboplatin-resistant disease. Patients with mucinous ovarian carcinoma have presentations and tumor biology that are similar to colorectal carcinomas and may benefit from colorectal regimens containing fluorouracil (FU) and oxaliplatin. Their tumors may also be KRAS wild-type or have HER2 amplification, and could benefit from drugs like cetuximab or trastuzumab. Patients with clear cell carcinoma of the ovary often harbor AIRD1a mutations, an early event in oncogenesis that is not a currently druggable target. Anecdotal cases and our biologic understanding of these malignancies suggest they might be preferentially sensitive to antiangiogenesis inhibitors. Focused international trials will be needed in both of these rare epithelial ovarian cancers to better define optimal treatment regimens.

The typical woman with ovarian cancer presents with advanced-stage serous carcinoma, and indeed the majority of biology, reagents (such as cell lines), and therapeutic recommendations are based on the results of trials heavily dominated by women with serous carcinoma of the ovary. In recent years, the clinical outcomes and more importantly underlying genetics of serous, clear cell, and mucinous cancers arising in or near the ovary has lead to an important shift in our understanding of the biology of what now appear to be completely separate malignancies, much like rectal cancer is different from bladder cancer. Although there is some overlap in clinical presentations and complications, therapeutic recommendations still do not differ despite the improved biologic understanding of these cancers.

Mucinous and clear cell tumors represent two epithelial tumors arising in or near the ovary. Unlike serous cancer of the ovary (sOC), both of these tumors are more commonly found confined to the ovary, and thus surveys of epithelial tumors confined to the ovary typically have a relatively high proportion of mucinous ovarian cancers (mOC) and clear cell tumors of the ovary (cOC).

MUCINOUS CANCER ARISING IN THE OVARY
Epidemiology and Risk Factors for mOC

Three percent of all epithelial ovarian cancers are mucinous, and a significant portion of these tumors present as local tumors within the ovary. Series of stage I epithelial tumors demonstrate that mOC represent approximately 30% of early-stage tumors and are usually cured by surgical resection. They have an improved 5-year disease-free survival of 90.8%, compared with sOC, 75.9%. Patients with mOC tend to have platinum-resistant disease, and when presenting with advanced-stage disease, these patients do not experience responses as positive as those experienced by patients with sOC. In a case-controlled study, 63% of mOC patients with stage III and IV disease had progression of disease while receiving treatment with single-agent carboplatin, single-agent paclitaxel, or platinum combination therapy, and an overall response rate of 26.3%, whereas patients with sOC had response rate of approximately 70%. Progression-free survival rates for mOC were lower compared with all epithelial ovarian cancer (eOC), 5.7 months and 14.1 months, respectively, whereas overall survival was 12 months and 36.7 months, respectively.

Risk factors for development of mOC may also differ from those for sOC. In contrast to patients with sOC, patients with mOC tend not have a family history of breast or ovarian cancer. BRCA1 and BRCA2 mutations are not associated with this histology. Risk factors for sOC such as low parity, no breastfeeding, and no use of oral contraceptives are not linked to mOC. A recent meta-analysis of epidemiologic studies has linked smoking history with mucinous cancer.
Family history, tubal sterilization, hysterectomy, age at menarche, and breastfeeding did not show significant correlation to development of mOC or borderline tumors.5

**Origin and Biology of mOC**
mOC is thought to arise from borderline or cystadenomas with alterations in ras/raf pathway as frequent early events in oncogenesis, specifically activating KRAS mutations.6,7
KRAS mutations are found in approximately 46% to 55% of cystadenoma precursors, 63% to 73% of borderline tumors, and 75% to 85% of invasive mOC. mOC likely forms in a stepwise fashion, with progression from a cystadenoma to a borderline tumor (usually found surrounding the invasive disease) to invasive tumor. One study has implicated the fimbriated fallopian tube as a possible site of origin of mOC, similar to recent studies in sOC.8 A subset of tumors harbors HER2 amplification, p53 mutations, and rare APC or CTNNB1 mutations. Some data suggests that these are distinct from the tumors with KRAS mutations and downstream mitogen-activated protein kinase (MAPK) pathway activation. Transcriptional profiling of mOC compared with other types of epithelial tumors arising in the ovary and various normal epithelium demonstrate that the RNA transcriptional pattern of mOC is distinct from other cancers arising in (or near) the ovary and more closely related to normal colonic epithelium compared with ovarian epithelium.7

**Presentation of mOC**
The pathologic and clinical presentation of mOC have substantial similarities to colorectal cancers (CRC) making discrimination between these malignancies challenging (Table 1).7 Most patients with mOC have measurable serum increases of carcinoembryonic antigen (CEA), like CRC, rather than cancer antigen (CA)-125, like sOC. Appendiceal cancer and CRC can mimic mOC with presentation of ascites, adnexal masses, or vaginal bleeding. A colonoscopy should be performed on all patients with suspected mOC to rule out a possible CRC. Seidman9 developed an algorithm to differentiate mOC from CRC. Ovarian tumors greater than 10 cm in size with unilateral ovarian involvement are more likely to be mOC than CRC.9 Immunohistochemical markers for mOC are more likely to be positive for CK 7, CK 20, and CEA, whereas for CRC only CK 20 and CEA are likely to be positive. Histologically, mOC are more likely to show a papillary pattern, expansile pattern of invasion. Metastatic disease from CRC shows a nodular growth pattern with an infiltrative pattern of invasion, and in some cases signet ring cells.

**Treatment of mOC**
When a mOC is expected or known, an appendectomy should be performed along with a careful evaluation of the GI tract to rule out a GI primary tumor with ovarian metastasis. In patients presenting with advanced-stage disease, the specific value of comprehensive surgical cytoreduction in women with mOC has not been specifically studied. However, in light of mOC’s relative resistance to chemotherapy, an argument can be made that such a procedure becomes more valuable.

Patients with localized tumors have a good prognosis and those with stage 1A disease can most likely undergo observation. Of note, these tumors are typically difficult to grade and often are admixed with premalignant tumors. For women with advanced-stage disease, controversy exists as to whether to offer to these women standard paclitaxel and carboplatin (as defined in trials largely predominated by women with sOC) or alternatively to provide offer regimens with efficacy in CRC, such as the current oxaliplatin-based regimes. Both irinotecan- and oxaliplatin-based regimes have been or are being explored in the treatment mOC. Most notably, the Gynecologic Oncology Group (GOG), in cooperation the Gynecologic Cancer Intergroup (GCIG), is currently conducting a clinical trial to compare carboplatin and paclitaxel ± bevacizumab with capetitabine and oxaliplatin ± bevacizumab to evaluate for progression-free survival and response rate in women with newly diagnosed mOC. In women with platinum sensitive disease defined as those with recurrence more than 6 months from primary platinum-based therapy, the response rate of mOC to re-treatment with platinum was 36% compared with 63% in women with other types of eOC.10 Hazard rates of death for women with advanced stage mOC compared with nonmucinous histologies was 2.15.7

Opportunities exist to explore the rational application of molecularly based therapeutic recommendations. Noting the use of EGFR inhibitors in the management of a subset of individuals with CRC, its use can be considered in patients with KRAS wild-type mOC, although this hypothesis has not yet been tested in a clinical trial. Although numerous studies evaluating EGFR inhibitors (both small molecule and antibodies) have been tested in eOC no studies have focused exclusively on this rare subset of patients. Likewise, HER2 is occasionally amplified in mOC. In a case cohort study of 33 cases of mOC, six patients had HER2 amplification and two
patients had significant responses to trastuzumab.\textsuperscript{11} Dual inhibition with trastuzumab and lapatinib has been reported in a case report of progressive mOC with several months of stable tumor burden.\textsuperscript{12}

Although there are few case reports of bevacizumab treatment of mOC, there are no studies to determine whether the activity of single-agent bevacizumab will be similar to the significant activity it demonstrates in sOC or, alternatively, the very modest single-agent activity seen in CRC.


clear cell carcinoma of the ovary

\textbf{Epidemiology and Risk Factors for cOC}

cOC is the second most common type of epithelial carcinoma arising in or near the ovary in North America. The collection of epithelial carcinomas arising in or near the ovary account for 90\% to 95\% of all malignant “ovarian tumors,” and approximately 5\% of these are cOC.\textsuperscript{2} Asian patients in the United States have a higher proportion of cOC than seen white, black/African American, or other populations (11.4\% vs. 4.8\%, 3.1\% and 5.5\%, respectively).\textsuperscript{13} The prevalence of cOC is higher in Asia—more than 15\% in Japan.\textsuperscript{14}

Patients with cOC present at an earlier age than patients with high-grade serous carcinomas, and can present with thromboembolic disease more commonly as well.\textsuperscript{14} In a Japanese group of women, 48.5\% of patients with cOC presented with stage I disease compared with 16.6\% of patients with sOC.

There are several risk factors for cOC. Women with cOC tend to be younger, have a higher body mass index, and have a history of endometriosis. Interestingly a history of smoking, a likely risk factor for mOC, may be slightly protective for cOC. On occasion, these tumors can be found arising in endometriomas, endometriotic cysts, or in extraovarian sites. Transcriptional profiling experiments of cOC demonstrate significant similarity to the RNA profile of normal endometrium, suggesting that these “ovarian” malignancies might actually represent malignancies from ectopic endometrium implanted in extrauterine sites via retrograde menstruation.\textsuperscript{15}

\textbf{Origin and Biology of cOC}

Recently, several groups have described that 50\% of cOC and, in certain cases, sites of endometriosis have mutations in adenine-thymine rich interactive domain 1A (\textit{ARID1A}), a tumor suppressor now thought to serve as an early mutational event in oncogenesis in these malignancies.\textsuperscript{16} \textit{ARID1A} is responsible for directing the SWI/SNF multiprotein complex to target sites on promoters serving as an epigenetic modulator of transcriptions.\textsuperscript{17} \textit{ARID1A} is part of the BAF250 protein complex, and cOC with mutations in \textit{ARID1A} correlated with decreased BAF250a expression by immunohistochemistry. Presumably, \textit{ARID1A} alterations influence the epigenetic regulation of genes directly associated with cOC oncogenesis. Interestingly, \textit{ARID1A} is often lost in von Hippel Lindau (\textit{VHL}) -mutated clear cell cancers of the kidney.

Additional genomic abnormalities have also been described.\textsuperscript{18} For example, 20\% of patients may also have a deletion of \textit{PTEN}, a tumor-suppressing gene from the \textit{PIK3CA} pathway, or \textit{KRAS} activation, which has also been shown to induce endometriosis associated with clear cell carcinomas. p53 mutations, ubiquitous in sOC, are not seen in cOC. In addition, the malignancy seems to have more genomic stability as compared with sOC.

\textbf{Treatment of cOC}

Because of the increased incidence of cOC in Japan, much of the surgical data come from retrospective studies of performed from that region. Although no prospective randomized surgical studies exist, retrospective studies suggest that lymphadenectomy adds little in early-stage cOC and that surgical debulking surgery is important in the management of advanced disease. Specifically, a Japanese retrospective analysis from a multicenter study of 254 patients with complete surgical staging demonstrated that the results of surgical debulking were prognostic for improved progression-free survival (PFS), with median PFS of 39, 7, and 5 months when there was no residual tumor, less than 1 cm of residual tumor, or greater than 1 cm of residual tumor postsurgery,\textsuperscript{19} respectively.

Currently, treatment recommendations for patients with cOC are similar to those for patients with sOC: platinum-based therapy, and specifically carboplatin and paclitaxel. Response rates to carboplatin and paclitaxel therapy range from 22\% to 56\% in trials, compared with 70\% in high-grade serous carcinoma.\textsuperscript{19} However, because of its low representation in the trials, the influence of platinum-based therapy on survival is not fully known. In a meta-analysis of 8,000 women from seven international trials of platinum-based front-line therapy, only 2.5\% of women had stage III/IV cOC.

\begin{table}
\centering
\caption{Comparison of Mucinous Tumors Arising in the Colon versus the Ovary}
\begin{tabular}{|c|c|c|}
\hline
\textbf{Characteristic} & \textbf{Colon} & \textbf{Ovary} \\
\hline
\textbf{Presentation} & Ascites, adnexal masses, vaginal bleeding & Ascites, adnexal masses, vaginal bleeding \\
\hline
\textbf{Size} & Bilateral, < 10 cm & Unilateral, >10 cm \\
\hline
\textbf{Immunohistochemistry} & CK 20, CEA & CK 7, CK 20, CEA \\
\hline
\textbf{p53 mutation} & 70\% & 25\% \\
\hline
\textbf{Histology} & Nodular growth pattern with an infiltrative pattern & Papillary pattern, expansile pattern of invasion \\
\hline
\end{tabular}
\end{table}

\textit{Abbreviation: CEA, carcinoembryonic antigen.}
and their risk of death was increased (hazard ratio = 2.18). Overall survival was 21.3 months compared with 40.8 months for patients with sOC. The Japanese GOG has conducted a trial comparing irinotecan and cisplatin versus carboplatin and paclitaxel in 99 patients with cOC as initial therapy, with no significant difference in PFS.

The future treatment of cOC will likely involve targeted therapies. Unfortunately, the ARID1A tumor-suppressor gene is not druggable or easily replaced with current technologies. However, several pathways have been shown to be overexpressed or activated in cOC. The IL6-STAT3-HIF pathway was found to be activated in cOC. Hypoxia-inducible factor (HIF) is an important transcription factor involved in angiogenesis and controls vascular endothelial growth factor (VEGF)-A expression. Staining of HIF1A was higher in cOC than in sOC (p = 0.0001). A variety of VEGF inhibitors have been explored in this setting. Sunitinib, a tyrosine kinase inhibitor of VEGF, platelet-derived growth factor receptor (PDGFR), and KIT was shown to decrease tumor burden in two patients in one study. In addition, a particularly durable partial response was reported in a patient with cOC treated with the antiangiogenic agent methoxyestradiol. Although the PI-3k/AKT/mTOR pathway is known to be activated in cOC, there still is no evidence that targeting this pathway is efficacious with currently available agents. Trials incorporating temsirolimus, a mammalian target of rapamycin (mTOR) inhibitor, was inactive as a single agent and was too toxic in combination with bevacizumab/liposomal doxorubicin and topotecan. Direct inhibitors of phosphoinositide 3-kinase (PI-3k) are in development and worthy of exploration.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

References


Revisiting the Role of Radiation Treatment for Non-serous Subtypes of Epithelial Ovarian Cancer

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OVERVIEW

Except for its palliative use, radiation has been largely abandoned in the management of ovarian cancers because of the recognized efficacy of chemotherapy agents. Whole abdominal irradiation (WAR), however, has been shown to be of adjuvant and curative value in ovarian cancer with microscopic or minimal residual disease in the pelvis, the so-called “intermediate risk group.” Recent hypothesis generating data from the use of adjuvant radiation following adjuvant chemotherapy in ovarian cancer has shown an incremental survival benefit for the rarer non-serous ovarian subtypes including clear cell, endometrioid, and mucinous. No incremental benefit was observed for the more common serous subtype. A retrospective examination of early trials using WAR as the sole postoperative treatment in ovarian cancer has determined that the majority of patients in these studies and cured by radiation actually had the non-serous subtypes. The recognition that the non-serous subtypes differ from the serous cancers in their stage of presentation, their molecular characteristics, their response to classic chemotherapy, and their outcomes suggest the non-serous subtypes should be treated as rare and different cancers. In addition to specific targeting therapies that may be developed, radiation should be reconsidered as part of the treatment armamentarium for these diseases.

Until about a decade ago, subtypes of ovarian carcinomas were recognized by using subjective criteria by pathologists using histomorphology. Although some types such as endometrioid, clear cell, mucinous, and low-grade serous carcinomas were recognized, because of their rarity (constituting less than 10% of ovarian cancers) and their apparently common origin in the surface epithelium of the ovary, these tumor subtypes were lumped together and treated similarly with the most common high-grade serous cancers. There was no clear recognition that they differed from the dominant serous subtype by virtue of their stage, extent at presentation, their response to conventional chemotherapy (now mainly carboplatin and paclitaxel) or by their differences in outcomes.

It is now recognized that the genetic and molecular abnormalities characterizing these morphologically different subtypes differ significantly from subtype to subtype. The implications of these differences are multiple in this era in which differing molecular signatures and driving pathways lead not only to opportunities for the investigation of treatment both with specifically and uniquely directed molecular targeting agents against rare subtypes. These differences also necessitate revisiting the role of the “old modality” of radiation therapy. Relatively new data has emerged supporting its differential effect on the rarer tumor subtypes.

Radiation therapy was used quite extensively for the curative and adjuvant management of low stage and low residual volume ovarian carcinoma of all tumor subtypes. This treatment was largely abandoned in the 1980s when it was recognized that cisplatin was an highly active systemic agent in ovarian cancer compared with previous alkylating agents, that radiation could have an effect on bone marrow reserve possibly precluding maximal chemotherapy utilization, and that the pharmaceutical market to some degree was driving the uptake of systemic therapy. These issues, despite the demonstrated efficacy of radiation, lead to the almost total demise of radiotherapy in the treatment armamentarium for ovarian cancers, except for its continued but uncommon use in the palliative setting. Other factors contributing to its dismissal included the recognition that wide-field irradiation in tolerable doses was largely ineffective in eradicating bulky residual disease in the peritoneal cavity. The dose of radiation required to do so could not be delivered safely without excessive toxicity to normal tissues particularly the small bowel (although higher doses could be delivered safely to pelvic residual disease).

However, multiple reasons exist now to reexamine the role of radiation treatment, particularly in the rare morphologic subtypes of clear cell, endometrioid, and mucinous cancers and those that very frequently present with pelvic confined disease (Table 1), which, when advanced, have low response
rates to conventional chemotherapies.\textsuperscript{3,12} This is in contrast to serous cancers that commonly present with advanced extensive and bulky peritoneal spread. This educational session will re-examine the patterns of disease presentation for these morphologic subtypes, and review the evidence to suggest that radiation—both pelvic confined and wider field—in low doses may potentially cure patients when used as the sole postoperative treatment and may be of incremental adjuvant value following conventional chemotherapies.

With respect to the utilization of radiation therapy in ovarian cancers, have we thrown the baby out with the bath water? Possible myths to consider include (1) all ovarian cancers have the same radio responsiveness (radio resistance), (2) radiation is intolerable in the doses necessary to sterilize disease (even microscopic), (3) radiation is too toxic to bowel and compromises delivery of systemic therapies, (4) radiation cannot be given after chemotherapy, (5) all histologies have the same propensity for peritoneal spread thus necessitating wide-field irradiation, and (6) the utility of radiation only depends on the grade and residuum of tumor, not the cell type.

There is definite evidence that radiation is active in ovarian cancers. Multiple publications have endorsed the incremental curative value of postoperative adjuvant WAR radiation alone in a subset of patients with ovarian cancers.\textsuperscript{8,9} The groups that constitute those cured with radiation include those at “intermediate risk.”\textsuperscript{9} These patients included those with stage I, II, and stage III disease grades 1, 2, and 3 and no residual disease post-surgery. The studies also included those with stage II and stage III disease with residuum less than 2 cm in diameter and confined to the pelvis to which a higher dose of radiation was given. At the time, patients were not selected or distinguished by their ovarian cancer morphologic subtype. In this era, aggressive ovarian and debunking or staging was not attempted so that a significant proportion of these stage II patients presumably with careful surgical staging would now be considered to have microscopic stage II (no obvious clinical residuum). One-hundred forty-seven patients were randomly assigned to pelvic irradiation plus or minus chlorambucil compared with WAR. After a 7-year follow-up, survival with WAR was 46% compared with 31% for the other study arms. Benefit was only seen in those with 2 cm or less macroscopic residual disease.\textsuperscript{12} A further study conducted between 1981 and 1990 with a median follow-up of 6.8 years and range from 1.5 to 10.0 years described a cohort of a 125 patients randomly assigned to two doses of abdominal pelvic irradiation in early ovarian cancer.\textsuperscript{14} Patients were randomly assigned between an abdominal dose of 2,250 cGy in 22 fractions (low dose) compared with 2,750 cGy in 27 fractions (high dose) with a standard pelvic boost of 2,250 cGy in 10 fractions. Patients were similar in median age group, approximately 53 and 55; the low-dose group had a cohort of 67 patients, the high-dose group 58. Their groups were comparably divided between stage I, II, and III: 43% stage I, 71% stage II, and 11% stage III. Although the cohorts were small, disease-free survival in the low-dose group was 76% and in the high-dose group 67%, which was not significantly different statistically. The 5-year overall survival was 83% in the low-dose group and 72% in the high-dose group (not significantly different). Eleven percent of patients recurred with a component in the abdomen and 12% in the pelvis alone.\textsuperscript{14} Although the patients did not have extensive attempts to achieve optimal surgical reduction of disease and repeated operations were not usually performed, the incidence of grade 3 late complications of bowel, liver, or bladder was only 5%. This study demonstrated that overall survivals and disease-free survivals were high. Between 1971 and 1985, 598 patients received WAR. Acute complications of nausea, vomiting, and diarrhea occurred in approximately 60% but only 4% had serious late bowel complications.\textsuperscript{15} Unfortunately, attempts to do randomized studies comparing WAR with cisplatin-based chemotherapies were largely unsuccessful.

A recent conference on clear cell carcinomas stimulated re-review of the cell types in patients included in the 2-dose study specifically seeking to examine whether there was evidence

| TABLE 1. Differences in Age, Race, and Stage Distribution at Presentation for Clear Cell and Serous Ovarian Cancers (SEER Data)\textsuperscript{12} |
|------------------|-----------------|-----------------|-----------------|-----------------|
| Age at Dx: Median (Range) | Clear Cell Carcinoma \( (n = 1,411) \) | Serous Carcinoma \( (n = 13,835) \) |
| Race: White/Asian | 82.5%/11.7% | 88.3%/4.4% |
| Stage: | | |
| I | 56.3% | 12% |
| IA | 34.3% | 5.9% |
| IB | 1.5% | 1.3% |
| IC | 18.6% | 4.2% |
| II | 11% | 7.2% |
| III/IV | 32.7% | 80.9% |

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**KEY POINTS**

- Histomorphologic and molecular characteristics differ markedly between subtypes of ovarian cancer.
- The nonserous subtypes—clear cell, endometrioid, and mucinous—present in early-stage rather than serous cancers and are relatively chemotherapy-resistant.
- There is evidence for a curative benefit for whole abdominal radiation as sole postoperative therapy in early-stage ovarian cancer, most of which were non-serous subtypes.
- Radiation and chemotherapy do not appear to have cross-resistance as demonstrated in studies of palliative irradiation after chemotherapy failure.
- An incremental survival benefit (43% in reduction in risk of death) appears attributable to radiation after chemotherapy in stage IC and II nonserous histologies (but no benefit in serous).
that the excellent outcomes were related to the histologic subtypes that were included.\textsuperscript{15} Although 80\% to 90\% of ovarian cancers are of the serous subtype, a study in intermediate risk ovarian cancer surprisingly showed only 29\% serous cancers. The majority were endometrioid at (59\%) mucinous (13\%) and clear cell (21\%). The implication of this distribution is that it is the non-serous histologies that dominate the low-stage ovarian cancers whose outcome is extremely favorable when treated with radiation therapy.

To focus specifically on clear cell carcinoma of ovarian cancer, a recent publication examined the stage distribution for various subtypes of ovarian cancer.\textsuperscript{5} The total cohort of patients was 1,009 of which 383 had stage I/II disease and 616 had stage III/IV (Table 2). Of the total cohort for high-grade serous type, 88\% were stage III/IV compared with only 36 in stage I/II. For clear cell cancer, 26\% were stage I and II compared with 5\% stage III/IV. For endometrioid, 27\% were stage I/II with only 3\% stage III/IV, and for mucinous type 8\% were stage I/II and 1\% stage III/IV. The implication of these data are that in the total cohort of 1,009 patients, 90\% of clear cell cancers are confined to the pelvis at presentation, similarly 90\% of endometrioid cancers are confined to the pelvis (often associated incidentally with endometriosis) and similarly 90\% of mucinous are confined to the pelvis. Postsurgical therapies (possibly by using pelvic irradiation alone) may be of a both adjuvant curative value. It could be postulated that for pelvic-confined disease in the non-serous subtypes, adjuvant radiation alone (perhaps even pelvic treatment only) or in combination with other potential molecular targeting therapies should be investigated for non-serous ovarian cancers.

Further data has been published examining a population-based outcome in British Columbia, Canada, that suggests WAR provides a survival benefit when added to chemotherapy particularly in low-stage ovarian clear cell carcinoma.\textsuperscript{7} This study retrospectively examined the outcomes for 241 patients with stage I or II clear cell ovarian cancer. Surgery consisted in more than 90\% of abdominal hysterectomy bilateral salpingo oophorectomy omentectomy washings and removal of suspicion nodes. Routine lymphadenectomy was not mandated. Patients were treated with three cycles of carboplatin and paclitaxel for 3 to 4 weeks. By a physician choice, 211 were treated with chemotherapy alone whereas 103 had the addition of pelvic and whole abdominal radiation in a dose of 22.5 Gy to the pelvis in 10 fractions, followed by 22.5 Gy in 22 fractions to the whole abdomen. Although the groups were not randomly assigned, the distribution of stage of disease was comparable between those with and without additional radiation. Overall, 5- and 10-year disease-free survival rates were 84\% and 70\% for stage IA/B, 67\% and 57\% for stage IC, and 49\% and 44\% for stage II, respectively. Cytologic status in patients with stage IC disease was important. The 5-year disease-free survival was 86\% when negative compared with 62\% when positive or unknown. When radiation was added to chemotherapy, there was no apparent incremental benefit for stage IA and IC with rupture only, although there was a 20\% difference that was not statistically significant. However, for the patients with stage IC disease with cystic or surface involvement, the disease-free survival when radiation was used was statistically improved with an absolute increase with radiation of 20\% at 5 years. This constituted a relative reduction in risk of recurrence of 49\% with the addition of irradiation for those with cystologic or surface positivity or in which this was unknown. The hypothesis generated from this retrospective series was that irradiation contributed to improved disease-free survival by reducing pelvic relapse rates from 76\% to 62\%. Abdominal recurrence occurred in 42\% with chemotherapy and only 13\% with whole abdominal and pelvic irradiation with 5-year disease-free survival being 25\% with chemotherapy and 81\% with irradiation. It would appear patients with stage IA and IC disease with rupture only do not have benefit from additional radiation but it may be beneficial for those with stage IC cystology or surface positivity (or unknown) and stage II. Of note is that even without sophisticated radiation techniques grade 3 and 4 late-radiation toxicities were extremely rare; grade 3 in 3\% and grade 4 in 1\% of patients, respectively. Another report in the literature suggests that irradiation may be a more effective strategy than chemotherapy, although the cohort was small (28 patients).\textsuperscript{16}

An examination of the use of radiotherapy after surgery was conducted in a population-based retrospective review of all women with ovarian cancer with no macroscopic residual following primary surgery.\textsuperscript{6} Two pathologists at the BC Cancer Agency reviewed tissues and assigned the histotype according to contemporary criteria, clear cell, endometrioid, mucinous, and other. All patients were given platin-based chemotherapy and by physician choice received adjuvant irradiation or not. Of the 703 identified patients, 351 received adjuvant irradiation. Ninety percent (305) were able to complete the planned irradiation. In analysis, the most important prognostic factor was stage III rather than stage I or II, but for those with stage I and II, the histotype was most important prognostic factor. For those with clear cell, endometrioid, and mucinous cancers, there was a 40\% reduction in disease specific mortality and 43\% in overall mortality, whereas those with serous or other cancers did not benefit from the adjuvant irradiation.

Modern techniques of radiation delivery—be it in the pelvis or in the abdomen—have become technically sophisticated.

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### TABLE 2. Eleven Percent of Early-Stage Ovarian Cancers Are Nonserous; 88% of Late-Stage Are Serous\textsuperscript{5}: 1,009/2,555 Ova Slides were Reviewed

<table>
<thead>
<tr>
<th>Cell Type/Gd</th>
<th>Stage I/II</th>
<th>Stage III/IV</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n)</td>
<td>383</td>
<td>616</td>
<td>1,009</td>
</tr>
<tr>
<td>High-Grade Serous</td>
<td>36%</td>
<td>88%</td>
<td>68%</td>
</tr>
<tr>
<td>Clear Cell</td>
<td>26%</td>
<td>5%</td>
<td>12%</td>
</tr>
<tr>
<td>Endometrioid</td>
<td>27%</td>
<td>3%</td>
<td>11%</td>
</tr>
<tr>
<td>Mucinous</td>
<td>8%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Low-Grade Serous</td>
<td>-</td>
<td>-</td>
<td>3%</td>
</tr>
</tbody>
</table>

Abbreviations: Gd, grade.
with the advent of conformal, normal tissue-sparing techniques, such as intensity-modulated radiation therapy, arc, or tomotherapy. These may (minimize any late toxicity) spare important structures such as the bowel and bone marrow. Conformal techniques of radiation boosts when used may contribute to reducing recurrent sites within radiation fields by allowing dose escalations to smaller volumes. The good survival data from the multiple trials by using wide-field irradiation in ovarian cancer in retrospect would appear to be attributable to the fact that non-serous histology constitutes most of the patients. They have a dominant pattern of pelvic confined disease with less likely risks of peritoneal disease and failure compared with serous cancers. There is ample evidence from the use of palliative irradiation for recurrent ovarian cancer that radiation in various doses results in response rates of up to 85% in patients who have received multiple lines of platinum and taxane containing prior chemotherapy. The utility of radiation in this setting including mostly those with serous cancers suggests that there is non-cross resistance between serous cancers and prior standard chemotherapy regimens. These data will be presented and provide the rationale for the assumption that incremental survival benefits in small volume non-serous cancers are attributable to the addition of radiation to chemotherapy. The role, however, that chemotherapy plays is unclear.

In conclusion, there is strong evidence to suggest that radiation treatment may be effective in the management of early-stage non-serous cancers and strong consideration should be given to its exploration in future trials focused on subtypes of ovarian cancer identified by both their histotype and molecular features. The identification of specific targeting agents, which may alter the radio responsiveness of these tumors, should be considered for incorporation into such trials. It is time to revisit the use of radiation, both pelvic and WAR, in non-serous ovarian cancers.

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References

GYNECOLOGIC CANCER

Ovarian Germ Cell Tumors in Young and Slightly Older Patients

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Updates in the Management of Ovarian Germ Cell Tumors

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OVERVIEW

Ovarian germ cell tumors are rare events at all ages—in pediatrics, adolescence, and during young adulthood. Combining the knowledge and experience of pediatric and gynecologic oncologists can lead to better outcomes for all. In this review, we intend to present the latest consensus on management of women and children with this disease and highlight the opportunities for collaboration and clinical research going forward.

Over the past three decades, the clinical outcomes of women with ovarian germ cell tumors (OGCT) have significantly improved, paralleling developments made in treatment for testicular cancer. Subsequently, the majority of women with OGCT survives the disease and suffers minimal morbidity from treatment. The main factor accounting for this success was the development of more effective chemotherapy regimens. Other advancements in the field include the development of a more precise surgical staging system, improved radiographic imaging, more sophisticated pathology assays, advancements in reproductive technology, and improved supportive care and symptom control that ensure safe delivery of treatment. Fertility-sparing surgical procedures enable young women with OGCT to preserve their reproductive potential. Ultimately, the positive clinical outcomes reflect the collaboration between different specialties (surgery, medical oncology, pathology, radiology). Given the observed improved survival with therapy, new directions of investigation target tailoring therapy, such that untoward adverse effects can be avoided and that survivors would lead healthy lives, devoid of long-term, treatment-related toxicities.

EPIDEMIOLOGY

OGCTs are rare tumors, accounting for 2% to 3% of all ovarian cancers and develop usually in young women. The median age for diagnosis is 16 to 20 (range 6 to 40 years). Ethnic and racial differences have been noted in an analysis extracted from the Surveillance, Epidemiology, and End Results (SEER) database, with increased incidence of OGCTs among pediatric black females compared with black males and among Hispanic girls age 10-19 compared with non-Hispanic girls. Interestingly, a case-cohort study from the Children’s Oncology Group that included 274 cases (195 OGCT and 79 testicular cancers) showed an inverse association between family history of ovarian or uterine cancers and GCT in girls (OR = 0.46, 95% CI 0.22-0.96).

PATHOLOGY

The current World Health Organization (WHO) classification of OGCTs includes benign tumors—almost all of which are dermoid cysts and their malignant derivatives—and primitive malignant germ cell tumors, which recapitulate normal embryonic and extra-embryonic cells and structures. The malignant OGCTs are classified as dysgerminoma, yolk sac tumor, embryonal carcinoma, polyembryoma, nongestational choriocarcinoma, mixed germ cell tumors, and teratomas (immature, mature, and monodermal types). Dysgerminoma is the female equivalent of seminoma and represents the most common OGCT. Five to 10% are associated with gonadoblastomas and develop in patients who are sexually mal-developed. Dysgerminoma is the most common OGCT in young adult women whereas yolk sac tumor is the most common histology in younger pediatric and adolescent women.

CLINICAL CHARACTERISTICS

Accurate diagnosis, evaluation, and treatment are essential for the cure of women diagnosed with OGCTs. Principles of diagnosis and treatment apply across all types of OGCTs, and except for few distinct characteristics, OGCTs have similar clinical presentation. Abdominal pain associated with a palpable pelvic-abdominal mass is the presenting symptom in approximately 85% of patients. Ten percent of patients present with acute abdominal pain caused by rupture, hemorrhage, or torsion of tumors and frequently mis-diagnosed as acute appendicitis. Less commonly, patients present with abdominal distention (35%), fever (10%), or vaginal bleeding.
(10%). Isosexual precocity can be caused by ectopic beta-human chorionic gonadotropin (HCG) production by tumor cells. Germ cell tumors secrete biologic markers (β-HCG and α-fetoprotein [AFP]) that are quantifiable in serum and serve as a tool for monitoring treatment results and for detection of subclinical recurrences. An endodermal sinus tumor to Yolk sac tumor secretes AFP, while choriocarcinoma produces β-HCG. Embryonal carcinoma can secrete both β-HCG and AFP but most commonly β-HCG. Although immature teratomas are associated with negative markers, a few tumors can produce AFP. Characteristically, dysgerminoma does not secrete β-HCG or AFP and detection of either marker should prompt pathologic reexamination to exclude the presence of nondysgerminomatous elements. Mixed tumors may produce either, both, or none of the markers, depending on their components. Lactic dehydrogenase (LDH) and CA125 levels can be elevated, however, they are nonspecific.7

**SURGICAL MANAGEMENT AND FERTILITY PRESERVATION**

Surgery is the initial step to obtain definitive diagnosis and provide initial treatment of patients with malignant OGCTs. Since these tumors most often present in patients of reproductive age, there must be an emphasis on fertility preservation. Fertility-sparing surgery appears to be safe and has demonstrated excellent survival after long-term follow-up. Multiple reports have demonstrated outcomes equivalent to patients undergoing hysterectomy with bilateral salpingo-oophorectomy.8,9 Since approximately 60% of these tumors are limited to one ovary at the time of surgery, unilateral salpingo-oophorectomy is recommended in females who desire future fertility. If both ovaries are involved—as occurs in 10% to 15% of dysgerminomas—bilateral salpingooophorectomy may be indicated, but every effort should be made to preserve fertility.10 The uterus can almost always be preserved, as it is not typically involved. Therefore, assisted reproduction with donor egg may be possible in the future for those patients requiring bilateral ovarian removal. Rarely, widespread uterine serosal involvement is found, necessitating hysterectomy. It is important to note that conservative surgery for fertility preservation does not imply ovarian cystectomy but rather a unilateral salpingooophorectomy with conservation of the normal appearing contralateral ovary, tube, and uterus. When an ovarian cystectomy has been performed for presumed benign ovarian disease and the postoperative diagnosis of immature teratoma is rendered, there may be little utility in excising the remaining ovarian tissue, as excellent survival has been reported.11 However, in this report, most of those patients received adjuvant chemotherapy. In patients who have completed childbearing, a hysterectomy and bilateral salpingooophorectomy is warranted.

The necessity and extent of comprehensive surgical staging is controversial. The recommendation has generally been for comprehensive staging to include peritoneal cytology, peritoneal biopsies, omentectomy, and retroperitoneal lymphadenectomy including bilateral pelvic and para-aortic nodes and removal of any suspicious tissue, with tumor reductive surgery to be performed in the event of disseminated disease. The benefits of lymphadenectomy were detailed in a SEER database review, which showed that 18% of patients with malignant OGCTs and 28% of patients with dysgerminomas had lymph node involvement. Lymph node positivity was a negative predictor of survival in this study, although other studies refute this association.12,13 One of the benefits of lymphadenectomy is to avoid chemotherapy for patients with negative nodes. A recent review in which one-half of patients underwent comprehensive staging showed that none of the stage IA patients recurred during observation without adjuvant chemotherapy, while approximately 40% of patients who were unstaged but apparent stage I did recur.14 However, germ cell tumors are extremely chemosensitive, therefore most untreated patients who recur can be salvaged with chemotherapy with excellent survival regardless of the extent of initial surgical staging.15 This has been used as evidence to recommend avoiding comprehensive surgical staging with lymphadenectomy and re-operation solely for the purpose of comprehensive staging when the diagnosis is made postoperatively. In addition, based on the known chemosensitivity of OGCTs, extensive tumor reductive surgery may be limited to avoid increased morbidity or a long postoperative recovery with a subsequent delay in chemotherapy.15

Surveillance visits following active treatment should consist of history, physical and pelvic examination, imaging, and relevant tumor markers quarterly for the first 2 years and biennially for 3 additional years.16 Most patients with OGCTs are cured, but when they recur, most do so within 1 year after diagnosis; recurrences are extremely rare after 2 years.17-20 Elevated tumor markers are sensitive for recurrent disease and should prompt immediate evaluation with imaging. It is essential that a biopsy or resection confirms the diagnosis of recurrent disease, as immature teratomas can recur with mature benign elements only or with benign gliosis, neither of which represent recurrence of malignant disease and do not
require chemotherapy. Surgical resection may yield some success and is a consideration in patients with immature teratoma.

**CHEMOTHERAPY**

The lessons learned from prospective, randomized trials in testis cancer have been applied to OGCTs leading to significant improvement in outcomes over the past decades. At present, cisplatin-based combination chemotherapy leads to cure for most women with OGCT. Historically, the first regimen used successfully in this setting was vincristine, dactinomycin, and cyclophosphamide (VAC). Although VAC therapy induced cures in early-stage disease, long-term survival of women with advanced tumors remained less than 50%. In a series from the University of Texas MD Anderson Cancer Center (MDACC), 86% of patients with stage I tumors were cured with VAC, but only 57% of patients with stage II and 50% of patients with stage III achieved long-term control and two patients with stage IV tumors succumbed to disease. In a similar Gynecologic Oncology Group (GOG) study evaluating VAC, 39 of 54 patients with complete surgical resection and 7 of 22 patients with incompletely resected tumors achieved long-term disease control. However, 13 of 15 patients with stage III and IV disease recurred within 12 months, suggesting that VAC was insufficient for advanced-stage and/or incompletely resected OGCTs.

As cisplatin-based regimens entered the clinical arena for testicular cancer, they were also investigated in women with OGCTs. First, the GOG evaluated vinblastin, bleomycin, and cisplatin (PVB) in patients with previously treated and untreated OGCTs. Importantly, one-third of patients enrolled in this trial had received prior radiation or chemotherapy. Four-year overall survival (OS) was 70% and 47 of 89 (53%) patients were disease free at 52 months. Subsequent experience in testicular cancer documented that etoposide was at best equivalent to vinblastine, dacarbazine, and cyclophosphamide (VAC). Although VAC therapy induced cures in early-stage disease, long-term survival of women with advanced tumors remained less than 50%. In a series from the University of Texas MD Anderson Cancer Center (MDACC), 86% of patients with stage I tumors were cured with VAC, but only 57% of patients with stage II and 50% of patients with stage III achieved long-term control and two patients with stage IV tumors succumbed to disease. In a similar Gynecologic Oncology Group (GOG) study evaluating VAC, 39 of 54 patients with complete surgical resection and 7 of 22 patients with incompletely resected tumors achieved long-term disease control. However, 13 of 15 patients with stage III and IV disease recurred within 12 months, suggesting that VAC was insufficient for advanced-stage and/or incompletely resected OGCTs.

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Patients with testicular cancer are stratified in good, intermediate, or high risk for recurrence based on clinical, pathologic, and serologic markers. Compared with testes cancer, clinical prognosticators are less well defined for OGCTs. Adverse factors include age older than 45, stage greater than I, incomplete surgical resection, and yolk sac tumor histology. Dose intensification has been studied in a randomized fashion for poor prognosis germ cell tumors but has not resulted in improved outcomes, as compared with standard dose BEP and is not recommended for OGCTs. At present time, the current treatment standard consists of three to four cycles of BEP chemotherapy. There is presumptive evidence in testis cancer that the timeliness of chemotherapy is associated with outcome. Thus, treatment should be administered on schedule, regardless of hematologic parameters.

Dysgerminoma represents a distinct category, given its exquisite radio- and chemosensitivity. As many as two-thirds of patients with dysgerminoma present with stage I at diagnosis. In the past, most women with dysgerminoma received postoperative radiotherapy. Given the risks of secondary malignancies, gonadal dysfunction, and sterility associated with pelvic radiotherapy, an alternative option for patients at low risk is postsurgical clinical surveillance. With this approach, 80% to 85% of patients with stage IA dysgerminoma are cured, but careful follow-up is required to ensure early detection of recurrences in those 15 to 25% of patients whose disease will recur. With this approach, 80% to 85% of patients with stage IA dysgerminoma are cured, but careful follow-up is required to ensure early detection of recurrences in those 15 to 25% of patients whose disease will recur. Given dysgerminoma’s exquisite chemosensitivity, virtually all patients can be salvaged at the time of recurrence, if early detection has been accomplished. An analysis that was focused on patients with dysgerminoma treated on GOG protocols revealed that 19 of 20 patients with stage III or IV incompletely resected tumors were disease free after BEP treatment. Another GOG study showed that carboplatin/etoposide is an alternative, less toxic regimen for dysgerminoma. These data support that nearly all patients with advanced dysgerminoma treated with chemotherapy are durable complete responders.

The large majority of patients with OGCTs are cured with surgery followed by chemotherapy. However, a small percentage of patients have persistent or progressive disease during treatment or recur after treatment. Most recurrences occur within 24 months from primary treatment. Like in testis cancer, treatment failures are categorized as platinum resistant (progression during or within 4 – 6 weeks) or platinum sensitive (recurrence beyond 6 weeks of initial therapy). Given the high curability rate of OGCTs with primary treatment, the management of recurrent disease represents a complex and often difficult issue and should be performed in a specialized center. Data to guide the management of patients with recurrent OGCTs are scant and by and large extrapolated from the treatment of testis cancer. Approximately 30% of patients with recurrent platinum-sensitive testis cancer can be salvaged with second-line chemotherapy (vinblastine, ifosfamide, and platinum [VeIP]), and this concept is translatable to OGCTs.

For patients with recurrent or persistent testicular cancer, high-dose therapy with carboplatin, etoposide with or without cyclophosphamide or ifosfamide, and stem cell rescue is superior to standard-dose salvage therapy. Although this approach has not been, and most probably will never be, tested prospectively in women with recurrent OGCTs because of the small numbers of patients, the concepts are very similar and support the
use of high-dose therapy in this setting. The single most important prognostic factor for patients with testis cancer is whether or not they are refractory to cisplatin. In patients who are truly cisplatin refractory, the likelihood of long-term survival and cure following high-dose therapy is low— and high-dose therapy is of debatable appropriateness. On the other hand, the likelihood of cure with high-dose salvage therapy in patients with platinum-sensitive disease is 50%. In general, one course of standard-dose therapy— usually cisplatin, vinblastine, and ifosfamide—is given. If an initial response is seen, then patients undergo the second course of high-dose chemotherapy (carboplatin and etoposide) with stem cell rescue. Referral to a specialized center for management of recurrent disease is desirable. Patients with platinum-refractory disease cannot be cured. Active agents in this setting include ifosfamide, taxanes, and gemcitabine, and referral for treatment with investigational agents is appropriate.

**LATE EFFECTS OF THERAPY**

Given that the majority of women with OGCTs are cured, persistence of long-term effects of treatment is highly significant. One of the most ominous late effects of chemotherapy, particularly for young survivors, is the risk for secondary malignancies. Etoposide, the backbone of the BEP regimen, is associated with development of acute myelogenous leukemia (AML) with a characteristic chromosomal translocation at the 11q23 locus. Etoposide-induced AML occurs within 2 to 3 years of exposure and is dose and schedule dependent. In GOG protocol 78 testing BEP, there was one case of AML among 91 patients. An additional case of lymphoma was diagnosed among survivors treated on that study, but relationship to treatment remained uncertain, as a correlation between chemotherapy and lymphoproliferative disorders is not established.

Chemotherapy also has long-term effects on gonadal function and leads to sterility. Older age at initiation of therapy, greater cumulative drug dose, and longer duration of therapy favor premature ovarian dysfunction. However, successful pregnancies after combination chemotherapy have been documented in patients with malignant OGCTs. In an MDACC review, 27 (68%) of 40 patients who had retained a normal contralateral ovary and uterus maintained regular menses consistently after completion of therapy favor premature ovarian dysfunction. However, successful pregnancies after combination chemotherapy have been documented in patients with malignant OGCTs. In a series from Milan, 138 of 196 patients underwent fertility-sparing surgery, and of those, 81 underwent adjuvant chemotherapy. After treatment, all but one woman recovered menstrual function and 55 conceptions were recorded.

The GOG recently completed an analysis evaluating the quality of life, reproductive, and psychosocial characteristics of survivors of OGCTs compared with matched controls. In this analysis, the survivors appeared to be well adjusted, were able to develop strong relationships, and were free of significant depression. The effect on fertility was modest or none in those patients who underwent fertility-sparing surgeries. Overall, these women appeared to be free of any major physical illnesses at a median follow-up of 10 years, as compared with matched controls. The only differences consisted of higher rates of reported hypertension (17% vs. 8%, p = 0.02), hypercholesterolemia (9.8% vs. 4.4%, p = 0.09), and hearing loss (5.3% vs. 1.5%, p = 0.09) compared with controls. Among chronic functional problems, numbness, tinnitus, nausea elicited by reminders of chemotherapy (vs. general nausea triggers for controls), and Raynaud’s symptoms were reported more frequently by survivors. Despite persistence of a few sequelae of treatment, in general, OGCT survivors enjoy a healthy life comparable to that of controls, justifying administration of curative treatment in full and timely dosing.

**FUTURE DIRECTIONS FOR CLINICAL TRIALS FOR OVARIAN GERM CELL TUMORS**

Avoidance of chemotherapy when cure can be achieved with surgery alone is a laudable goal, given the late effects of BEP noted above. Several small trials in adult women and a recently completed study in the Children’s Oncology Group suggest that surveillance after surgery is a reasonable strategy for women with a non-seminomatous germ cell tumor (NSGCT), International Federation of Gynecology and Obstetrics (FIGO) stage Ia or Ib disease. Among adult women, five prior studies have reported on surveillance after surgery alone is a laudable goal, given the late effects of BEP one case of AML among 91 patients. An additional case of lymphoma was diagnosed among survivors treated on that study, but relationship to treatment remained uncertain, as a correlation between chemotherapy and lymphoproliferative disorders is not established.

Chemotherapy also has long-term effects on gonadal function and leads to sterility. Older age at initiation of therapy, greater cumulative drug dose, and longer duration of therapy favor premature ovarian dysfunction. However, successful pregnancies after combination chemotherapy have been documented in patients with malignant OGCTs. In an MDACC review, 27 (68%) of 40 patients who had retained a normal contralateral ovary and uterus maintained regular menses consistently after completion of chemotherapy, and 33 women (83%) had regular menses at follow-up. Twelve patients had successful pregnancies. In a series from Milan, 138 of 196 patients underwent fertility-sparing surgery, and of those, 81 underwent adjuvant chemotherapy. After treatment, all but one woman recovered menstrual function and 55 conceptions were recorded.

The GOG recently completed an analysis evaluating the quality of life, reproductive, and psychosocial characteristics of survivors of OGCTs compared with matched controls. In this analysis, the survivors appeared to be well adjusted, were able to develop strong relationships, and were free of significant depression. The effect on fertility was modest or none in those patients who underwent fertility-sparing surgeries. Overall, these women appeared to be free of any major physical illnesses at a median follow-up of 10 years, as compared with matched controls. The only differences consisted of higher rates of reported hypertension (17% vs. 8%, p = 0.02), hypercholesterolemia (9.8% vs. 4.4%, p = 0.09), and hearing loss (5.3% vs. 1.5%, p = 0.09) compared with controls. Among chronic functional problems, numbness, tinnitus, nausea elicited by reminders of chemotherapy (vs. general nausea triggers for controls), and Raynaud’s symptoms were reported more frequently by survivors. Despite persistence of a few sequelae of treatment, in general, OGCT survivors enjoy a healthy life comparable to that of controls, justifying administration of curative treatment in full and timely dosing.

**TABLE 1. Prior Studies of Surveillance in Stage I Non-dysgerminoma Ovarian GCT**

<table>
<thead>
<tr>
<th>Author</th>
<th>Stage</th>
<th>Total N (Recurrence)</th>
<th>EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patterson**</td>
<td>IA</td>
<td>22 (8)</td>
<td>74%</td>
<td>91%</td>
</tr>
<tr>
<td>Dark**</td>
<td>IA</td>
<td>6 (2)</td>
<td>66%</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Baranzelli**</td>
<td>I</td>
<td>12 (6)</td>
<td>50%</td>
<td>92%</td>
</tr>
<tr>
<td>Mitchell**</td>
<td>I</td>
<td>3 (0)</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Gobel**</td>
<td>IA/B</td>
<td>42 (3)</td>
<td>83%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Abbreviations: GCT, germ cell tumor; N, patients; EFS, event-free survival; OS, overall survival.
carcinoma—has allowed much more informed shared decision making between physician and patient about his or her clinical choices. Therefore, hoping to refine our understanding of the prognostic factors for risk of recurrence among women, the COG and GOG have proposed a joint trial that would recommend surveillance for patients with stage Ia or Ib disease.

For women with FIGO stages Ic, II, and III, the expected cure with BEP is quite high (> 95%) as noted above. Since survival is so high, it would be prudent to consider ways in which toxicity can be reduced. Carboplatin has a much more benign toxicity profile than cisplatin and has proven clinical activity in germ cell tumors. However, randomized studies of carboplatin compared with cisplatin in men with testicular cancer indicated it was an inferior choice.68 The British pediatric clinical trials organization, Children’s Cancer and Leukemia Group (CCLG), has been using carboplatin in place of cisplatin since 1989 with excellent reports of EFS and OS in their cohorts. The British regimen (JEB) consists of carboplatin 600 mg/m² (area under curve 7.9) on day 2, etoposide 120 mg/m² day 1 through 3, and bleomycin 15 IU/m² on day 3. Of note, this dose of carboplatin used on the CCLG protocol is 20 to 70% higher than what had been used in the adult male testicular trials. In a comparison of British and American clinical outcomes in girls treated on CCLG compared with COG clinical trials with ovarian stage II and III tumors, there was no significant difference in outcome between PEB and JEB (PEB = pediatric BEP; cisplatin 100 mg/m² every 3 weeks; etoposide 500 mg/m² every 3 weeks and bleomycin 15 IU/m² in week 1 of each 3-week cycle)69 (Fig. 1). However, this analysis was not a randomized controlled trial. Hence, the COG and GOG are proposing that the standard regimen BEP be compared in a randomized fashion with JEB for adolescent and young adults up to age 25 with ovarian NSGCT.

Although the incidence of stage IV disease in women with ovarian germ cell tumors is rare, the outcome is clearly inferior to lower stages. In the COG and CCLG combined dataset, adolescents older than age 11 with stage IV ovarian cancer had EFS of only 70% (95% CI, 54% to 81%).70 Therefore, in future trials, we will propose that women with stage IV ovarian germ cell tumors be included in the “poor-risk” category. The number of women per year with a stage IV ovarian cancer is probably approximately 15 patients per year, and this precludes the possibility of a randomized, controlled trial just in adult women. But hopefully this limitation can be overcome if future poor-risk trials of germ cell tumors combine patients with pediatric and adult ovarian and testicular germ cell tumor. If a combined trial could be accomplished, sufficient sample size would be available for randomized comparisons of new therapies that have promise to improve the current poor prognosis for patients with metastatic ovarian germ cell tumor.

**Disclosures of Potential Conflicts of Interest**

Relationships are considered self-held and compensated unless otherwise noted. Relationships marked “L” indicate leadership positions. Relationships marked “I” are those held by an immediate family member; those marked “B” are held by the author and an immediate family member. Relationships marked “U” are uncompensated.

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**References**

4. Tavassoli FA, Devilee P (eds). Pathology & Genetics: Tumours of the


GYNECOLOGIC CANCER

Pathways in Gynecologic Malignancies

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PI3K Pathway in Gynecologic Malignancies

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OVERVIEW

Alterations in PI3K signaling are common in gynecologic malignancies. Alterations detected vary with gynecologic cancer type, histologic subtypes within these, and clinical phenotypes. The distinction into type I and type II endometrial and ovarian carcinomas is reflected in distribution of changes detected in several of the PI3K members. PIK3CA mutations and amplifications are common in endometrial, ovarian, and cervical cancers. PTEN mutations and deletions are frequent in endometrial cancers. Several immunohistochemical studies of protein expression have explored these and other potential surrogate markers for PI3K pathway activation. Biomarkers to measure level of PI3K activity in clinical samples are not established. Whether amplifications, mutations, and deletions of the PI3K pathway members, and in particular change in their expression levels, result in clinically relevant pathway activation needs to be further explored. Also, to what extent these alterations drive the tumor behavior and are critical targets for therapeutics to improve patient survival needs to be further tested to establish predictive biomarkers for response to PI3K inhibition.

The most frequent pelvic gynecologic malignancies are endometrial, ovarian, and cervical cancers, representing about 15% of all cancers and cancer-related deaths among women.1 Ovarian carcinoma is the most lethal, dominated by the epithelial type that is responsive to chemotherapy but seldom cured by chemotherapy.2 Attributed to cytoreductive surgery and combination chemotherapy with platinum and taxanes, 5-year survival is 45%, about a 10% increase over the last decades. Ovarian cancers are classified morphologically into subtypes according to their resemblance to normal gynecologic tissues: serous (fallopian tube), endometrioid (endometrium), mucinous (endocervical glands), and clear cell (glycogen rich vaginal nests). Using a low-grade and high-grade distinction, ovarian cancers may be classified as type I (20%), which includes all low-grade serous, low-grade endometrioid, mucinous, and clear cell tumors, and type II, which includes high-grade serous and endometrioid and undifferentiated tumors. Ovarian cancers are molecularly heterogeneous, to some extent reflected in this type I and type II distinction.

Endometrial cancer is the least lethal of the gynecologic malignancies. Approximately 75% of cases are diagnosed with the tumor confined to the uterine corpus.3 Despite this, 20% will recur after primary surgery and have limited response to systemic therapy. The categorization into two subtypes is the most common basis for determining risk of recurrence. The majority of cases are type I, associated with estrogen hyperstimulation and obesity, often endometrioid histology, low grade and stage, and associated with good prognosis. In contrast, type II cancers are characterized by high patient age, stage, and grade; nonendometrioid histology; and poor outcome.

For cervical cancers, the etiological role of infection with high-risk human papilloma viruses (HPV) is well established, with progression from persistent HPV infection through precancerous lesions to invasive cancer.4 This forms the basis for vaccination and screening programs to detect and treat precursor lesions, largely demonstrated to be successful in resource-rich countries. The dominating histologic subtypes are squamous cell carcinomas and adenocarcinomas, the latter being associated with poorer prognosis.

The phosphatidylinositol-3-kinases (PI3Ks) are a family of enzymes involved in cellular functions altered in cancer. The lipid kinases catalyze phosphorylation of phosphatidylinositol to activate signaling pathways regulating important cellular functions.5,6 Inappropriate cooperation of elements in the PI3K signaling has been shown to disrupt the regulation of cellular growth and proliferation, differentiation, motility, apoptosis, and intracellular trafficking (Fig. 1). Thus, large efforts are made to develop inhibitors of the PI3K pathway and molecular markers to predict response to such treatment in cancer.7

Three classes of PI3Ks with different isoforms within each class are identified. The class most implicated in cancer is the Class IA PI3Ks consisting of one regulatory and one catalytic subunit. The catalytic subunit PIK3CA (p110α) and regulatory subunit PIK3R1 (p85α) compose the heterodimer coupled to and activated by receptor tyrosine kinases (RTKs).6 Ligand binding to receptor tyrosine kinases (EGFR, HER2, VEGFR, FGFR2, IGFR1, PDGFR), leads to tyrosine phosphorylation of
the intracellular receptor domain and activation of PI3K signaling. PI3K phosphorylates phosphatidylinositol-2-phosphate (PIP2) to PIP3. The tumor suppressor phosphatase and tensin homolog (PTEN) counteracts this by dephosphorylating PIP3 to PIP2. PIP3 propagates intracellular signaling by binding to AKT and the phosphoinositide dependent kinase 1 (PDK1). Ligand-independent activation of PI3K signaling is seen with specific somatic mutations of receptor tyrosine kinases or other PI3K pathway members rendering the pathway constitutively active.8 PI3K may also be activated by RAS (Fig. 1).

PI3K ALTERATIONS IN OVARIAN CANCERS

Both clinically and molecularly, ovarian cancer is a heterogeneous disease. Still, the increasingly used classification into types I and II ovarian cancers is also reflected in distinct molecular abnormalities evidenced by specific alterations in the PI3K signaling pathway among others.9,10 Around 70% of ovarian cancers show PI3K signaling activation attributed to a range of potential mechanisms.10 AKT2 and PIK3CA amplifications have been reported for all histologic subtypes.11 Activating mutations in PIK3CA is seen in up to 50% in endometrioid and clear cell subtypes.12,13 Loss of inhibition through inactivating mutations in PTEN, seen in 3% to 8% of the endometrioid and lower grade tumors, is also suggested to contribute to high PI3K signaling.12,14 Mechanisms for PI3K signaling activation is also presumed to involve autocrine and paracrine signaling through tyrosine kinase growth factor receptors.

Applying the type I and type II distinction, type I ovarian carcinomas are expressing IGFIR, p53 wild-type, and have frequent activation mutations in RAS and PIK3CA as well as inactivating PTEN mutations.10,14 Type II cancers in contrast, are characterized by p53 mutations and a high level of genomic instability and inactivating aberrations in the BRCA genes.12 A range of chromosomal regions, of which several are potentially treatable with drugs, are found to be amplified in type II cancers, including regions harboring ERBB2, EGFR, PIK3CA, AKT1, and PIK3R1 (Table 1).

PI3K ALTERATIONS IN ENDOMETRIAL CANCERS

Several players in the PI3K-signaling pathway are altered in endometrial cancer, suggesting PI3K/mTOR signaling as a key target for therapy in endometrial carcinomas. This is also reflected in ongoing clinical trials.3,18,19 The role of PI3K signaling in the biologically different type I and type II endometrial cancers is only partially understood (Table 1). Type I cancer is associated with hormone receptor positivity and FGFR2, KRAS, and PTEN mutations, yet amplifications are less common. Type II cancers in contrast are dominated by hormone receptor–negative tumors and harbor more often amplifications for the PIK3CA and ERBB2 regions, also found to predict poor outcome.19

PIK3CA mutations are found in both endometrioid and nonendometrioid cancers and have been linked to sustained proliferation in the disease. Mutations in PIK3R1 and PIK3R2, reported in endometrial cancer,20,22 have also been suggested as a novel mechanism for regulation of PTEN protein stability20 and to increase AKT activation.21 PTEN is frequently mutated in sporadic endometrial cancer, up to 80% reported for the endometrioid subtype. Mutations, deletions, promoter hypermethylation, and miRNA

<table>
<thead>
<tr>
<th>KEY POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alterations in PI3K signaling are common in gynecologic malignancies.</td>
</tr>
<tr>
<td>• The type of alterations detected varies with histologic subtypes and clinical phenotypes.</td>
</tr>
<tr>
<td>• PIK3CA mutations and amplifications, PTEN mutations and deletions, and immunohistochemical protein expression of these and other PI3K pathway members have been suggested as surrogate markers for PI3K pathway signaling.</td>
</tr>
<tr>
<td>• Biomarkers to measure the level of PI3K activity in clinical samples have not been established.</td>
</tr>
<tr>
<td>• Predictive biomarkers for response to PI3K inhibition have not been established.</td>
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</tbody>
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overexpression are all suggested mechanisms involved in the regulation of PTEN expression and function, also affecting PI3K signaling.18

Also, alterations in KRAS known to influence PI3K signaling are common in endometrial cancer.23 Activating KRAS mutations are more common in type I endometrial cancers, and, recently, KRAS gene amplification and overexpression, but not mutation, were found to associate with aggressive disease and increase from primary to metastatic endometrial cancer lesions.23

Recent studies have also suggested a link between estrogen receptor loss and PI3K activation in several independent patient cohorts, suggesting a rationale for investigating ER-alfa’s potential to predict response to PI3K/mTOR inhibitors in clinical trials.24 Estradiol has been found to activate PI3K/AKT signaling in both an ER-alfa-dependent and independent manner.25

TABLE 1. PI3K Pathway-Related Alterations in Endometrial, Ovarian, and Cervical Cancer

<table>
<thead>
<tr>
<th>Target</th>
<th>Alteration</th>
<th>EC - TYPE</th>
<th>OC - TYPE*</th>
<th>CC - TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I (%)</td>
<td>II (%)</td>
<td>I (%)</td>
</tr>
<tr>
<td>ERBB2</td>
<td>Amplification</td>
<td>1</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>FGFR2</td>
<td>Mutation</td>
<td>10–16</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PTEN inactivation</td>
<td>Mutation, deletion, methylation</td>
<td>50</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>AKT</td>
<td>Mutation</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Amplification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td>Mutation</td>
<td>11–26</td>
<td>2–4</td>
<td>30</td>
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<tr>
<td></td>
<td>Amplification</td>
<td>2</td>
<td>10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>Mutation</td>
<td>30</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Amplification</td>
<td>2–14</td>
<td>46</td>
<td>&lt;1</td>
</tr>
<tr>
<td>PIK3R1</td>
<td>Mutation</td>
<td>43</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: EC, endometrial cancer; OC, ovarian cancer; CC, cervical cancer; SCC, squamous cell carcinoma; AC, adenocarcinoma.

* Type II ovarian cancer includes high-grade serous and endometrioid and undifferentiated tumors.

PI3K ALTERATIONS IN CERVICAL CANCERS
Among the gynecologic cancers, cervical cancer is the least studied regarding PI3K signaling. The region also harboring PIK3CA on chromosome 3q has been reported to influence the transition from severe dysplasia to invasive cancer of the uterine cervix.26 Also, molecular studies of the PI3K/AKT pathway in uterine cervical neoplasias have demonstrated frequent PIK3CA amplification and AKT phosphorylation.27

The receptor tyrosine kinase ERBB2 oncogene has been found to be amplified in squamous cell and even more frequent in adenocarcinomas of the uterine cervix,29 thus implicating another targetable and possible mechanism for activation of PI3K signaling in this disease. The human papillomavirus 16 E6 oncoprotein has also been reported to interfere with the insulin signaling pathway by binding to tuberin.30

CONCLUSION
Several alterations in pathway members of PI3K signaling have been reported to be present and relevant for phenotypes in ovarian, endometrial, and cervical cancers. Whether amplifications, mutations, and/or deletions of the pathway members and in particular the resulting changes in their expression levels, lead to clinically relevant pathway activation, needs to be further explored. Also, to what extent these alterations drive tumor behavior and are critical targets for therapeutics to improve patient survival demands further testing.28

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References

The prevalence of overweight and obesity in the United States and elsewhere has increased dramatically in recent decades.1 The actual figures reported vary widely depending on whether they are based on measured or self-reported height and weight information but, regardless of how the data were collected, the trends are the same. Using measured height and weight data from the US National Health and Nutrition Examination Surveys (NHANES), Fig. 1 shows how the probability of a woman aged 18–74 years being obese, defined as a body-mass index (BMI, calculated as weight/height squared) \( \geq 30 \text{ kg/m}^2 \), has changed over time. Although the probability remained fairly constant at 16% to 17% between 1959 and 1980, it more than doubled over the next 25 years to reach 36% in 2007–2008.2 Furthermore, these figures do not include the approximately 29% of the population now classified as overweight but not obese (BMI 25–29.9 kg/m\(^2\)).3

It is well accepted that excess body weight is a risk factor for many chronic diseases including cardiovascular disease, diabetes, and several types of cancer including adenocarcinoma of the esophagus, colorectal, kidney, and postmenopausal breast cancer.4 Obesity has also been associated with reduced survival after a diagnosis of breast cancer.5 However, although it has long been known that obese women have an increased risk of developing endometrial cancer,6 the relation between obesity and risk of other gynecologic cancers and the potential influence of body size on survival among women diagnosed with gynecologic cancer are less well understood.
are sometimes grouped with other endometrioid cancers as type 1, and sometimes with other high-grade cancers as type 2. Early epidemiological studies did not attempt to separate the different histologic types of endometrial cancer; thus, most of the available information regarding risk factors, including the strong association with obesity, pertains primarily to the low-grade endometrioid cancers that comprise the majority of any case group. Much less is known about risk factors for the less common high-grade cancers, although clinical series have suggested they are less strongly associated with exposure to estrogen, hence their description as “nonestrogen-dependent.” Data from recent prospective studies suggest that although obesity is most strongly associated with increased risks of endometrioid cancers, it does also increase risk of the more aggressive nonendometrioid cancers, albeit to a lesser extent (Table 1).8,9

Given the increasing prevalence of obesity worldwide, it is therefore not surprising that age-standardized incidence rates of endometrial cancer have also been rising in many countries, particularly among postmenopausal women (Fig. 2A).10 It is likely that at least a proportion of this change is a result of the increasing prevalence of obesity, as even within countries such as the United States where endometrial cancer rates have been fairly constant over recent years, this overall trend masks an increase in the incidence of the endometrioid cancers that are most strongly associated with obesity (Fig. 2B).11

Further work has suggested that, although body-life in early adulthood is associated with risk, the strongest associations are with adult weight gain and recent weight,12,13 and there is some evidence that those who report sustained weight loss are no longer at increased risk.12,14 It has also been proposed that the process of “weight cycling,” whereby women repeatedly lose and then regain weight, might further increase cancer risk as a result of the redistribution of body fat from peripheral to central locations and replacement of lean body mass by fat mass. Results are, however, conflicting for endometrial cancer with some, but not all studies reporting increased risks among women who report weight cycling.14

Obesity is also strongly associated with endometrial cancer mortality in the general population15 although this may largely reflect the increased incidence among obese women. Interpreting data assessing the relation between body size

**KEY POINTS**

- Obesity greatly increases risk of low-grade endometrial cancers, with more modest increases in risk seen for high-grade cancers.
- There is currently insufficient data to draw any definitive conclusions about the association between obesity and risk of recurrence of, or death from, endometrial cancer.
- Obesity increases risk of ovarian cancer, although it may not influence risk of the high-grade serous cancers that account for the majority of ovarian cancer deaths.
- Obesity is associated with reduced survival following a diagnosis of ovarian cancer.
- There is currently insufficient evidence to draw any conclusions regarding the relation between obesity and risk of, and survival following, other gynecologic cancers.

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**FIG 1.** Temporal changes in the adjusted probability of obesity, overall and by degree of obesity, among women age 18-74 in the United States. (Drawn from Ljungvall and colleagues 2012.2)
and survival among women diagnosed with endometrial cancer is not straightforward. Overall, the majority of women diagnosed with endometrial cancer will not die from their cancer but rather from some other cause. In the US, only 19% of women diagnosed between 1973 and 1988, a period chosen to allow 20 years follow-up, died from their endometrial cancer, compared with 36% from cardiovascular diseases, 20% from other malignancies, and 26% from other causes. However, the proportion of endometrial cancer deaths varied dramatically over time, with 50% of deaths in the first 5 years after diagnosis due to endometrial cancer, compared with 13% between 5 and 10 years, and only 2% more than 10 years after diagnosis. As discussed above, the association between obesity and cancer risk is strongest for low-grade cancers. Women diagnosed with high-grade tumors are thus much less likely to be obese than those with low-grade cancers; they are also much more likely to die from their disease, and many of these deaths will occur during the first few years following diagnosis. Short-term studies are thus likely to see lower all-cause mortality among more obese women, with this difference largely attributable to the fact that they have less aggressive disease. In the long-term, however, we would expect studies to show a positive association between obesity and all-cause mortality as cardiovascular disease takes over as the leading cause of death.

There are, thus, two questions to be answered. First, is obesity independently associated with an increased risk of recurrence of, or death from, endometrial cancer? Few studies have presented data with adequate control for subtype and/or grade of disease to address this; however, the few that have, found little evidence for an association. One exception was a US-based study that observed a borderline significant association between body size at diagnosis and endometrial-cancer-specific mortality among women with endometrioid tumors [hazard ratio [HR] for a 5-unit increase in BMI, 1.17, 95% confidence interval [CI] 0.98–1.4). This association was, however, driven by the small number of women with high-grade endometrioid tumors (HR 1.39, 95%CI 1.04–1.85; 16 deaths). There was no association among women with nonendometrioid tumors. On balance, it seems unlikely that body size has a major influence on the risk of endometrial cancer recurrence or death; however, there are currently insufficient data to draw any definitive conclusions.

The second question is whether obesity is associated with increased mortality from other causes among women diagnosed with endometrial cancer compared with the general population. Studies have variously reported significant inverse, null and significant positive associations between BMI and all-cause mortality following a diagnosis of endometrial cancer, but interpretation of these data is hampered by the differing lengths of follow-up and variable control for confounding. Furthermore, none has directly compared survival among women with endometrial cancer relative to women in the general population with a similar distribution of body size. In a recent review of this area, the authors noted that in four studies that reported an association between BMI at diagnosis and all-cause mortality, the magnitude of the association (HR 1.9–2.8 for BMI ≥30 vs. <25 kg/m²) was comparable to that seen among the general population.

**OVARIAN CANCER**

Ovarian cancer is a very heterogeneous disease. Approximately 90% of ovarian cancers appear to arise from the epithelial surface of the ovary with the remaining 10% comprising sex-cord stromal tumors and germ cell tumors. Most work to date has focused on the epithelial cancers and further reference to ovarian cancer will refer to this subgroup. The epithelial group can be further subdivided into four major histologic groups including serous cancers, the most aggressive type that comprise 50% to 60% of all invasive epithelial cancers; endometrioid cancers, that resemble their endometrial counterparts; clear cell cancers; and mucinous tumors, that resemble cancers of the endocervix or intestine. Furthermore, these cancers can be frankly invasive or what are described as borderline or low malignant potential cancers that have many of the features of invasive cancer but do not invade the surrounding tissue. It is now well accepted that risk factors for the different histologic subtypes can vary, and that there is further heterogeneity within subtypes. For example, at a molecular level, low-grade invasive serous cancers appear more similar to their borderline counterparts than to high-grade invasive serous cancers. Analysis of risk factors for ovarian cancer must, therefore, take this heterogeneity into account. [Note: the majority of what are commonly described as serous ovarian cancers are now thought to originate from the fallopian tube but, following current convention, these cancers will be considered as ovarian in the following discussion.]

Results from individual studies evaluating the relation between body size and risk of ovarian cancer are inconsistent; however, in a recent analysis that pooled data from 47 studies including more than 25,000 cases, a 5-unit increase in BMI

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**TABLE 1. Relative Risks (RR) and 95% Confidence Intervals (CI) for the Association between Obesity and the Different Histologic Subtypes of Endometrial Cancer**

<table>
<thead>
<tr>
<th>First Author, Year, Country</th>
<th>No. Cases</th>
<th>BMI Comparison (kg/m²)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1/Type 2*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bjorge, 2007, Norway⁶</td>
<td>716/992</td>
<td>≥30 versus 18.5–24.9</td>
<td>2.69 (2.42–2.98)</td>
</tr>
<tr>
<td>Yang et al, 2012, USA⁷</td>
<td>1312/138</td>
<td>≥30 versus &lt;30</td>
<td>2.93 (2.62–3.28)</td>
</tr>
</tbody>
</table>

* Exact classifications varied but in general Type 1 included all endometrioid cancers and Type 2 included serous, clear cell and other high-grade cancers.
FIG 2. (A) Incidence rates of endometrial cancer among women age 50 and older, age standardized to the world population. (Drawn from Ferlay and colleagues 2010.)

(B) Overall and subtype-specific incidence rates of endometrial cancer in the United States, age standardized to the 2000 U.S. standard population. (Drawn from Duong and colleagues 2011.)
CERVICAL CANCER

The major risk factor for cervical cancer is infection with a carcinogenic strain of the human papillomavirus (HPV), particularly HPV16 or HPV18; however, not all women infected with these viruses go on to develop cancer, so other factors must also play a role. Several studies have suggested that increasing obesity is associated with increased risk of cervical cancer, particularly adenocarcinoma, but others have found no association. A positive association between obesity and risk of adenocarcinoma but not squamous cell carcinoma of the cervix would be consistent with observations that rates of adenocarcinoma have been increasing in many countries while rates of squamous cell carcinoma have been falling (Fig. 3). It is, however, difficult to separate out the effects of the introduction of cytologic screening, particularly on incidence rates of invasive squamous cell cancer, although it appears screening has been less effective at reducing the incidence of adenocarcinomas. In a series of period-cohort analyses conducted across 13 European countries, Bray and colleagues noted the differing incidence trends but concluded that the patterns were consistent with the idea that both subtypes share a common etiology.

Obesity is also associated with cervical cancer mortality in the general population; however, recent studies have suggested that among women with cervical cancer, increasing body size is associated with longer survival. In these studies, however, the biggest differences have been seen for underweight women who appear to have poorer survival, and it is possible that this is because they have more advanced disease and/or experience more complications during treatment. Further data are limited although, as with endometrial cancer, it might be expected that, in the long-term, obesity would be associated with increased all-cause mortality. There is currently little evidence to suggest that recurrence-free and cervical cancer-specific survival differ among overweight and obese women compared with normal weight women.

OTHER CANCERS

Cancers at other gynecologic sites are rare. Collectively, vaginal and vulvar cancers account for less than 5% of all gynecologic cancers and less is known about their etiology, although they often co-occur with cervical cancer and, like cervical cancer, both are associated with HPV infection. Small studies conducted in the early 1990s suggested a possible association between obesity and risk of vulvar cancer, but no association with survival. An association has also been reported between adolescent adiposity and risk of clear cell adenocarcinoma of the vagina among women exposed to diethylstilbestrol in utero. There are, however, too few data to draw any reliable conclusions regarding the role of obesity in the etiology of these rare cancers.

### TABLE 2. Relative Risks (RR) and 95% Confidence Intervals (CI) for the Association between Obesity and the Different Histologic Subtypes of Ovarian Cancer in Two Large Pooled Analyses

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Serous Cancers</th>
<th>Mucinous Cancers</th>
<th>Endometrioid Cancers</th>
<th>Clear Cell Cancers</th>
<th>Borderline Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2012</td>
<td>1.00</td>
<td>1.19*</td>
<td>1.07*</td>
<td>1.05</td>
<td>1.29*</td>
</tr>
<tr>
<td>Olsen et al, 2013</td>
<td>0.98</td>
<td>1.19*</td>
<td>1.37*</td>
<td>1.06</td>
<td>1.24*</td>
</tr>
</tbody>
</table>

* p < 0.05.
MECHANISMS
There are several mechanisms whereby obesity might influence risk of and/or survival following gynecologic cancer. Adipose tissue is very hormonally and metabolically active. It converts androgens to estrogen and is the main source of endogenous estrogen among postmenopausal women. It has long been known that exposure of the uterus to estrogen in the absence of progesterone leads to uncontrolled proliferation and development of endometrial hyperplasia, a precursor to the low-grade endometrioid subtype of endometrial cancer. It is almost certainly the higher estrogen levels among overweight and obese women that are at least partially responsible for their increased risks of developing low-grade endometrial cancers; this may also explain some of their increased risk of high-grade endometrial and ovarian cancers. Fat cells also produce a range of adipokines including leptin, adiponectin, and inflammatory mediators such as interleukins 6 and 8. Leptin is known to act as a growth factor in breast, endometrial, and prostate cancer cell lines and also promotes angiogenesis. It is also possible that insulin resistance and impaired glucose metabolism that often accompany obesity may increase cancer risk and/or have an adverse effect on outcomes. Evidence to support this hypothesis comes from studies suggesting that metformin, a common diabetes medication, is associated with reduced cancer risk and increased survival among patients with cancer.

There are additional reasons why obesity might influence survival after a diagnosis of ovarian cancer. It is possible that the tumors that develop in bigger women are biologically more aggressive than those in normal weight women, although, as noted above, it appears that the most aggressive subtype of ovarian cancer is not more common among big women. It is also possible that obese women may not receive an appropriate dose of chemotherapeutic drugs for their body size. The most common drug used to treat ovarian cancer is carboplatin, and the dose is calculated based on a patient’s body-surface area (BSA). Because the drug is associated with several side effects, clinicians are often reluctant to prescribe the full dose to big women, capping it at a BSA of 1.8 or 2.0. Obesity is also associated with other comorbidities such as diabetes and cardiovascular disease, which may, again, lead to women being treated with reduced doses of chemotherapy. Further work is, however, required to identify whether differential chemotherapy dosing can explain the apparent differences in survival by body size and to evaluate the other possible mechanisms whereby body size might influence outcomes.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.
References


GYNECOLOGIC CANCER

Peritoneal Cancers, Heated Controversy

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Pathologic Diagnosis, Origin, and Natural History of Pseudomyxoma Peritonei

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OVERVIEW

Mucinous ascites and pools of mucin within the peritoneal cavity associated with neoplastic, mucinous epithelium are the characteristic features of pseudomyxoma peritonei (PMP). Clinically, PMP presents with abdominal distension and gelatinous ascites. In female patients, pelvic masses can be seen. Radiologic findings on computed tomography include scalloping of the hepatic and splenic margins and dense ascites. Surgically, PMP is encountered as grossly visible mucin in the peritoneal cavity. The presence of mucin outside of the appendix, in the right lower quadrant, and beyond is an important diagnostic finding. The appendix may be distended or ruptured. In women, there is often bilateral surface involvement of the ovaries, raising the differential diagnosis of primary ovarian neoplasms; however, these are extremely rare causes of PMP. Because of the association between appendiceal lesions and metastatic mucinous neoplasms of the ovary, appendectomy in the setting of any mucinous peritoneal or ovarian process may be prudent, even if the appendix is grossly normal. The gastrointestinal tract, especially the hepatopancreato biliary system, also needs to be assessed by the surgeon. Pathologically, PMP arises almost exclusively from low- or high-grade mucinous neoplasms of the appendix. These neoplasms must be distinguished both from rare benign causes of mucinous ascites and from nonappendiceal primary tumors. PMP has a protracted clinical course with progressive fibrous adhesions and obstructive disease; aggressive surgical and cytoreductive therapy with hyperthermic intraperitoneal chemotherapy has been reported to improve clinical outcomes.

Pseudomyxoma peritonei (PMP) is a clinicopathologic syndrome that is characterized by mucinous ascites and pools of mucin, including neoplastic, mucinous epithelium within the peritoneal cavity. PMP is an infrequently encountered syndrome with an unusual clinical and pathologic presentation and poses unique diagnostic and management challenges. Controversies exist regarding the exact origin of PMP, the diagnostic nomenclature, and the appropriate clinical management.

HISTORY

Since the initial description of PMP as a complication of appendiceal “mucocele” in 1973, the understanding of PMP pathogenesis and the favored nomenclature have evolved.

PATHOGENESIS

The pathogenesis of PMP has long been debated. Early theories included “mucinification of the abdominal mesothelium” stimulated by the mucin itself; our current understanding is that the vast majority of cases are primary appendiceal mucinous neoplasms (Fig. 1A and B). In instances in which the appendix is distended or ruptured at the time of surgery and pathologic analysis reveals carcinoma within both the appendix and the mucinous ascites, the diagnosis is straightforward. However, cases that primarily present as pelvic masses in female patients or that do not have a grossly identifiable dominant tumor mass can be diagnostically challenging.

Ovarian mucinous tumors associated with PMP almost exclusively arise as metastatic lesions arising from the appendix. However, PMP is 2–3 times more common in women than in men. Furthermore, it has long been acknowledged that the syndrome could, rarely, be related to an ovarian primary tumor. True PMP of ovarian origin has been associated with mature cystic teratomas. Mucinous ovarian tumors comprise up to 20% of ovarian neoplasms and are benign in the majority of cases. Mucinous cystadenomas or cystadenocarcinomas of the ovary may present with mucinous ascites, usually secondary to rupture of the cystic tumors. Primary ovarian mucinous tumors are generally unilateral and present as a large pelvic mass. The neoplastic cells grow within the ovarian stroma rather than on the ovarian surface. This is in contrast to the picture generally seen with PMP of appendiceal origin, where the tumor is bilateral and on the ovarian surface. Molecular analysis of K-RAS...
and loss of heterozygosity studies on synchronous tumors of the appendix and the ovaries has supported the appendiceal origin of these tumors.13

In the emerging molecular era, our understanding of the histogenesis of all tumors is becoming more nuanced, with the recognition of the capacity of mature cells to activate dormant genetic material within their molecular machinery and regain “stemness.”14 Within this framework, we can recognize and accommodate the various reports of PMP arising from nontypical primaries, i.e., the pancreas, colon, small bowel, urachus,15 and the peritoneum itself.

**NOMENCLATURE**

In 1996, Sugarbaker strictly defined PMP as a grade 1 mucinous adenocarcinoma arising from an appendiceal adenoma.16,17 Similar nomenclature was embraced by the Armed Forces Institute of Pathology, with any viable tumor cells present in the mucin warranting the diagnosis of adenocarcinoma.18 However, within the pathology literature, there was an early recognition that the clinicopathologic entity of PMP could be classified in subtypes with different clinical outcomes and pathologic findings. Ronnett and colleagues proposed a classification distinguishing “disseminated peritoneal adenomucinosis” (DPAM) from “peritoneal mucinous carcinomatosis” (PMCA).5 DPAM represented the classic PMP with paucicellular mucinous ascites and an indolent clinical course, and PMCA had a higher percentage of overtly malignant cells/cell groups and a poorer prognosis. Both DPAM and PMCA were thought to arise from gastrointestinal primaries.19,20 A refined system, in which PMCA was further divided into PMCA and PMCA-I (intermediate), subclassified the “carcinomas” into lesions that would behave more like traditional colorectal carcinomas (PMCA) and those more likely to have a progressive indolent course (PMCA-I). Survival outcomes were better for DPAM and PMCA-I patients as compared with PMCA patients.20

The use of the designation “adenoma” within the DPAM terminology was confusing for some, as the lesion did not behave like an in situ adenomatous lesion as seen in the rest of the gastrointestinal tract.21 Similarly, use of the term “adenocarcinoma” for a lesion that does not behave like a colonic adenocarcinoma, in that it is not locally invasive and does not metastasize, has also been criticized.21 Proposed terminology in the pathology literature has included “mucinous neoplasm of low malignant potential,” or “low-grade appendiceal mucinous neoplasm.” In 2010, the American Joint Committee on Cancer (AJCC) and the World Health Organization (WHO) divided PMP into two subtypes based on the grade of the epithelium within the peritoneal mucin. Low-grade epithelium garnered the designation “low-grade mucinous adenocarcinoma,” and high-grade epithelium was designated “high-grade mucinous adenocarcinoma.”13,22 A review of 274 cases of PMP classified according to the WHO criteria and correlated to survival data revealed an overall 5-year survival of 63% for low-grade mucinous adenocarcinoma compared with 23% for high-grade mucinous adenocarcinoma. Low-grade lesions were more likely to be of appendiceal origin, and a subset of high-grade lesions was actually associated with colorectal adenocarcinomas.23

**DIAGNOSTIC CRITERIA**

Clinically, PMP may present as abdominal distension, abdominal pain related to obstruction or with localizing...
symptoms mimicking acute appendicitis. In female patients, the initial symptoms may be pelvic pressure and palpable ovarian masses. PMP occurs as an incidental surgical finding in up to 20% of cases.10 Most patients will have increases in the serum tumor markers carbohydrate antigen (CA) 19–9 and carcinoembryonic antigen (CEA), which is useful both for diagnosis and for managing treatment efficacy and recurrence following therapy.10

Imaging by ultrasound can be misleading because the paucicellular mucinous ascites resembles free intraperitoneal fluid.10 CT is more helpful, as located spaces with characteristic scalloping of hepatic and splenic margins are pathognomonic of PMP and have densities that are higher than nonmucinous ascites.10,21 CT also aids in preoperative planning by demonstrating the extent of disease.

Surgically, PMP is generally encountered as grossly evident mucin in the peritoneal cavity. In many cases, it is an unexpected finding at the time of laparotomy.21 In most cases of PMP arising in female patients, bilateral involvement of the ovaries by multilocular mucin-filled cysts is present. Often, an appendiceal primary will be subtle and may not be grossly appreciated.12 There are reports in the literature of patients treated surgically for presumed mucinous lesions of the ovary where an appendiceal primary later became evident.7 In other cases, mucinous aggregates are discovered incidentally in surgical specimens, such as hernia sacs, thus necessitating a search for the primary neoplasm.12 In many institutions, it has become standard to perform an appendectomy routinely in the staging of ovarian neoplasms. In a recent retrospective review24 of 155 appendectomies performed during staging for presumed ovarian mucinous neoplasms at a single institution, three appendiceal neoplasms were identified, which were all grossly abnormal. One lesion was a primary low-grade mucinous tumor of the appendix, and two were appendiceal carcinoids. All 152 grossly normal appendectomies were histologically benign. During the same 15-year time period, 19 primary mucinous appendiceal tumors were resected at the same institution; of those, 16 presented with PMP, and the remaining three had grossly abnormal appendices. No normal-appearing appendix harbored a tumor. Although these findings may bring into question the practice of appendectomy at the time of oophorectomy, it is interesting to note that the authors found no increase in complications in patients who received appendectomy, and many have advocated the continued practice of routine appendectomy in cases of mucinous ovarian or peritoneal lesions.24

Pathologically, mucinous ascites and pools of mucin with variable amounts of neoplastic mucinous epithelium (Figs. 1C and D) within the peritoneal cavity characterize PMP. Although these findings are consistent with PMP, it is a clinicopathologic syndrome, and the job of the pathologist does not end with identification of mucin or mucin-producing epithelium. The biological potential of the lesion depends on several factors that can be further characterized on pathology. The first goal is to identify the organ of origin. The vast majority of cases of PMP have a primary neoplasm in the appendix. The appendiceal lumen may be distended by copious amounts of mucin. The tumor cells in the appendix are generally of low nuclear grade and may be elongated and hyperchromatic. Sampling is important, and the appendix must be submitted entirely for microscopic evaluation.10 Metastatic spread to the ovaries is common.13 Correlation of radiologic and surgical findings, along with ancillary techniques such as immunohistochemistry (IHC), may be useful in cases where an appendiceal primary cannot be established. Epithelia from different sites express different keratins by IHC and can therefore help to identify the location of the primary tumor. Ovarian epithelium, and most tumors arising from the ovary, express cytokeratin 7 (CK7) and are negative for CK20, while colonic and appendiceal epithelium and tumors are positive for CK2025 but do not stain for CK7. A subset of tumors will not express this classic pattern of cytokeratins and will require the use of additional IHC markers, such as CDX2, another marker for epithelium and tumors arising from the gastrointestinal and pancreato-biliary systems, along with clinical correlation.21

Appendiceal mucinous neoplasms, when limited to the appendix, are indolent lesions with 96% disease-free survival at 5 years. Escape of the mucin-producing epithelium from the appendix, as is seen in PMP, even to the periappendiceal fat or serosa of the appendix, decreases disease-free survival to 66% to 67%.13 Spread of mucin beyond the right lower quadrant is an adverse prognostic indicator. In staging appendiceal neoplasms that present as PMP, the AJCC/WHO guidelines classify intraperitoneal metastasis beyond the right lower quadrant as pathologic stage M1a.26 The cytologic grade of the tumor cells, determined by the degree of epithelial cellularity and cytologic atypia, correlates with disease outcomes. Cytologically low-grade lesions have a 63% to 86% 5-year survival, and cytologically high-grade tumors have a 5-year survival of only 38% to 44%.13

The main differential diagnostic considerations in cases of mucinous ascites are between appendiceal mucinous neoplasms of low malignant potential and peritoneal carcinomatosis. Peritoneal carcinomatosis most commonly arises from the colon, appendix, stomach, and ovary and is characterized by invasive implants of mucinous adenocarcinoma. It is important to distinguish between these two entities, as metastatic disease is common in peritoneal carcinomatosis, and clinical outcomes are poor when compared with PMP.27 Benign disease can also present with a PMP-like picture. Endometriosis may be characterized by degenerative myxoid changes, and inflammatory conditions of the appendix can result in extravasated mucin. Careful surgical and pathologic examination of the relevant organs is necessary to exclude occult malignancy in these cases.27

**DISEASE PROGRESSION AND TREATMENT**

Although the tumor masses of PMP are not locally invasive, the mucin is locally destructive, and complications arise from fibrosis and obstruction.21 Appendiceal lesions with spread beyond the appendix are associated with progressive PMP,
The author(s) indicated no potential conflicts of interest.

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GYNECOLOGIC CANCER

Treatment and Trials: Ovarian Cancer in Women Older than 65

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Treatment and Trials: Ovarian Cancer in Older Women
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OVERVIEW

Ovarian cancer (OC) is a disease of elderly women. The disease spreads insidiously and presents at an advanced stage at initial diagnosis for most patients. Several groups reported at least a two-fold increased risk of death in women older than 65. Various theories have been proposed to explain this survival disparity in older women, including: (1) more aggressive cancer with advanced age, (2) inherent resistance to chemotherapy, (3) individual patient factors such as multiple concurrent medical problems, and (4) physician and health-care biases toward the elderly that lead to inadequate surgery, less than optimal chemotherapy, and poor enrollment in clinical trials. As a result of this high clinical variability, oncologists need to be more familiar with the comprehensive geriatric assessment to better identify vulnerable patients at higher risk of complications. Several geriatric tools are available to assess the physiologic and functional capacities of older patients and to better individualize treatment. This paper gives an overview of the management of elderly patients with OC, in particular the integration of chemotherapy, surgery, and geriatric assessment to improve treatment tolerance and survival outcomes.

Ovarian cancer (OC) is the leading cause of mortality among patients with gynecologic malignancies. More than half of all OC occurs in women older than 65. Management of advanced ovarian cancer (OC) typically starts with the combination of extensive debulking surgery and postoperative platinum and paclitaxel chemotherapy. This approach has resulted in an improvement of the survival rates over the last decades with a median survival exceeding 50 months in most published series.

Despite the growing age of the general population, particularly in western countries, and the fact that 60% of cancers occur in people older than 65, elderly patients are still under-represented in clinical trials. In the Southwest Oncology Group (SWOG) analysis of data on 16,396 patients enrolled in 164 trials during the 1990s, patients with OC older than 65 accounted for only 30% of all included patients. Similarly, in a recent Surveillance, Epidemiological, and End Results (SEER) survey, only 9% of patients with cancer older than 75 were included in clinical trials of new therapies.

In the most recent series, elderly patients with OC continue to have poor survival outcomes compared with their younger counterparts. The poor prognosis is partly the result of reduced use of standard chemotherapy. Reports have suggested that only half of women over the age of 65 receive standard first-line platinum-based therapy and the likelihood of their receiving it decreased with age, independent of comorbidity. Hershman’s group reported that only half of women over age 65 with advanced ovarian cancer were treated with platinum-based chemotherapy. However, survival improved by 38% in the treated women, similar to the benefits described in randomized controlled trials among younger patients.

Because primary chemotherapy is a potentially curative treatment in conjunction with cytoreductive surgery, it is important to explore these options with all patients regardless of age. Careful consideration of the chemotherapy dosing, scheduling, route (intravenous vs. intraperitoneal), and timing (neoadjuvant or postoperative) is essential. To determine the safest and most effective treatment, one should consider a pretreatment geriatric assessment (GA) of validated geriatric domains, including functional dependence, organ function, comorbidity, polypharmacy, social support, and cognition/psychosocial factors. Although prospective studies dedicated to older patients with ovarian cancer are few (but growing), there have been several retrospective studies to help guide us as we present options for our older patients.

ROLE OF PRIMARY CYTOREDUCTIVE SURGERY (CRS)

The practice of performing primary CRS followed by platinum-based chemotherapy compared with neoadjuvant chemotherapy (NACT) with interval CRS (iCRS) is a controversial topic internationally. The survival benefit of performing a primary CRS has never been proven in prospective trials, but ancillary data analysis of several cooperative group chemotherapy trials found that residual tumor < 1 cm was associated with superior survival as compared with patients...
with residual disease > 1 cm. This goal has shifted further to obtaining no gross residual disease at the conclusion of CRS. Studies suggest that those patients with zero residual tumor at conclusion of CRS have significantly longer survival than those patients previously considered optimal at 0 cm to 1 cm. Gynecologic Oncology Group (GOG) protocol 158 compared paclitaxel/carboplatin to paclitaxel/carboplatin in patients with <1 cm residual disease following surgery and found median progression free survival (PFS) of 19 to 20 months and overall survival (OS) of 49 to 57 months. GOG 182 compared a variety of doublets and triplets compared with paclitaxel/carboplatin and separated out no gross residual from gross residual < 1 cm. Patients with gross residual < 1 cm had median PFS and OS of 16 and 40 months, respectively. Those with no gross residual had median PFS and OS of 29 and 68 months, respectively. An ancillary review of GOG protocols 114 and 172 (both intraperitoneal (IP) delivery of cisplatin) found median PFS and OS of 43 and 110 months, respectively, among those patients with no gross residual disease. This is compared with median PFS and OS of 110 and 0 months, respectively, among those patients with no gross residual disease at conclusion of CRS. Studies suggest that those patients with zero residual tumor at conclusion of CRS have significantly longer survival than those patients previously considered optimal at 0 cm to 1 cm and associated with higher complication rates.

**KEY POINTS**

- Ovarian cancer is predominantly a disease of the elderly. Approximately 80% of women with ovarian cancer have a FIGO stage III/IV disease at initial presentation.
- Elderly patients with ovarian cancer have poorer survival, undergo proportionally fewer surgical procedures, receive less aggressive treatments, and are less likely to be referred to a gynecologic oncology specialist.
- The outcome benefit of achieving no gross residual disease following surgical cytoreduction may be lost on those elderly patients who tolerate the surgery poorly—emphasizing the need for validated preoperative assessments to help guide appropriate patients to surgery and avoid unnecessary complications for those who should have alternative treatment.
- Given the clinical variability observed in elderly patients, chemotherapy should be tailored to the extent of the disease and the patient’s overall health/prognosis, and it should be guided by a geriatric assessment (GA) that includes measures of functional status, comorbid medical conditions, cognition, psychological status, social functioning, support, and nutritional status.
- Cooperation is needed between geriatricians, medical oncologists, and gynecologic oncologic surgeons to improve the treatment guidelines in this growing and vulnerable patient population.

An alternative to primary CRS is neoadjuvant chemotherapy (NACT). This has been evaluated in a large prospective randomized trial comparing primary CRS with NACT and iCRS. In this study, PFS and OS were identical in the two arms (12 months and 30 months, respectively), but perioperative complications were lower in those patients receiving neoadjuvant chemotherapy. However, the strongest predictor of survival was CRS to no gross residual disease. The authors note that careful analysis of important predictive factors of debulking surgery resulting in no residual tumor, such as comorbidities, age, disease burden, location of metastatic sites, performance status, and stage, should be considered when deciding on NACT or primary CRS.

Certainly, patients present with advanced ovarian malignancies for whom primary CRS is not indicated; for example, those with very poor performance status and those with obvious unresectable disease. For the remainder of patients who present, including those younger than 70 and older than 80, the ability to assess who is fit enough to undergo aggressive CRS followed by chemotherapy and who should...
be offered an alternative pathway, such as NACT and iCRS or primary chemotherapy alone, is an unmet need. Patients with OC have unique presentations and challenges compared with patients with other solid tumors. For example, CRS for ovarian cancer requires a large abdominal laparotomy. Even with widespread malignancy, an aggressive surgery is performed, which may include bowel resections, splenectomy, and other procedures, as compared with most other solid tumors in which widespread malignancy is considered a contraindication to CRS. Patients may present with poor nutrition values and poor performance status as a result of rapid accumulation of ascites and not because of underlying medical comorbidities. If we use a generalized preoperative assessment for these patients, we may exclude many who might benefit from aggressive primary CRS. However, by not validating a preoperative tool in this vulnerable population, we risk excess morbidity and mortality in those patients with too little reserve to tolerate primary CRS followed by chemotherapy.

MODELS OF PREOPERATIVE ASSESSMENT

Traditional models of preoperative assessment, including Lee, Eagle, ASA, and others, do not consider the multisystem assessment needed to evaluate elderly patients with OC. Exploration of other preoperative assessments is ongoing to include assessments of frailty, the comprehensive geriatrics assessment, and the preoperative assessment of cancer in the elderly (PACE).

Frailty

Frailty is defined as a state of decreased physiological reserve and increased susceptibility to suffer disability in response to stressors.22–24 How frailty is measured varies between a physical assessment and a more physiological assessment.

Makary and colleagues used a validated scoring system of physical frailty in a prospective study of patients older than 65 presenting for elective surgery. The frailty score was based on five domains, which included weight loss, weakness, exhaustion, low physical activity, and slowed walking speed.22 This frailty score was then compared with more conventional preoperative assessments such as the ASA score, Lee’s revised cardiac index, and Eagle score. Frailty was found to correlate with postoperative complications with an adjusted odds ratio of 1.78 to 2.13 for intermediately frail patients and 2.48 to 3.15 in frail patients. Frailty was also correlated with increased length of stay (65% to 89% longer stays for frail patients) and nontraditional discharge.23

Other investigators have looked at physiological frailty as a predictor of outcome in preoperative patients. Domains studied included comorbidity, function, nutrition, cognition, geriatric syndrome assessment, and extrinsic frailty (social support).23

Using this assessment of frailty found the following factors were associated most closely with six month mortality: cognitive dysfunction, lower albumin, having fallen in the previous six months, lower hematocrit, functional dependence, and increased comorbidities. Having four or more of these markers predicted six month mortality with a sensitivity of 86%.24 In a follow-up study with 223 patients and using the same assessments, the authors found that timed up and go > 15 seconds, any functional dependence, Charlson score of 3 or greater, and hematoctrit 35 or less were the variables most predictive of postoperative institutionalization.24

Comprehensive Geriatric Assessment (CGA)

The CGA is a multidisciplinary assessment of the elderly patient across multiple domains. The CGA has been adapted for use in elderly patients with cancer to try to predict complications due to chemotherapy and to make appropriate modifications for those patients at risk.25 Studies evaluating the CGA in the preoperative setting are rare to date, with two notable exceptions. Kristjansoon and colleagues evaluated the CGA in patients undergoing surgery for colorectal cancer and found that those patients classified as intermediate or frail were more likely to have postoperative complications than those classified as fit.26 Using an abbreviated assessment, Kothari and colleagues used the CGA to predict postoperative outcomes in patients undergoing thoracic surgery and found that answers to certain questions predicted postoperative morbidity. For example, dependency in the instrumental activity of daily living (IADL) of “shopping” as well as affirmative answers to questions 2 and 12 of the geriatric depression scale (GDS) (“Have you dropped many of your activities and interests?” and “Do you feel pretty worthless the way you are now?”) predicted major postoperative complications as well as location of discharge among elderly patients.27

Preoperative Assessment of Cancer in the Elderly (PACE)

The PACE tool was developed to combine elements of the CGA with surgical risk assessment tools. Instruments included in the PACE are a mini-mental state inventory, activities of daily living (ADLs), instrumental activities of daily living (IADLs), Geriatric Depression Scale (GDS), brief fatigue inventory (BFI), ECOG performance status (PS), ASA, and Satariano’s index of comorbidities. This tool has been studied prospectively among 460 patients undergoing surgery for breast cancer, gastrointestinal cancer, genitourinary cancer, and others. Endpoints of interest were 30 day morbidity, mortality, and hospital stay. Researchers found no significant association of age with postoperative complications. IADL, moderate to severe BFI, and abnormal PS were most predictive of 30 day morbidity. ADL, IADL and PS were associated with extended hospital stay.28,29 Although promising, use of the PACE in a population of patients with “higher risk surgeries” has not yet been performed.

Given the importance of preoperative assessment in general and the increasing geriatric population, a position paper was released in 2012 outlining best practices for optimal preoperative assessment of the geriatric patient.30 In this document, there is a checklist that covers the expected
surgical assessment. This is a comprehensive assessment incorporating almost all domains described in the assessment tools above.

Conclusion
A validated instrument for presurgical assessment of the elderly or patients with OC who have performance status challenges does not yet exist. There are several excellent assessments under study for breast and other solid tumors that may lend themselves to this unique population, but prospective study is imperative to remove the guess work from assessing a patient’s fitness for surgery.

WHICH CHEMOTHERAPY FOR ADVANCED OC IN THE ELDERLY?
There is a lack of prospective data from clinical trials of chemotherapy tolerance in elderly patients; most published reports are retrospective series or secondary analyses of large clinical trials carried out in a healthier, younger population. Nonetheless, from these reviews, several strategies have been described to improve the tolerability of the first-line treatment, including single-agent carboplatin, low-dose weekly schedules, and baseline dose reductions. The goal of each of these strategies is to reduce toxicity while maintaining efficacy.

First-Line Chemotherapy
In 1997, the GINECO group in France launched a dedicated elderly women ovarian cancer (EOC) program. Between 1998 and 2003, two prospective studies were conducted to assess the tolerability of the current standard platinum-based chemotherapy regimens. In both studies, the selected population comprised elderly patients 70 and older, with liberal inclusion criteria, and a baseline geriatric assessment (GA) was performed. In the first study (EOC 1), 83 patients (median age 76) with stage III/IV OC received carboplatin (AUC 5) and cyclophosphamide (600 mg/m²) on day one every 28–day (CC) combination for six cycles. The rate of the completion of all six cycles of the CC regimen was 72% with minimal toxicities. Moreover, GA predicted toxicity and overall survival. In the multivariate analysis, three factors appeared to have a prognostic value of toxicity: symptoms of depression at baseline (p = 0.006), dependence (p = 0.048), and performance status ≥ 2 (p = 0.026). Independent prognostic factors identified for overall survival (OS) (Cox model) were depression (p = 0.003), FIGO stage IV (p = 0.007), and more than six medications per day (p = 0.043). The second study (EOC 2) assessed the feasibility of carboplatin (AUC 5) with paclitaxel (175 mg/m²) (CP) once every three weeks for six cycles in 75 elderly patients. The feasibility of the CP regimen was 68%.

These two studies were pooled in a retrospective multivariate analysis (EOC 1+2) to assess predictive factors of survival. Tables 1 and 2 summarize the main patient characteristics and toxicities in the two studies. Patients in the EOC 2 appeared to be younger with better performance status (PS) than those in the EOC 1, indicating a selection bias due to concern that CP regimen could be associated with a higher toxicity. CP regimen had more hematologic (grade 3–4) toxicity (Table 2). Surprisingly, despite a higher proportion of patients with optimal CRS (< 1 cm residual disease) in the CP regimen (40% compared with 21%), the survival curves were similar. Predictive factors of poor prognosis were advanced age, depression symptoms at

### Table 1. Patients and Disease Characteristics in the EOC 1 and EOC 2 Studies

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>CC Group</th>
<th>CP Group</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Total n (%)</td>
<td>83 (100)</td>
<td>72 (100)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>76</td>
<td>75</td>
<td>0.4</td>
</tr>
<tr>
<td>Range</td>
<td>70–90</td>
<td>70–89</td>
<td></td>
</tr>
<tr>
<td>Performance status n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>47 (56)</td>
<td>53 (74)</td>
<td>0.08</td>
</tr>
<tr>
<td>2–3</td>
<td>36 (44)</td>
<td>19 (26)</td>
<td></td>
</tr>
<tr>
<td>Ascitis n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIGO initial stage n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>62 (76)</td>
<td>56 (78)</td>
<td>0.7</td>
</tr>
<tr>
<td>IV</td>
<td>20 (24)</td>
<td>16 (22)</td>
<td></td>
</tr>
<tr>
<td>Histological grade n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9 (11)</td>
<td>6 (8)</td>
<td></td>
</tr>
<tr>
<td>2–3</td>
<td>37 (44)</td>
<td>36 (50)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>37 (45)</td>
<td>40 (42)</td>
<td>0.4</td>
</tr>
<tr>
<td>Histological subtype</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous papillary</td>
<td>61 (73)</td>
<td>52 (71)</td>
<td>0.9</td>
</tr>
<tr>
<td>Optima initial surgery (size of residual lesions) n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10 mm</td>
<td>17 (21)</td>
<td>29 (41)</td>
<td>0.03</td>
</tr>
<tr>
<td>≥ 10 mm</td>
<td>65 (79)</td>
<td>42 (59)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CC, carboplatin and cyclophosphamide; CP, carboplatin and paclitaxel; FIGO, International Federation of Gynecology and Obstetrics.

### Table 2. Incidence of Severe Toxicities in the CC and CP Regimens (Percentage of Patients with Toxicities)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>EOC 1 (CC regimen)</th>
<th>EOC 2 (CP regimen)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia (&lt; 50 × 10^5/L)</td>
<td>39.5%</td>
<td>9.7%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Neutropenia grade 3–4</td>
<td>8.1%</td>
<td>53%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>3.5%</td>
<td>8.3%</td>
<td>0.4</td>
</tr>
<tr>
<td>Anemia grade 3–4</td>
<td>10.5%</td>
<td>5.5%</td>
<td>0.2</td>
</tr>
<tr>
<td>Alopecia</td>
<td>16.3%</td>
<td>92.9%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Neuropathy grade 3</td>
<td>0</td>
<td>13.9%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Abbreviations: EOC, elderly women ovarian cancer; CC, carboplatin and cyclophosphamide; CP, carboplatin and paclitaxel.
baseline, and FIGO stage IV. The use of paclitaxel was found to be an independent factor for poor survival (hazard ratio (HR) = 2.42, p = 0.001).

The MITO-5 (Multicenter Italian Trial in Ovarian cancer) phase II study assessed the tolerability of a weekly combination of carboplatin (AUC 2) plus paclitaxel (60 mg/m$^2$) on days one, eight, 15, every four weeks for six cycles in a small trial of 26 vulnerable patients 70 and older with stage IC to IV. In this study, 54% patients had two and more comorbidities and high functional dependency (ADL: 31%, IADL: 69%). RECIST response rate was 38.5% and median overall survival was 32.0 months. Toxicity was low with 23 patients (89%) treated without any defined-unacceptable toxicity (primary study end point). A weekly schedule of paclitaxel may be a good alternative.

A large retrospective analysis reported the outcome and toxicity differences seen in the 620 patients older than 70 who were enrolled in the GOG 182 phase III trial studying triplet-chemotherapy regimens for patients with newly diagnosed OC. Older patients had poorer performance status, lower completion rates of all eight chemotherapy cycles, and increased toxicities, particularly grade 3+ neutropenia and grade 2+ neuropathy. Older women had significantly shorter overall survival (37 vs. 45 months, p < 0.001), consistent across all regimens and adjusted for major prognostic factors. To address this disparity, a prospective study (GOG273) restricted to patients older than 70 with newly diagnosed stage III to IV OC is underway and near completion. Physicians select one of two treatment regimens: carboplatin (AUC5) single agent or carboplatin (AUC5) with paclitaxel (135 mg/m$^2$). Pharmacokinetics, geriatric variables, tolerability, and outcomes will be collected.

Neoadjuvant Chemotherapy (NACT)

NACT is the delivery of chemotherapy before a CRS. NACT use is gaining popularity in both the United States and Europe, particularly for older and frail patients. By shrinking cancer before surgery, several reports suggest that NACT increases the chance of an optimal CRS (defined as < 1 cm disease postsurgery) with less surgical morbidity and no significant effect on survival. The only prospective randomized study of NACT versus primary CRS followed by adjuvant chemotherapy was recently published from the European Organization for Research and Treatment of Cancer (EORTC). The 632 patients with newly diagnosed stage IIIc or IV epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer were randomized to either primary CRS followed by six cycles of platinum-based chemotherapy or to three cycles of NACT platinum-based followed by an iCRS followed by an additional three cycles of platinum-based chemotherapy. The two cohorts had similar baseline characteristics (age, performance status, histology type, grade, and stage). The median age was 62 years in the primary surgery group and 63 years in the NACT group. No subgroup analysis was reported based on older age. NACT was not inferior to primary surgery; the median overall survival was 29 months in the primary debulking group and 30 months in those assigned to NACT. Although outcomes were equivalent, the median survival in each arm was relatively short suggesting that the trial may have selected for a poor prognostic group of patients. The authors found that one of the main predictors of survival was no gross residual disease and so the question of NACT versus primary CRS remains controversial as pertains to those patients for whom no gross residual disease is a reasonable expectation.

Elderly women, particularly those with high comorbidities and frailty, are at highest risk of surgical morbidity and may be the most appropriate candidates for NACT. In one retrospective study, Glasgow and colleagues compared the outcomes of 104 women 70 years or older with advanced ovarian cancer who received NACT followed by iCRS (42 patients) and those who underwent primary surgery followed by platinum-based chemotherapy (62 patients). Age and comorbidity were similar in the two groups. Functional status or geriatric assessment variables were not reported. Compared with the primary surgery cohort, women who underwent NACT were more likely to have stage IV disease (57% vs. 29%, respectively), serous histology (74% vs. 53%, respectively) and no visible residual disease after surgery (71% vs. 28%, respectively). Patients who received NACT had reduced perioperative morbidity compared with the primary surgery group, including less blood loss at surgery, fewer small bowel resections required (0% vs. 15%, respectively), fewer thromboembolic events (0% vs. 10%, respectively), and fewer hospital days (6.5 days vs. 11.7 days, respectively). Although the primary surgery group had a higher survival, there was no statistically significant difference reported: NACT compared with primary surgery PFS (25 vs. 19 months, respectively; p = 0.08) or overall survival (25 vs. 39 months, respectively; p = 0.09). This study, although small and single center, reinforces the finding that NACT followed by interval CRS does appear less complicated by morbidity. However, the non-significant trend toward increased progression free and overall survival among those patients who underwent primary CRS, even among an elderly population, continues the controversy surrounding the best treatment modality for these patients.

Guidelines are necessary to determine which patients are most suitable candidates for NACT. Aletti identified a high-risk group of women who do not appear to benefit from primary surgery, and this may be a suitable group of women best served with a NACT approach. Risk features include stage IV disease, high initial tumor distribution, poor performance status (ASA score ≥ 3), poor nutritional status (albumin < 3.0g/dL), and age older than 75 years. Although each patient plan must be individualized, these criteria are reasonable to use as guidelines for a NACT approach.

Intraperitoneal Chemotherapy

Cisplatin-based intraperitoneal (IP) chemotherapy has a demonstrated significant survival benefit for patients with an optimal CRS for stage III OC and is a standard of care at many U.S. cancer centers. Despite growing acceptance of its superior survival advantages, several concerns remain:
technical difficulties (IP catheter placement and complications), and increased toxicities (renal dysfunction, neuropathy, hearing loss). In GOG 172, 39% of the 205 women who received IP cisplatin-paclitaxel were elderly: 26% (61 to 70 years), 12% (71 to 80) and 1% (older than 80).41 Their functional status was good (92%, GOG performance status 0 to 1). Regardless of age, less than 50% of all patients were able to complete four or more cycles of the IP regimen because of toxicity.

How does an oncologist apply these results to their older population? First, the major limitation to the study was that patients received IP cisplatin. By the age of 70, renal function may have declined by as much as 40%, and this reduction in glomerular filtration rate (GFR) may lead to enhanced toxicity of drugs, particularly those with significant renal excretion, such as cisplatin. On GOG172, patients were required to have a serum creatinine < 1.2 mg/dL; however, creatinine clearance is a more sensitive marker for renal dysfunction and should be used.42 The second limitation was the use of paclitaxel, as its drug clearance declines with age and its toxicities such as neuropathy and cytopenias heightens.43 Even with the overall survival benefit demonstrated with intraperitoneal therapy, widespread adoption of this modality has been slow secondary to the limitations discussed. Studies of modified GOG 172 regimens are ongoing including those which eliminate the day 8 intraperitoneal paclitaxel, substitute intraperitoneal carboplatin for cisplatin, substitute intravenous docetaxel for paclitaxel and incorporating all intravenous weekly paclitaxel with intraperitoneal cisplatin. Such modifications may maintain the survival benefit and lessen the toxicity of intraperitoneal therapy.

Two studies have reported on the tolerability of a modified IP regimen in an older patient population with good PS and low comorbidity.44,45 Both retrospective studies concluded that the older patients were less likely to complete all planned cycles of IP and to require more dose modification, but they had similar survival and toxicity outcomes. Reasons for the higher discontinuation rate of IP therapy among the elderly was not clear as toxicity outcomes were similar. The authors suggested that earlier development of toxicities among the elderly IP patients may account for the observed rate of discontinuation.45 If IP chemotherapy is offered as an option to older women, one needs to carefully select patients with good functional status, adequate kidney and hearing function, and an understanding that toxicities may arise earlier in the course of treatment as compared with IV chemotherapy alone.

Chemotherapy for Recurrent Disease

Treatment for recurrent OC is divided into relapse at ≤ 6 months since last platinum-containing chemotherapy administration, as platinum “resistant” and > 6 months as platinum “sensitive.” For platinum-sensitive patients, trials show survival advantage to a doublet-combination with carboplatin and either paclitaxel, liposomal doxorubicin, or gemcitabine.46,47 The combination of carboplatin and paclitaxel (CALYPSO Study) was significantly associated with a higher incidence of neurologic toxicity (neuropathy > grade 2) among patients older than 70 years (25% compared with 16%, respectively; p = 0.006). Although the proportion of older patients comprised only 16% (median age 73 years) of the study population, the prevention of severe neurologic toxicity would advocate for the use of pegylated liposomal doxorubicin rather than paclitaxel in elderly women.

For platinum-resistant disease, chemotherapy is typically given as single agent and responses range from 10% to 25% with a median duration from four to eight months. Common options include liposomal doxorubicin, topotecan, gemcitabine, weekly paclitaxel and vinorelbine.48 Unfortunately, few studies have been reported in older patients with OC. Based on extensive studies from lung and breast cancer in older patients, most of these single-agent drugs are well-tolerated.49,50 Gronlund and colleagues described their experience with topotecan (1 mg/m² over five days) in 57 elderly patients with platinum-resistant OC and found no significant differences in toxicity profile or response between an older (older than age 65) or younger (younger than 65) cohort. Performance status was a better predictor of response and survival in both cohorts.51 Currently, most oncologists use liposomal doxorubicin or weekly topotecan for older patients with platinum-resistance, given an improved toxicity profile.52,53 Recent data are showing support for antivascular strategies such as bevacizumab. Hypertension and arterial thrombosis risk may be heightened in an elderly patient with more comorbidities. Previously reported high bowel perforation rates (as high as 11%) have been greatly diminished with recent data from a prospective phase III trial demonstrating a 2.8% rate of perforation among those treated with bevacizumab as compared to 1.2% in those treated without. Age was not mentioned as a risk for bowel perforation in this study.54

Because these chemotherapy options offer primarily palliation, many argue for a focus on better supportive measures, rather than more chemotherapy. In one study, there was a significant cost difference with no appreciable improvement in survival in a comparison of patients with OC treated aggressively with chemotherapy with those enrolled in hospice at the final months of their life. The authors suggest that earlier hospice enrollment is beneficial, particularly in the older frail patients with a poor prognosis.55

IMPACT OF GA IN TREATMENT, CLINICAL OUTCOMES

Although fit and healthy patients up to age 70 may tolerate standard chemotherapy well, patients over age 75 or those with vulnerability criteria are at a higher risk of complication from chemotherapy. A GA provides a patient’s functional status (i.e., ability to live independently at home and in the community), comorbid medical conditions, cognition, psychologic status, social functioning-support, and nutritional status. In the cancer setting, several studies have demonstrated the predictive value of GA for estimating the risk of
severe toxicity from chemotherapy and survival outcomes.\textsuperscript{56,57}

In elderly patients with OC, the importance of the GA has been outlined in the EOC 1 and 2 studies, as previously discussed. However, a comprehensive GA can be time-consuming; there is clearly a need for simple and short screening questionnaires. Two examples of shorter surveys include the Vulnerable Elders Survey-13 (VES-13) and the Cancer and Aging Research Group (CARG) Geriatric Assessment and Toxicity Score. VES-13 is a self-administered survey that consists of one question for age and 12 additional questions assessing self-rated health, functional capacity, and physical performance.\textsuperscript{58} CARG-GA is a feasible assessment (mean time to completion is 27 minutes, mostly self-administered) and the shorter toxicity score predicted grade 3 to 5 chemotherapy toxicity.\textsuperscript{59} The 11-point toxicity score accounts for high-risk factors: 1) age 72 and older, 2) cancer type (GI or GU), 3) standard chemotherapy dosing, 4) polychemotherapy regimens, 5) anemia, 6) renal dysfunction (CrCl < 34 mL/min), 7) decreased hearing, 8) falls in last six months, 9) assistance with taking medication (IADL), 10) limited walking one block (MOS), and 11) decreased social activity (medical outcomes study [MOS]). A score ranging from 0 to 23 can be tabulated and used to identify patients at greatest risk of high chemotherapy toxicity.

A prospective phase II study (EOC 3)\textsuperscript{60} confirms the importance of geriatric assessment. From 2007 to 2010, 111 elderly patients (70 years and older) with stage III to IV OC were treated with first-line carboplatin (AUC5) every three weeks for six cycles. The cohort was frail and older than most reported studies. Median age was 78 (41% older than 80), 43% had PS ≥ 2, 27% had ≥ 3 major comorbidities, 69% ≥ 4 co-medications, ADL score < 6 in 55%, IADL score < 25 in 75%, and HADS (Hospital Anxiety and Depression Scale) ≥ 15 in 37% of patients. The chemotherapy completion rate was 74%; toxicities were manageable. The median survival was 17.4 months (95% CI, 13.3 to 21.4). The authors identified six prognostic factors of poorer survival: low albumin (<35 g/L), low ADL score (<6), low IADL score (<25), lymphopenia (<1G/L) and a high HADS score (>14). Based on these predictive factors, the authors developed a scoring system. The Geriatric Vulnerability Score (GVS) was validated on a bootstrap analysis to predict survival, both in the EOC 2 and EOC 3 studies.\textsuperscript{19,60} With a cutoff of three, the number of factors identified two groups of patients with different prognostic outcomes and tolerance to chemotherapy. Indeed, patients with a GVS score ≥ three had a worse OS (11.5 months vs. 21.7 months, respectively; HR, 2.94; p < 10 – 4); experienced a lower rate of chemotherapy completion (65% compared with 82%, respectively); odd ratio (OR) = 0.41; p = 0.04; a higher incidence of severe adverse events (53% compared with 29%, respectively; OR = 2.8; p = 0.009); and higher incidence of unplanned hospitalization (53% compared with 30%, respectively; OR = 2.6, p = 0.02). The use of GVS score appears helpful in selecting those at greatest risk; validation studies with larger cohorts are needed.

CONCLUSION

Identification of vulnerable elderly patients is crucial to overcome inter-individual variability in surgery and chemotherapy tolerance and, therefore, efficacy. To improve treatment guidelines, more clinical trials specifically designed for older patients should be implemented. In addition, enhanced cooperation between geriatricians, medical oncologists, and gynecologic oncologic surgeons will improve pre-treatment assessment and post-treatment care in our elderly patients.

Disclosures of Potential Conflicts of Interest

The author(s) indicated no potential conflicts of interest.

References


