The vaginal radical trachelectomy: An update of a series of 125 cases and 106 pregnancies

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ARTICLE INFO

Article history:
Received 3 November 2010
Available online 20 January 2011

Keywords:
Radical trachelectomy
Fertility preservation
Cervical cancer
Obstetrical outcome

ABSTRACT

Objective. To review our first consecutive 125 vaginal radical trachelectomies (VRT) to assess the oncologic, fertility and obstetrical outcomes.

Methods. Data from our prospective database was used to identify all VRT planned between October 1991 to March 2010 in patients with early-stage cervical cancer (stages IA, IB and IIA). Chi-square test, Fisher’s exact test and Student t-test were used to compare baseline characteristics and Kaplan–Meier survival curves were constructed and compared with the use of the log-rank test.

Results. During the study period, 140 VRT were planned and 125 were performed. The median age of the patients was 31 and 75% were nulliparous. The majority of the lesions were stage IA2 (21%) or IB1 (69%) and 41% were grade 1. In terms of histology, 56% were squamous and 37% were adenocarcinomas. Vascular space invasion was present in 29% of cases, and 88.5% of the lesions measured ≤ 2 cm. The mean follow-up was 93 months (range: 4–225 months). There were 6 recurrences (4.8%) and 2 deaths (1.6%) following VRT. The actuarial 5-year recurrence-free survival was 95.8% [95% CI: 0.90–0.98], whereas it was 79% [95% CI: 0.49–0.93] in the group where the VRT was abandoned (p = 0.001). Higher tumor grade, LVSIs and size > 2 cm appeared to be predictive of the risk of abandoning VRT (p = 0.001, p = 0.025 and p = 0.03 respectively). Tumor size > 2 cm was statistically significantly associated with a higher risk of recurrence (p = 0.001). In terms of obstetrical outcome, 58 women conceived a total of 106 pregnancies. The first and second trimester miscarriage rates were 20% and 3% respectively, and 77 (73%) of the pregnancies reached the third trimester, of which 58 (75%) were delivered at term. Overall, 15 (13.5%) patients experienced fertility problems, 40% of which were due to cervical factor. Twice (80%) were able to conceive, the majority with assisted reproductive technologies.

Conclusion. VRT is an oncologically safe procedure in well-selected patients with early-stage disease. Lesion size > 2 cm appears to be associated with a higher risk of recurrence and a higher risk of abandoning the planned VRT. Fertility and obstetrical outcomes post VRT are excellent.

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Introduction

With childbearing being one of the most important goals in life, fertility preservation has become a very important component of the overall quality of life of young cancer survivors. Neglected for a long time, the issue of fertility preservation is receiving more attention and is now studied in a more comprehensive way. In 2006, the American Cancer Society has made recommendations to encourage physicians to discuss fertility issues in reproductive age cancer patients prior to initiating cancer treatments [1]. The psychosocial impact of cancer-related infertility in women treated for gynecologic malignancies is significant with a high proportion of these women experiencing feelings of depression, grief, stress and sexual dysfunction [2,3]. Recent data confirms that the emotional and physical impact of impaired or loss of fertility can be long lasting [4].

The most common cancers in women aged less than 40 are breast cancer, melanoma, cervical cancer, non-Hodgkin’s lymphoma and leukemia [5]. According to the SEER data, up to 42% of all cervical cancers are diagnosed in women prior to the age of 45 [6]. Data from the Sloan-Kettering indicate that up to 40% of women who have undergone a radical hysterectomy at their center would have been eligible for a radical trachelectomy [7]. Therefore, particularly in countries where cervical cancer screening is in place, a significant proportion of cervical cancer is diagnosed at an early stage, frequently in women aged less than 40, such that a significant proportion of these patients may be interested in a treatment modality that preserves fertility without jeopardizing oncologic outcome.

The radical trachelectomy is now an accepted treatment modality for the surgical management of early-stage cervical cancer in women wishing to preserve fertility. The oncologic and obstetrical results that have accumulated over the last 2 decades have confirmed a recurrence rate <5% and promising obstetrical results [8].

We have previously reported our oncologic and obstetrical results in our first 72 patients and our first 50 pregnancies [9,10]. We now
Material and methods

This is a prospective series of 140 consecutive planned vaginal radical trachelectomies in women with a diagnosis of early-stage cervical cancer wishing to preserve their fertility potential over an 18-year period, from October 1991 to March 2010. All records were kept prospectively in a computerized database. The technique of the vaginal radical trachelectomy has been described thoroughly elsewhere [11].

All patients were aware that the trachelectomy procedure could be abandoned if metastatic nodes were identified at laparoscopy or if more extensive endocervical tumor spread was discovered at the time of surgery (in which case a vaginal radical hysterectomy or Schauta operation was performed). Thus, a fully informed and signed consent obtained from each patient. Thorough review of the surgical complications was conducted and detailed oncologic outcome and obstetrical information were obtained from patients and referring physicians. A detailed gynecological and colposcopic evaluation was performed to determine the size of the lesion, the presence or absence of visible residual disease and the degree of endocervical extension. A pelvic MRI was not systematically obtained in the early years of the series but was performed systematically later on.

A complete obstetrical history was obtained to identify patients with potential underlying infertility problems although the procedure was not denied to patients with a history of infertility. Infertility work-up to document fertility potential was not required prior to the procedure. Patients were arbitrarily advised to wait 6 to 12 months after the trachelectomy procedure before attempting to conceive, although this is purely arbitrary. Pregnant women were followed either by their general obstetrician or by a maternal–fetal medicine consultant and were asked to keep us informed of the pregnancy management and evolution. Perinatal information was obtained via chart review and telephone calls to patients and their obstetricians when possible. Pregnancy management was not uniform because patients were followed by a wide variety of obstetricians and high-risk consultants. Thus, management and timing of the delivery was left at the discretion of the treating obstetrician. All patients were delivered by cesarean section.

Statistical analysis

The baseline characteristics were compared using Chi-square test or Fisher exact test for categorical variables and Student t-test for continuous variables. The primary end points were recurrence-free survival and disease-specific survival. Recurrence-free survival was calculated from the date of surgery to the date of the evidence of recurrence or the last available follow-up visit. Disease-specific survival was calculated from the date of surgery to the date of death from cancer or the last available follow-up visit. Kaplan–Meier survival curves were constructed and compared with the use of the log-rank test. All tests were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed using the STATA version 10 software (Stata Corp., College Station, Tx).

Results

Patients and tumor characteristics

A VRT was offered to 140 women with early-stage cervical cancer during an 18-year period but the procedure was actually performed in 125 (89%). The median age was 31 (range: 20–42). Table 1 summarizes tumor characteristics, with comparison between patients who had the planned trachelectomy and patients who did not. The majority of patients (69%) had stage IB1 disease and 21% had stage IA2 disease. Only 7 patients (5%) had stage IA1 disease but all had vascular space invasion, and 3 had stage IIA (2%). Overall, 41% of the lesions were grade 1.

In terms of histology, the majority of patients had squamous cell carcinoma (56%), the others had adenosquamous lesions (37%) or adenosquamous lesions (7%). There was one small cell neuroendocrine subtype diagnosed on final pathology and 3 glasy cell tumors all of which were classified as adenosquamicomas for analysis. In terms of lesions size, 124 patients (88.5%) had lesions measuring 2 cm or less and 16 patients had lesions measuring more than 2 cm (11.5%). Lymphovascular space invasion (LVI) was present in 40 cases (29%). The diagnosis of cancer was established by conisation or LEEP in 99 patients (71%) and by cervical biopsy alone in 41 patients (29%). A total of 78 patients (62%) had no evidence of residual disease on the trachelectomy specimen (or only foci of residual low grade or high grade lesions). This is not surprising considering that 73% of VRT patients had either a cone or a LEEP as a diagnostic procedure.

An average of 26 pelvic nodes (range: 6–107) was obtained at surgery. The mean blood loss was 215 mL (range: 25–1200 mL) and the mean operating time was 236 min (range: 100–455). The average hospital stay was 3.5 days (range: 1–9).

Complications of the VRT

Intraoperative complications occurred in 7 cases (5.6%) (Table 2). Three were vascular injuries directly related to the laparoscopic lymphadenectomy. Two required a laparotomy for repair early in the series and the third one was repaired by laparoscopy. There was one trauma to the superficial epigastric artery at the time of trocar insertion which was controlled by extrinsic compression with an inflated Foley catheter balloon. There were also 3 complications related to the trachelectomy itself including 2 cystotomies both immediately repaired vaginally and one patient required a laparotomy for uncontrollable bleeding from the parametarial area. Of note, only 2 patients required blood transfusion and there were no ureteral injuries.

Table 1

<table>
<thead>
<tr>
<th>Tumor characteristics</th>
<th>Total (n=140)</th>
<th>VRT (n=125)</th>
<th>No VRT (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA1 with VSI</td>
<td>7 (5%)</td>
<td>7 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>IA2</td>
<td>30 (21%)</td>
<td>29 (23%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>IB1</td>
<td>97 (69%)</td>
<td>85 (68%)</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>IB2</td>
<td>3 (2%)</td>
<td>2 (2%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>IIA</td>
<td>3 (2%)</td>
<td>2 (2%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>10 (7%)</td>
<td>3 (2%)</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>78 (56%)</td>
<td>69 (55%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>52 (37%)</td>
<td>48 (39%)</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>10 (7%)</td>
<td>8 (6%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Size</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2 cm</td>
<td>121 (86%)</td>
<td>111 (89%)</td>
<td>10 (66%)</td>
</tr>
<tr>
<td>&gt; 2 cm</td>
<td>19 (14%)</td>
<td>14 (11%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>LVSI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>100 (71%)</td>
<td>93 (74%)</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>Yes</td>
<td>40 (29%)</td>
<td>32 (26%)</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy alone</td>
<td>41 (29%)</td>
<td>34 (27%)</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>Cone or LEEP</td>
<td>99 (71%)</td>
<td>91 (73%)</td>
<td>8 (53%)</td>
</tr>
</tbody>
</table>

LVSI: lymphovascular space invasion.
Postoperative complications are summarized in Table 2. Most were related to delayed return of bladder function requiring self-catheterization (16%), to urinary tract infection (8%) and to vulvar hematoma/edema (7%) from skin trauma secondary to the retraction at the time of surgery. The majority of patients who had bladder dysfunction required self-catheterization for less than 2 weeks, except in 4 patients where it lasted longer before normalizing. Four patients (3%) also developed suprapubic hematomas. Ten patients (8%) developed lymphocele but only 3 required percutaneous drainage (3%) also developed suprapubic hematomas. Ten patients (8%) developed vulvar edema (7%) from skin trauma secondary to the retraction at the time of surgery. The majority of patients who had bladder dysfunction required self-catheterization for less than 2 weeks, except 3 patients where it lasted longer before normalizing. Four patients (2%) developed postoperative pelvic abscess successfully managed conservatively with intravenous antibiotics.

### Oncologic outcome

#### Abandoned VRT

Since our last publication [9], only 5 more VRT have been abandoned, for a total of 15/140 (11%). As seen in Table 1, there were statistically more grade 3 tumors (p = 0.001), presence of LVI (p = 0.025) and lesion size > 2 cm (p = 0.005) in the group of patients where the 15 abandoned VRT cases were previously reported and include a patient with a stage IIA grade 3 squamous lesion who recurred in the parametria 18 months later, failed radiation therapy and rapidly developed lung metastasis and died of disease despite palliative chemotherapy.

- The second was a patient with a small cell neuroendocrine tumor discovered on final pathology. Despite aggressive adjuvant chemotherapy, she rapidly developed widespread metastatic disease and died of disease.
- The third recurrence was unusual in that the patient recurred in the mesocolon 15 months post VRT. She underwent a bowel resection which confirmed the same histopathology as her cervix cancer (adenosquamous). She received adjuvant radiation therapy and is without evidence of disease.
- The fourth patient had a stage IIB1 adenocarcinoma measuring 1.5 cm. She had a close margin on final pathology and chose to be followed conservatively. She developed a recurrence on the residual cervix 3 years post VRT. She underwent a radical hysterectomy followed by a combination of chemo-radiation. She is alive and well since.
- The fifth patient had a 1.5 cm squamous cancer with no evidence of residual disease on the trachelectomy specimen. She developed a 2 cm parametrial recurrence 6 years post VRT despite regular normal follow-ups. Unfortunately the recurrence was diagnosed precisely as the patient was found to be pregnant (6 weeks). She underwent a laparoscopic staging of paraaortic nodes and an elective abortion followed by chemo-radiation. She is alive and well 2 years later.
- The last recurrence was recently diagnosed in a young 21 year-old woman with a rapidly growing adenocarcinoma. The lesion measured 2.5 cm but was strictly exophytic on pelvic examination and MRI. The lymph nodes were negative and the margins on final pathology were free by 12 mm. A recurrence was documented 9 months later in the left parametria, while her cervical lesion was exclusively located on the right side of the cervix on MRI. She underwent a laparoscopic ovarian transposition followed by chemo-radiation. She had a complete response based on clinical examination and follow-up MRI. Of note, her HPV-DNA was positive at the time of recurrence.

As can be seen in Table 3, 3 of the 6 recurrences occurred in patients with lesions measuring > 2 cm. Size of the lesion > 2 cm was statistically associated with a higher risk of recurrence (p = 0.002). LVI was present in only one patient with cancer recurrence. Univariate analysis did not demonstrate a relationship between recurrence and other tumor characteristics such as histology, grade and LVI.
Conversely, one patient was found to have a micrometastasis in one of her sentinel nodes on frozen section, so the VRT was abandoned. On final pathology, the micrometastasis turned out to be a benign naevus and thus considered a false positive of the frozen section. The patient was reoperated and the VRT was completed successfully.

**Tight margin on final pathology**

A total of 11 patients (9%) had a free endocervical margin less than 5 mm on final pathology. Only one recurred and the recurrence was on her residual cervix. Five patients underwent a secondary LEEP or cone, either at the time of the VRT or as a subsequent procedure. Four were completely pathologically negative and one had residual disease cleared by 5.5 mm.

**Neoadjuvant chemotherapy (NACT)**

A total of 4 patients have received neoadjuvant chemotherapy prior to VRT. All had lesions measuring >3 cm. Three received a combination of Taxol–Ifosfamide–Platinum and were previously reported [12] and one received Gemcitabine and Cisplatin. None of the patients have recurred.

**Adjunctive hysterectomy**

A total of 6 patients (4.8%) elected to have a subsequent hysterectomy in the absence of an oncologic indication for the following reasons: rapidly enlarging fibroid (15 cm), recurrent infection possibly related to the cerclage, cancer phobia, menorrhagia associated with uterine fibroids, symptomatic endometriosis and choice of the patient at the time of cesarean section. None of the hysterectomy specimen contained residual cancer.

**Obstetrical outcome**

The majority of women were nulliparous (75%), 20% had one previous child and 5% had more than one child prior to the trachelectomy procedure. A total of 58 women conceived a total of 106 pregnancies. Our obstetrical results are consistent with those of our previous report on 50 pregnancies [10].

Of the 58 women who conceived post VRT, 30 had one pregnancy (52%), 16 had 2 pregnancies (28%), 5 had 3 pregnancies (9%), 6 had 4 pregnancies (10%) and one had 5 pregnancies (2%). The latter patient had 4 consecutive first trimester miscarriages before finally having a successful pregnancy with the help of progesterone support in the first trimester.

**First trimester**

A total of 21 pregnancies (20%) had a first trimester miscarriage. All patients either miscarried spontaneously or were managed successfully with misoprostol (Cytotec, Pharmacia) with or without curettage. In addition, 4 women elected to undergo pregnancy termination, including the patient who was diagnosed with a cancer recurrence at the time of pregnancy (Table 4).

**Second trimester**

Only 3 patients (3%) had a second trimester loss, all reported in our previous publication [10]. One patient chose to terminate her pregnancy at 16 weeks for social reasons.

**Third trimester**

A total of 77 pregnancies (73%) reached the third trimester (Table 4). As can be seen, only 4 women (4%) delivered with significant prematurity (<32 weeks), where most of the neonatal morbidity and mortality occurs. Another 14% of patients delivered with milder degree of prematurity, between 28 and 36 completed weeks, and the vast majority of patients (55%) delivered at term (>37 weeks) by elective cesarean section. So, of the 77 women who reached the third trimester, 58 (75%) delivered at term. One woman...
Table 4
Obstetrical outcome (n = 106).

<table>
<thead>
<tr>
<th>Event</th>
<th>N</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester miscarriage</td>
<td>21</td>
<td>20%</td>
</tr>
<tr>
<td>Second trimester miscarriage</td>
<td>3</td>
<td>3%</td>
</tr>
<tr>
<td>Therapeutic abortions</td>
<td>5</td>
<td>4%</td>
</tr>
<tr>
<td>Third trimester deliveries</td>
<td>15</td>
<td>14%</td>
</tr>
<tr>
<td>24 to 31 6/7 weeks</td>
<td>4</td>
<td>4%</td>
</tr>
<tr>
<td>32 to 36 6/7 weeks</td>
<td>15</td>
<td>14%</td>
</tr>
<tr>
<td>&gt; 37 weeks</td>
<td>58</td>
<td>55%</td>
</tr>
</tbody>
</table>

Table 5
Infertility causes, fertility treatment and pregnancy outcome.

<table>
<thead>
<tr>
<th>Cause</th>
<th>N</th>
<th>Fertility treatments</th>
<th>Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical factor</td>
<td></td>
<td>Cervical dilatation and IVF</td>
<td>Yes</td>
</tr>
<tr>
<td>Cervical dilatation then conceived naturally</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Cervical dilatation and Smit sleeve then conceived naturally</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Cervical dilatation and Smit sleeve</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Cervical dilatation and Clomid/IUI</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Cervical dilatation and Smit sleeve and IVF*</td>
<td></td>
<td>Trying</td>
<td></td>
</tr>
<tr>
<td>Ovulatory dysfunction</td>
<td>3</td>
<td>IVF</td>
<td>Yes</td>
</tr>
<tr>
<td>Polycystic ovary</td>
<td>1</td>
<td>Clomid/IUI</td>
<td>Yes</td>
</tr>
<tr>
<td>Endometriosis</td>
<td>2</td>
<td>Conceived naturally</td>
<td>Yes</td>
</tr>
<tr>
<td>Tubal factor</td>
<td>1</td>
<td>Tubal permeation then conceived naturally</td>
<td>Yes</td>
</tr>
<tr>
<td>Unknown causes</td>
<td>2</td>
<td>Conceived naturally</td>
<td>Yes</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>IUI</td>
<td>Yes</td>
</tr>
</tbody>
</table>

IVF: in vitro fertilization.
IUI: intrauterine insemination.

Neonatal outcome

There were 4 neonatal deaths, including two from neonatal sepsis at 24 weeks and one at 31 weeks, and one from Trisomy-18 born at term. The first 3 were presented in our previous publication [10]. The other patient had an uneventful pregnancy until 24 weeks when she developed a rapidly progressing chorioamnionitis with rupture of the membranes and underwent rapid cesarean section. The baby was born alive but died within 24 h of Klebsiella sepsis. The mother also suffered a severe endometritis and wound infection. One patient with a twin pregnancy developed a twin–twin transfusion problem and had to be delivered prematurely at 31 weeks strictly for obstetrical reasons. Both twins survived and are doing well. Besides these 2 cases, all our patients have delivered at 33 weeks or beyond since our last publication.

Neoadjuvant chemotherapy (NACT)

A total of 4 patients have received neoadjuvant chemotherapy prior to VRT. Since our previous publication [12] none of the patients have recurred, and 3 have become pregnant; one patient had 2 successful deliveries at term, one patient had transient ovarian failure and cervical stenosis but got pregnant following cervical dilatation, use of Clomid and intrauterine insemination and delivered at 36 weeks. The third patient had been unable to conceive for years, and surprisingly conceived 3 months following an attempt at cervical dilatation. Unfortunately she miscarried at 8 weeks. The last patient has not been trying to conceive so far.

Cervical stenosis

A total of 15 patients (10%) have developed documented cervical stenosis post VRT but only 3 were symptomatic. One had cyclic dysmenorrhea and 2 developed hematometria. All had successful cervical dilatation under general anesthesia. In 3 patients a Smit sleeve was left in place to keep the cervix opened. One got pregnant naturally, one is trying to conceive with IVF and one will have a second attempt to be followed by IVF.

Fertility outcome

Excluding patients who recurred (6), those who received adjuvant treatment (3) and those who had a hysterectomy (5), a total of 15 patients out of the remaining 111 patients experienced some infertility problems (13.5%). Of those, 6 (40%) were due to cervical factor. As shown in Table 5, the other causes of infertility were unrelated to the VRT and were due to ovulatory factor, tubal factor, endometriosis, polycystic ovary and unknown causes. Two patients had two fertility problems (cervical stenosis and ovulatory dysfunction). Twelve patients (80%) have been able to conceive while one is undergoing fertility treatment.

Discussion

Oncologic outcome

We report one of the largest single institution series of vaginal radical trachelectomies. Compared to our previous report, tumor characteristics are largely unchanged except for a 4% increase in the proportion of adenocarcinomas, 8% more LVSI and 8% more stage IB1 (Table 1). Morbidity of the procedure remains low (5.7%) (Table 2) and compares favorably with data reported in other series [13–15].

Abandoned tracheectomy

The planned radical tracheectomy was abandoned intraoperatively in 15 cases (11%), most of the time because of the discovery of lymph node metastasis (60%) or more extensive endocervical extension (30%). The same rates have been reported in other series [13–15]. Interestingly, we found that grade 3, presence of LVSI and size of lesions >2 cm were predictive of the risk of abandoning the VRT, with a p value of 0.001, 0.025 and 0.005 respectively (Table 1).

Patients whose planned tracheectomy was abandoned were treated with adjuvant chemoradiation in most cases yet their outcome was statistically worse than patients who underwent the planned trachelectomy (5-year recurrence-free survival of 79% vs 96%, p = 0.001) (Fig. 1).

As such, in order to avoid unnecessary surgery, we believe that all efforts should be made to identify patients with metastatic disease or more extensive endocervical tumors by routinely performing a pelvic MRI preoperatively and by performing SLN mapping and intraoperative frozen section analysis to rule out the presence of lymph node metastasis. We acknowledge that frozen section analysis is not perfect and that in our series 36% of the micrometastasis were missed, but conversely 64% of the lymph node metastasis were correctly identified intraoperatively which spared those patients unnecessary surgery.

Recurrences

As stated above, 15 VRTs were abandoned, leaving 125 completed VRT for analysis. Contrary to other authors, we do not consider our series as an intent-to-treat study since this strategy of analysis is used for randomized controlled trial, and there is obviously no randomization in our series. Therefore we do not include in our recurrence rate analysis patients in whom the VRT was abandoned because of adverse features discovered intraoperatively. Conversely, patients who had the VRT performed and who were found postoperatively to have adverse features requiring adjuvant treatment are kept for analysis.
In the VRT group, the recurrence rate in our series was 4.8% and the death rate 1.6% for a 5-year recurrence free survival of 96% [95% CI: 0.90–0.98] (Fig. 1). Our data compare very favorably to that of the literature. Indeed, Gien et al. recently reviewed the literature on 600 cases and report an overall recurrence rate of 5.3% and death rate of 3.2% [16]. It is also reassuring that no differences in the recurrence rate were noted in 3 comparative studies comparing radical trachelectomy and radical hysterectomy [13,17,18].

Three of the 6 recurrences (50%) in the VRT group occurred in patients with lesions measuring >2 cm (Table 3). Size of lesions >2 cm was statistically associated with the risk of recurrence (p = 0.002). This association has been noted by others as well [13,14]. Tumor size >2 cm is also a risk factor for cancer recurrence in patients undergoing radical hysterectomy [13,17]. The presence of LVSIs alone as a risk factor is not considered an absolute contraindication for this procedure [9,14,19]. This issue is controversial and patients should still be informed of the higher risk of recurrence particularly when LVSIs are extensive [19,20]. However, in our series, LVSIs was not found to be associated with a higher risk of recurrence. Histology and grade did not seem to be separate risk factor for recurrence however small cell neuroendocrine tumors have clearly a more aggressive behavior requiring multimodality treatment [16,21,22]. Since the pattern of recurrence and spread is systemic, the choice of local treatment has probably very little impact on the overall outcome.

One patient recurred 6 years post VRT, emphasizing the need for careful and long-term follow-up. Ball et al. have had a similar experience [23]. It is unclear if these 2 cases truly represent a recurrence (considering the long delay and the numerous normal evaluations prior to the recurrence) or a second primary. The residual endocervical canal may represent an at-risk epithelium for a new HPV infection or reactivation of dormant HPV infection. Monitoring patients post-trachelectomy with HPV DNA testing may be an interesting avenue to explore.

One recurrence occurred in the residual cervix 3 years post VRT in a patient who had a suboptimal margin on the trachelectomy specimen and who chose to be followed conservatively, emphasizing the importance of careful follow-up in those patients. Conversely, 10 patients had a margin of <5 mm on the VRT specimen and none recurred but 5 had a secondary LEEP or cone procedure to ensure a safer margin. In Marchiole’s report, 2 patients with margins less than 5 mm refused to receive adjuvant treatment and none recurred [13]. In another series, one patient with <5 mm margin recurred in the corpus uteri 3 months after VRT and one patient developed an adenocarcinoma in situ 2 years post VRT, refused definitive treatment and developed an invasive cancer 10 months later [24]. The conservative follow-up of patients with suboptimal endocervical margins on final pathology requires careful individualized discussion with patients, weighing the potential higher risk of local recurrence vs the recommendation for adjuvant radiation therapy which usually leads to permanent loss of fertility. There may be a value of HPV DNA testing post trachelectomy in the follow-up of patients with suboptimal margins.

**Lymph node metastasis**

Overall, 14/140 patients were found to have lymph node metastasis (10%), of which 9 were diagnosed intraoperatively on frozen section (64%) and their VRT were abandoned, and 5 were missed on frozen section and diagnosed on final pathology (36%). Two of those patients received adjuvant chemoradiation and 3 elected to be followed conservatively. None of those 5 patients have recurred. The same observation has been reported by Marchiole et al. [13]. The numbers are too small to draw conclusions with regards to the safety of withholding adjuvant treatment in patients with microscopic lymph node metastasis.

The issue of the role or need for adjuvant treatment in patients with only one lymph node micrometastasis is controversial at this point. Since the presence of micrometastasis is considered a risk factor for recurrence, most authors recommend the use of adjuvant treatment usually in the form of adjuvant (chemo)-radiation, which unfortunately ruins fertility potential. In the future, the role of adjuvant chemotherapy alone should be further investigated in this group of patients, as it would offer systemic treatment while preserving fertility options in most patients.

**Frozen section of sentinel lymph node (SLN)**

As mentioned above, 36% of micrometastasis were missed on frozen section analysis. The low sensitivity of the frozen section analysis to detect micrometastasis has been reported by others. For instance, Fader et al. correctly identified micrometastasis on frozen section in only 33% of their cases [25]. It is hoped that in the future new molecular techniques will be implemented to improve the sensitivity of the frozen section analysis.

**Completion hysterectomy**

In our series, 6 patients (4.8%) chose to have an elective hysterectomy for a variety of non-oncologic reasons. None were found to have cancer in the residual cervix. The decision to perform a definitive hysterectomy once the family plans are completed is a matter of debate. There is no data to support that it should (or should not) be done. The issue has to be discussed with patients to offer individualized recommendations. We do not recommend routine hysterectomy while others propose a cesarean-hysterectomy to women who have completed their childbearing [26].

**Obstetrical outcome**

We report one of the largest series of pregnancies post VRT with 58 women conceiving 106 pregnancies. The majority (52%) had one pregnancy post VRT. 28% had 2 pregnancies, and 21% had 3 pregnancies or more. Our rate of first trimester and second trimester losses are 20% and 3% respectively, comparable to the rates reported in the general population, 5% of women elected to have pregnancy termination, including one in the second trimester, and 73% of the pregnancies reached the third trimester. Overall, 4% of all the pregnancies ended up with significant prematurity (<32 weeks), 14% with milder degree of prematurity (32–36.6 weeks) and 55% reached term (>37 weeks). However, of the 77 pregnancies who reached the third trimester, 58 (75%) delivered at term (Table 4). Those results compare very favorably with the literature [27,28].

Indeed, a recent review of the literature totaling 200 pregnancies by Jolley et al. indicates that 66% of pregnancies following radical trachelectomy ended up with a live birth, compared with 73% in our series [27]. Their reported preterm delivery rate (<37 weeks gestation) was in the range 20–30%, similar to ours at 18% [27,28]. However, about half ended with significant prematurity (<32 weeks) where most of the neonatal morbidity occurs, compared to only 4% in our series. Overall, 58 of the 106 pregnancies in our series (55%) culminated with the birth of a healthy newborn at term compared to 42% in Jolley’s series [27]. There were 3 neonatal deaths probably related to the VRT due to neonatal sepsis presumably from ascending chorioamnionitis at 24 and 31 weeks of gestation. The other death was unrelated to VRT and due to Trisomy-18.

Nevertheless, pregnancies post-VRT remain at higher risk of prematurity and complications. A specialist in maternal-fetal medicine should probably be involved early in the care of those patients [29]. Unfortunately, there are limited data and no definitive guidelines regarding the management of pregnancies following VRT and recommendations are often extrapolated from the obstetrical literature on premature labor and premature rupture of membranes secondary to incompetent cervix [27]. We and others do not recommend reduced physical activity unless there are signs of cervical shortening and recommend follow-up of cervical length
with serial ultrasounds [10,27,30] but do not recommend routine antibiotics or antenatal corticosteroids [27]. Others favor a more strict management [31]. In view of the short scarred cervix and the proximity of the uterine vessels, a vaginal delivery may be hazardous and a lateral cervical tear extending to the uterine arteries may be catastrophic. For those reasons, a planned low-transverse cesarean section is recommended at around 37–38 weeks of gestation. Others favor low midline classical cesarean section because of the potential risk of the transverse incision extending into the uterine vessels [32].

**Fertility outcome**

In our series, only 15% experiences fertility problems of which 40% were due to cervical stenosis. Luckily 80% of women were able to conceive most of the time with the help of assisted reproductive technologies (Table 5). Managing tight cervical stenosis with a nearly invisible cervical opening can be quite challenging. We have been successful in dilating the cervix under general anesthesia using tiny lacrimal probes and progressively dilating the cervical os enough to temporarily suture in place a Smith sleeve (plastic catheter used by radiation oncologists) to keep the cervical os opened while the patient prepares for intrauterine insemination or for embryo transfer following in vitro fertilization. Otherwise, the cervical os tends to stenose again quite rapidly. Others have used Malecot catheters successfully [33]. A thorough review of options available for the management of fertility-related issues has recently been published [34]. Managing infertility problems following fertility-preserving surgery is a real challenge [35]. This issue represents a major source of stress, anxiety and frustration for patients.

Besides the fertility issue, cervical stenosis, whether symptomatic or not, remains a significant problem post VRT as it makes follow-up pap smear evaluation suboptimal and very challenging and is a cause of significant patient distress. We believe the problem is under reported particularly when asymptomatic and we agree with Carter et al. that using a symptom diary at the time of follow-up visits would be very helpful [36].

**Neoadjuvant chemotherapy (NACT)**

Our data and that of others support the concept of NACT to chemoreduce the size of the lesion prior to proceeding with a fertility-preserving surgery [37–40]. We have treated 4 patients with NACT and none have recurred. Our experience indicates that even though there is some transient chemotherapy-induced ovarian failure, fertility outcome is not jeopardized. Indeed, of the 4 patients who received NACT, 3 conceived a total of 4 pregnancies, including 3 live births. The other had a first trimester miscarriage. Our last patient was treated with Carboplatin and Gemzar to avoid hair loss and reduce gonadotoxicity. Robova et al. recommend this approach for patients with lesions >2 cm or infiltrating >50% of the cervical stroma [40].

We think NACT followed by either a radical trachelectomy or conization is a better alternative than performing a radical trachelectomy upfront, because of the high likelihood of postoperative adjuvant radiation in light of the high-risk features on final pathology in patients with larger-size lesions. The experience of MSKCC reveals that performing the trachelectomy abdominally allows for the removal of wider parametrium compared to the vaginal approach [41]. However, in their series up to 46% of patients received adjuvant radiation therapy thus defeating the primary purpose of the trachelectomy which is to preserve fertility.

In addition, the radicality of the abdominal approach and non-preservation of the uterine arteries may reduce fertility compared to the vaginal approach. Obstetrical data post abdominal trachelectomy is limited compared with VRT [16], but in a recent series of 61 abdominal trachelectomy, the cumulative pregnancy rate was only 13% [42], whereas the reported cumulative fertility rate post VRT is in the range of 55% [32,43]. This observation needs to be further studied in larger-size series, but if confirmed, this information will be of importance when discussing treatment options with patients. Adaptation of the procedure to preserve uterine arteries and functional reconstruction to reduce cervical incompetence may prove to be valuable [44].

**Summary**

Based on our experience with 140 candidates for VRT, we made the following observations which may be of value when counseling patients interested in VRT:

- The recurrence rate is less than 5% and death rate is less than 2%.
- Intraoperatively, approximately 10% of planned VRT patients will be abandoned, mainly because of the detection of lymph node metastasis (60%).
- Postoperatively, an additional 4–5% of patients will be found to have high-risk features on final pathology (mostly positive nodes) for which adjuvant treatment is recommended.
- Overall, the risk of lymph node metastasis is approximately 10–12%, two-third of which are detected intraoperatively by frozen section analysis of the sentinel node.
- Conversely, one third of patients with negative sentinel nodes on frozen section will be found to have micrometastasis on final pathology when the nodes are submitted to the ultrastaging procedure.
- Approximately 5% of patients choose to undergo a complementary hysterectomy for benign conditions at some point in the follow-up period.
- Lesions measuring >2 cm are associated with an increased risk of recurrence and an increased risk of abandoning the planned VRT.
- NACT is a reasonable option for patients with larger size lesions (>2 cm), with excellent response rate and a reasonable chance of conceiving.
- The first and second trimester miscarriage rate is comparable to that of the general population (20 and 3% respectively).
- The rate of severe prematurity (<32 weeks) is <5% and rate of milder prematurity (32–36.6 weeks) is <20%.
- The majority of pregnancies (approximately 75%) will reach the third trimester, and of those 75% will be delivered at term (>37 weeks).
- Approximately 15% of women will experience fertility problems following VRT and most will require some form of assisted reproductive technologies.
- Cervical stenosis related to the VRT procedure is the cause of infertility in 40% of cases.

**Future directions**

The introduction of the radical trachelectomy procedure has been a major breakthrough in the management of early-stage cervical cancer and its gradual implementation convinced the gynecologic oncology community that it is an acceptable alternative in well-selected cases where fertility preservation is an issue. In the future, even more conservative surgical approach such as a simple trachelectomy or large cone with sentinel node evaluation may be adequate for patients with IA2 and small IB1 lesions, considering that the rate of parametrial extension in small lesions is very low (<1%) [45,46]. A pilot study of 40 patients from Rob et al. suggests that this approach is feasible in carefully selected cases [47]. If it proves to be safe, it would certainly reduce the morbidity of the radical trachelectomy and further simplify treatment.

**Conflict of interest statement**

The authors declare that there are no conflicts of interest.
References


