Vaginal radical trachelectomy: An update

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Abstract

The vaginal radical trachelectomy has emerged as a valuable fertility-preserving treatment option for young women with early-stage disease. Cancer-related infertility is associated with feelings of depression, grief, stress, and sexual dysfunction. Data have shown that the overall oncological outcome is safe and that the obstetrical outcome is promising. In this article, we analyze the data on the vaginal radical trachelectomy published over the last 10 years in the context of what we have learned, what issues remain unclear, and what the future holds.© 2008 Elsevier Inc. All rights reserved.

Keywords: Vaginal radical trachelectomy; Fertility sparing; Early-stage disease

Introduction

Fertility preservation has become an important component of the overall quality of life of young cancer survivors. The American Cancer Society has recently 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]. The vaginal radical trachelectomy (VRT) has emerged as a valuable fertility-preserving treatment option for young women with early-stage disease. Accumulating data confirm that the overall oncological outcome is safe and that the obstetrical outcome is very promising. Analyzing data published over the last 10 years provides an opportunity to appreciate what we have learned, what issues remain unclear, and what are the future directions.

Indications for the procedure

The indications for VRT have essentially remained unchanged since they were first proposed in 1998 [4]. They were recently further refined by Sonoda et al. [5]. Based on a retrospective study at Memorial Sloan-Kettering Cancer Center, it was estimated that 40% of patients who underwent a radical hysterectomy at their institution would have been candidates for a VRT [6].

Investigation

A preoperative pelvic magnetic resonance imaging (MRI) is extremely helpful in selecting patients for VRT. The sagittal T2-weighted images, in particular, allow a clear assessment of the tumor size and location, extension towards the endocervical canal, length of the endocervical canal, and very importantly, the distance between the upper margin of the lesion and the isthmus [7]. Nowadays, a pelvic MRI is a mandatory preoperative imaging study, particularly in patients with a macroscopic lesion [8].

Morbidity of the procedure

Marchiole et al. recently compared 118 radical vaginal trachelectomies to 139 radical vaginal hysterectomies. Intraoperative and postoperative complications were 2.5% and 21%, respectively, and comparable between the two groups [9]. Similar results were reported by others [5,10,11]. Another group found that VRT is associated with less operative and short-term morbidity compared to abdominal radical hysterectomies, but
there were some long-term morbidities specifically associated with VRT (vaginal discharge, irregular bleeding or prolonged amenorrhea, deep dysmenorrhea, cervical suture problems, etc) [12].

Oncological outcome

Recent reviews of the published literature totaling more than 600 cases confirm an overall recurrence rate of < 5% and death rate of < 3% (Table 1) [5,9,10,13–17]. These results are comparable to those of radical hysterectomies for similarly sized lesions [9].

Sites of recurrence

Nearly 40% of recurrences occur in the parametrium or pelvic sidewall, possibly due to insufficient parametrial excision or to the presence of microscopic lymph-vascular space invasion (LVSI), and 25% were in the pelvic, paraaortic, and/or supraclavicular nodes [11]. Sentinel node mapping in the surgical management of cervical cancer may reduce the risk of potentially missing nodal micrometastasis and aberrant lymph node draining sites [11,18]. A total of five centropelvic recurrences have been reported; four of these were in patients with adenocarcinomas, possibly explained by the multifocal nature of this type of lesion [14].

Risk factors for recurrence

Lesion size

Lesions ≥2 cm are clearly associated with a higher risk of recurrence [9,11,16,19]. In the series by Marchiole et al., 6 (86%) of 7 patients who had lesions >2 cm recurred: 6 (29%) of 21 patients with lesions >2 cm recurred versus only 1 (1.6%) of 62 patients with lesions <2 cm [9]. Patients with very exophytic lesions with minimal stromal invasion may still be candidates for VRT even if the lesion measures more than 2 cm [15].

LVSI

The presence of LVSI also appears to be associated with a higher risk of recurrence (12% versus 2%) [9,11]. However, others do not consider the presence of LVSI alone as an absolute contraindication for this procedure [11,19,20]. This issue remains controversial, and patients should be informed of the potential higher risk of recurrence, particularly when LVSI is extensive [21,22].

Histology

Adenocarcinomas are not clearly associated with a higher risk of recurrence, although 3 of the 4 recurrences reported by Hertel et al. were adenocarcinomas [14]. Adenosquamous histology does not seem to increase recurrence rate either [11]. Neuroendocrine tumors are clearly a very aggressive variant of cervical cancer. These patients should probably not be offered fertility-sparing surgery [9,11,19].

Indications for adjuvant treatment

Despite careful patient selection, 10–12% of patients are found to have more extensive endocervical disease at the time of surgery or positive nodes on frozen section leading to abandoning the procedure in favor of adjuvant radiation therapy or completion radical hysterectomy [9,10,11,19].

Positive nodes, margins, or parametrium

In a review of 7 series, Beiner et al. showed that approximately 10% of patients are found to have positive nodes, positive margins or positive parametrium on final pathology and require adjuvant treatment [11]. Interestingly, in the series of Marchiole et al., 3 of 5 women with nodal micrometastasis chose not to have adjuvant radiation therapy and did not recur [9]. In the series of Hertel et al., 4 patients were found to have positive nodes on final pathology despite negative frozen section. All 4 refused adjuvant radiation therapy but accepted chemotherapy (carboplatin/ifosfamide) in order to preserve fertility. They are all alive without recurrence [14].

Close surgical margins

Occasionally, the margins obtained on frozen section are adequate, but the margins on final pathology are close (<5 mm). In Marchiole’s report, 2 patients with margins <5 mm refused to receive adjuvant treatment and none recurred [9]. Three of our patients had close margins (5, 4, and 1 mm), and one recently recurred on the residual cervix [19]. In another series, 1 patient with <5 mm margin recurred in the corpus uteri 3 months after VRT, and 1 patient who developed adenocarcinoma in situ 2 years post-VRT, refused definitive treatment and developed an invasive cancer 10 months later [14]. A conservative approach may thus be more risky.

The decision to recommend adjuvant radiation therapy must be weighed carefully. A VRT approach requires careful individualized discussions and weighing the potential higher risk of recurrence versus recommending adjuvant treatment, which will probably lead to permanent loss of fertility.

Follow-up

There are no definitive guidelines with regards to the follow-up of patients following VRT. In general, a colposcopic

Table 1

<table>
<thead>
<tr>
<th>Author</th>
<th># of patients</th>
<th>Median follow-up (range)</th>
<th>Recurrence rate (%)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marchiole [9]</td>
<td>118</td>
<td>95 (31–234)</td>
<td>7 (6%)*</td>
<td>5 (4%)*</td>
</tr>
<tr>
<td>Plante [13]</td>
<td>115</td>
<td>74 (4–204)</td>
<td>4 (3%)*</td>
<td>2 (2%)*</td>
</tr>
<tr>
<td>Shepherd [10]</td>
<td>112</td>
<td>45 (1–120)</td>
<td>3 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Hertel [14]</td>
<td>100</td>
<td>29 (1–128)</td>
<td>3 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Covens [15]</td>
<td>93</td>
<td>30 (1–103)</td>
<td>7 (7.5%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Sonoda [5]</td>
<td>36</td>
<td>21 (3–60)</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Burnett [16]</td>
<td>19</td>
<td>21 (22–44)</td>
<td>2 (10.5%)</td>
<td>?</td>
</tr>
<tr>
<td>Schlearth [17]</td>
<td>10</td>
<td>48 (28–84)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>603</td>
<td></td>
<td>27 (4.5%)</td>
<td>15 (2.5%)</td>
</tr>
</tbody>
</table>

* Including a case of neuroendocrine tumor.
examination with a cervical cytology (± endocervical curettage) is recommended every 3–4 months for the first 3 years, every 6 months for the next 2 years, and yearly thereafter [23]. Some advocate a follow-up pelvic MRI at 6, 12, and 24 months [23]. These MRIs should be read by radiologists familiar with patients who have had a VRT as some of the anatomical changes secondary to the procedure may be misinterpreted as cancer recurrence [24].

Follow-up cytologies post-VRT are frequently associated with abnormal results, which can raise considerable worries. Singh et al. reported a 2% false-positive result, most often due to the presence of atypical endometrial cells [25]. These can be misinterpreted as atypical cells of undetermined significance or tubal metaplasia [26]. Up to 41% of smears contained squamous cells only [25]. Shepherd et al. proposed to report these smears as unsatisfactory in the first 2 years and negative thereafter [23]. In the Singh et al. study, cytology identified recurrence in 2 cases long before it became clinically apparent [25]. Therefore, a good colposcopic evaluation of patients with abnormal Pap tests and good communication with an experienced cytopathologist are critical [10].

The decision to perform a definitive hysterectomy once the family plans are completed is a matter of debate. There are no data to support that it should (or should not) be done. The issue has to be discussed with patients to offer individualized recommendations.

**Obstetrical outcome and management**

A literature review totaling 256 pregnancies indicates that 62% of pregnancies following VRT will reach the third trimester, of which 65% will reach term (Table 2) [5,10,13,14,16,17,27,28]. The preterm delivery rate (<37 weeks) is in the range of 28%, but only 12% will end with significant prematurity (<32 weeks) where most of the neonatal morbidity occurs. Overall, 40% of all pregnancies will culminate with the birth of a healthy newborn at term.

### First-trimester miscarriage

The rate of first-trimester miscarriage following a VRT is comparable to the rate in the general population (16–20%) [29–32]. Conservative management is recommended initially as most patients will miscarry spontaneously. Otherwise, Misoprostol (Cytotec) can be given to stimulate contractions [30,32], or a dilatation and curettage may need to be performed.

### Second-trimester miscarriage

The rate of second-trimester miscarriage following VRT is twice the rate of the general population (8.6% versus 4%), usually a result of underlying chorioamnionitis, activating the cytokine cascade and leading to the premature rupture of membranes (PROM) [29,31]. It is recommended to be conservative, and most patients will deliver spontaneously vaginally without necessarily removing the cerclage. A dilatation and evacuation (D&E) or removal of the cerclage and labor induction with misoprostol may be necessary [28]. A hysterotomy is the last option and is usually indicated in septic patients [16].

### Pre-term delivery (PTD)

The main concern with pregnancies following VRT is the higher rate of premature labor and delivery. The presumed causes are either mechanical or infectious or a combination of both [33]. The rate of premature birth varies substantially amongst the different teams [30], probably due to the amount of cervix left at the time of VRT [30,33].

### Antepartum management

There are no guidelines and limited data regarding the management of pregnancies following VRT [34]. Some authors advocate routine genital tract infection screening, prophylactic antibiotic, bed rest and/or reduced physical activities, and the

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Obstetrical outcomes after vaginal radical trachelectomy</th>
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</thead>
<tbody>
<tr>
<td>Author</td>
<td>#Pregnancies</td>
</tr>
<tr>
<td>Plante [13]</td>
<td>87</td>
</tr>
<tr>
<td>Mathevet [27]</td>
<td>56</td>
</tr>
<tr>
<td>Shepherd [10]</td>
<td>55</td>
</tr>
<tr>
<td>Bernardini [28]</td>
<td>22</td>
</tr>
<tr>
<td>Hertel [14]</td>
<td>18</td>
</tr>
<tr>
<td>Sonoda [5]</td>
<td>11</td>
</tr>
<tr>
<td>Burnett [16]</td>
<td>3</td>
</tr>
<tr>
<td>Schlearth [17]</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>256</td>
</tr>
</tbody>
</table>

TAB, therapeutic abortions.
EUP, extruterine pregnancies.
SB, stillbirth.
a Onesets of twins.
b Twosets of twins.
c Delivered after 35 weeks.
routine administration of steroids for fetal lung maturation [33]. Jolley et al. do not recommend routine antibiotics, and they reserve antenatal corticosteroids to women who show signs of preterm labor and PROM [29]. Antepartum visits every 2 weeks between 18–28 weeks and weekly thereafter have been suggested along with serial ultrasound measurements of cervical length [35]. In patients with PROM without signs of chorioamnionitis, expectant management is a reasonable option until 32–34 weeks of pregnancy [29]. Patients should be well informed that pregnancies following VRT are associated with a higher risk of complications, and a specialist in fetal–maternal medicine should probably be involved early in the care of these patients [34].

Fertility outcome

Causes of infertility

In two recent series, 70–79% of all women attempting to conceive succeeded spontaneously [5,31]. The estimated cumulative fertility rate is in the range of 55%, with the majority succeeding within a year of attempting [10,28]. Some degree of subfertility following VRT probably exists due to various degrees of cervical stenosis, lack of cervical mucus, subclinical chronic endometritis, adhesion formation, subclinical salpingitis, etc [28,33,36]. In patients who are unable to conceive, a complete infertility work-up should be performed, since the cause of infertility may be unrelated to the VRT.

Cervical stenosis

Approximately 10–15% of patients may develop cervical stenosis following VRT [12,31]. Most patients are asymptomatic, although some may experience monthly cramps, pain, and hematometra. Even though most patients become pregnant naturally despite cervical stenosis, some may require the help of assisted reproductive technologies [36]. Intrauterine insemination (IUI) and embryo transfer (ET) following in vitro fertilization (IVF) can be particularly challenging in these patients [36–38].

Patients with advanced maternal age or with a questionable history of infertility should be encouraged to seek a preoperative consultation with an infertility specialist [5]. Since patients who underwent a trachelectomy frequently present with distress and reproductive concerns, a thorough preoperative counseling is mandatory to ensure that they have realistic expectations with regards to fertility issues and obstetrical outcome [39].

Future alternatives

Neoadjuvant chemotherapy (NACT)

Cervical lesions > 2 cm are clearly associated with a higher risk of cancer recurrence following VRT [11,19]. The use of NACT has recently been used to chemo-reduce the size of the lesion, making it possible, in good responders, to perform a fertility-sparing surgery [40–42]. Using the same concept, we have treated 3 patients with a combination of Taxol/Ifosfamide/Platinum [43]. Two had a complete pathological response and 1 had only residual dysplasia. There have been no recurrences so far. One patient delivered 2 healthy babies at 38.5 weeks of gestation 1 year apart. Another patient, aged 36, conceived with IUI and recently delivered at 36 weeks (unpublished data). Rob et al. recently reported on 5 women treated with NACT followed by simple trachelectomy and nodes with excellent tumor response in 4 [44]. One woman delivered at term and 1 is currently pregnant. The concept of NACT is certainly appealing and warrants further investigation. In the future, non-gonadotoxic and perhaps a less aggressive chemotherapy regimen should be evaluated to reduce the impact on ovarian function [43].

Ultraconservative fertility-sparing surgery

Patients with very early invasive cervical cancer (IA2 and early IB1) probably will not benefit from a VRT procedure since the chances of tumor spread to the parametral tissue is very low [45]. Studies have shown that 62–67% of patients do not have any residual cancer in the trachelectomy specimen if they had a diagnostic cone [9,10,19]. Therefore, a simple trachelectomy or a large cold knife cone involving the removal of most of the cervical tissue is probably sufficient in these cases.

Rob et al. treated 26 patients with stage 1A1–1B2 lesions in a two-step outpatient treatment approach [46]. Four patients had positive lymph nodes identified on frozen section (15%) and underwent a definitive radical hysterectomy. One patient developed a central recurrence, successfully treated with chemo-radiation. A total of 15 pregnancies have occurred, with 8 living children [46].

The concept of an ultraconservative treatment approach warrants further investigation to evaluate the oncological safety in a larger group of patients. Strict selection criteria and a detailed pathological evaluation of the cone specimen will be of paramount importance to avoid recurrences and deaths in these highly curable patients. The obstetrical impact of a large cone will also need to be studied considering that conization alone is associated with a significant increase in preterm delivery and PROM [47,48].

Conclusion

The management of early-stage cervical cancer has evolved tremendously over the last 2 decades in favor of minimally invasive surgical techniques that have allowed the development of fertility-preserving options for young women with low-risk lesions. Continued research will determine if fertility-preserving surgery is safe in larger size lesions following NACT and if less aggressive surgery is safe in very small lesions.

Conflict of interest statement

The author has no conflicts of interest to declare.
References


