Radical Trachelectomy: A Fertility-Sparing Option for Early Invasive Cervical Cancer

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ABSTRACT: For the past 15 years gynecological oncologists have been seeking ways to preserve woman's fertility when treating invasive cervical cancer. For some women with small localized invasive cervical cancers, there is now hope for pregnancy after treatment. Many cases of cervical cancer are diagnosed in young woman who wish to preserve their fertility. As more women are delaying childbearing, fertility preservation has become an important consideration. The standard surgical treatment for stage IA2-IB1 cervical cancer is a radical hysterectomy and bilateral pelvic lymphadenectomy. This surgery includes removal of the uterus and cervix, radical resection of the parametrial tissue and upper vagina, and complete pelvic lymphadenectomy. Obviously, the standard treatment does not allow future childbearing. Radical trachelectomy is a fertility-sparing surgical approach developed in France in 1994 by Dr. Daniel Dargent for the treatment of early invasive cervical cancer. Young women wishing to bear children in the future may be candidates for fertility-preservation options. The radical trachelectomy operation has been described and performed abdominally, assisted vaginally by laparoscopy and robotically. In this review we discuss the selection criteria for radical trachelectomy, the various possible techniques for the operation, the oncological and obstetric outcomes, and common complications.

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Cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in females worldwide, accounting for 9% (529,800) of the total new cancer cases responsible for 275,100 deaths in 2008. More than 85% of these cases and deaths occur in developing countries [1]. In the United States, each year 12,200 new cases of cervical cancer are diagnosed and 4200 women die from this disease annually. It is estimated that 43% of all cases of invasive cervical cancer in the U.S. are diagnosed in women younger than 45 years of age.

HISTORICAL PERSPECTIVES OF THE TRACHELECTOMY

In 1948 Novak proposed that cervicectomy was a reliable treatment approach for cervical intraepithelial neoplasias. In the 1950s a Romanian gynecologist, Aburel, described a technique called subfundic radical hysterectomy for the management of microcarcinoma and in situ carcinoma of the cervix. In 1977, Bughardt and Holzer reported that removal of the uterine fundus and adnexa was not required for the management of small cervical tumors. In 1994 Daniel Dargent in Lyon [2,3] first described vaginal radical trachelectomy with laparoscopic lymph node dissection as a fertility-preserving technique. The technique was modified by Shepherd et al. [4] in London, and subsequently Roy and Plante [5] in Quebec showed that successful pregnancy could occur after this treatment. As a result, the technique of radical trachelectomy with laparoscopic pelvic lymph node evaluation has become established as a possible alternative for the surgical management of small early-stage cervical cancers in women anxious to conserve their fertility.

PROPOSED SELECTION CRITERIA FOR RADICAL TRACHELECTOMY

- A desire for future fertility
- A proven diagnosis of cervical cancer
- Squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma
- Tumor size less than 2 cm
- Stage IA1 disease with lymph vascular space invasion, stage IA2 disease or stage IB1 disease
- Tumor limited to the cervix as confirmed by preoperative pelvic magnetic resonance imaging or PET-CT
- No evidence of clinical pelvic lymph node metastases
- No previous documentation of infertility

All patients must be aware that the chances of successful fertility after radical trachelectomy are lower. Patients older than 40 years of age are counseled regarding their inherent risk of fertility based on age alone [2].

RADICAL TRAHCELECTOMY: SURGICAL TECHNIQUE

Radical trachelectomy may be performed either abdominally, vaginally, laparosocpically, or robotically. The feasibility and safety of some of these techniques have been well established, whereas for others the oncological data on outcome are only

PET-CT = positron emission tomography-computed tomography

preliminary. The decision to use newer techniques should be directed by patient variables as well as the surgeon's training and competence with laparoscopy, robotics, or vaginal surgery [6].

- *Radical abdominal trachelectomy*. The procedure begins with the inspection and removal of the pelvic lymph nodes that are then sent for frozen section. If any grossly positive nodes are detected the procedure is aborted. The round ligaments are transected and the paravesical and pararectal spaces are developed. The uterine arteries are ligated and transected bilaterally at their origin from the internal iliac arteries so the ureters can be separated from the parametria. A bladder flap is created, and the bladder is pushed away from the cervix and the rectovaginal space is developed. The cervix is amputated approximately a centimeter below the uterine-cervical junction. The uterosacral ligaments are transected and the bladder is pushed even lower. The vagina is cut in such a manner as to leave enough clear margins. The surgeon removes the cervix, parametrium and upper 2 cm of the vagina. After the cervix is amputated the trachelectomy specimen is sent for frozen section evaluation to assure that the cervical margins are free of disease. The uterine corpus with its blood supply from the uterine and ovarian arteries is retained and anastomosed to the remaining vagina. A cerclage is placed where the cervix used to be to allow the patient to carry a pregnancy. Future delivery is achieved by cesarean section.

Radical trachelectomy should be regarded as an optional surgical approach in the management of early cervical cancer in a young patient who wants to preserve her fertility

- *Radical vaginal trachelectomy*. This procedure begins with laparoscopic pelvic lymphadenectomy. The vaginal procedure is started by placing the patient in the lithotomy position. A circumferential incision is made in the upper vagina. The supracervical ligament is cut, and the bladder base is mobilized. Posteriorly, the pouch of Douglas is opened and the pararectal spaces are exposed. The uterosacral ligaments are then divided. The vesicovaginal ligaments are then identified, and the paravesical spaces are entered laterally. At this point, the ureters are identified by palpation after which the vesicovaginal ligaments are separated from the cervix. The uterine artery is identified, and a right-angle forceps is passed through the para-isthmic window just underneath the uterine artery to define the upper limit of the cardinal ligaments. The cardinal ligaments are then divided. The cervix is amputated below the cervical isthmus, and the trachelectomy specimen is sent for frozen section

ONCOLOGIC OUTCOMES FOR RADICAL VAGINAL TRACHELECTOMY

A review published in 2007 by Dursun and collaborators [7] summarized the oncological outcome of 520 patients who had undergone a radical vaginal trachelectomy. The median age for all patients reported was 31 years. The median follow-up time was 48 months. The majority of patients (60%) had a diagnosis of squamous cell carcinoma, with adenocarcinoma being the second most common histological subtype (40%). Similar results were reported by Beiner et al. [8] in a study where 90 patients underwent radical vaginal trachelectomy; 50% of their patients were reported to have adenocarcinomas.

In a study of 100 patients who underwent radical vaginal trachelectomy combined with laparoscopic pelvic lymphadenectomy, Hertel and team [9] reported that the recurrence rate after radical vaginal trachelectomy was not significantly different between squamous cell carcinoma and adenocarcinoma. Overall, in 24% of patients undergoing a radical vaginal trahcelectomy the preoperative biopsy specimen showed lymph-vascular space invasion. The majority of patients (88%) had tumors less than 2 cm in size. The median time of surgery was 213 minutes. With a median follow-up time of 48 months, the overall recurrence rate was 4.2% and the death rate from cervical cancer was 2.8% These results are comparable to those of radical hysterectomies for similarly sized lesions, with the advantages of less aggressive surgery, shorter hospital stay, lower blood loss, quicker return of bladder function, and fertility preservation.

In another study, Diaz and colleagues [10] compared the outcomes of 40 patients with stage IB1 cervical cancer, who underwent radical trachelectomy (radical vaginal hysterectomy in 28 and radical abdominal hysterectomy in 12) and 110 patients with stage IB1 cervical cancer who underwent radical hysterectomy. The median follow-up time was 44 months. The 5 year recurrence-free survival rate was 96% for the radical trachelectomy group compared to 86% for the radical hysterectomy group. The authors concluded that for selected patients with stage IB1 cervical cancer, fertility-sparing radical trachelectomy appears to produce oncologic outcomes similar to those after radical hysterectomy. Table 1 summarizes these studies.

There is increasing evidence in the literature that not only is radical trachelectomy feasible and safe but the oncologic outcomes are similar to those of equivalent patients undergoing radical hysterectomy.

RECURRENCE

Recent reviews of the published literature totaling more than 600 cases confirm an overall recurrence rate of < 5% and death rate of < 3% [9-12]. These results are comparable to those of radical hysterectomies for similarly sized lesions [12].

Nearly 40% of recurrences after vaginal radical trachelectomy occur in the parametrium or pelvic sidewall, possibly due to insufficient parametrial excision or to the presence of microscopic lymph-vascular space invasion, and 25% occur in the pelvic, para-aortic and/or supraclavicular nodes [12]. Sentinel node

Table 1. Oncologic outcomes after vaginal radical trachelectomy

Author [ref]	No. of patients	Median follow-up (mon)	Histology	Recurrence rate (%)	Death rate (%)
Dursun et al. [7]	520	48	Squamous cell carcinoma 60% Adenocarcinoma 40%	4.2	2.8
Beiner et al. [8]	90	51	Adenocarcinoma 50% Squamous cell carcinoma 43% Adenosquamous carcinoma 7%	5.5	3.3
Hertel et al. [9]	100	48	Squamous cell carcinoma 69% Adenocarcinoma 31%	4.2	2.8
Diaz et al. [10]	40*	44	Squamous cell carcinoma 50% Other 50%	4	2.5

* The study population comprised 28 patients who had radical vaginal hysterectomy and 12 patients who had radical abdominal hysterectomy

Table 2. Risk factors for recurrence and histology after vaginal trachelectomy

Lesion size	Lesions ≥ 2 cm have a higher risk of recurrence [13,22,23,28-30]
Lymph-vascular space invasion	The presence of LVSI also appears to be associated with a higher risk of recurrence (12% vs. 2%) [23,28,30]
Adenocarcinomas	Not clearly associated with a higher risk of recurrence [9]
Adenosquamous histology	Does not seem to increase recurrence rate either [23,30]
Neuroendocrine tumors	A very aggressive variant of cervical cancer. These patients should probably not be offered fertility-sparing surgery (22,23,28,30]

LVSI = lymph vascular space invasion

mapping in the surgical management of cervical cancer may reduce the risk of potentially missing nodal micrometastasis and aberrant lymph node draining sites [13,14]. Table 2 summarizes the risk factors for recurrence after vaginal trachelectomy.

OBSTETRIC OUTCOME AFTER RADICAL VAGINAL TRACHELECTOMY

Although most patients become pregnant spontaneously after radical vaginal trachelectomy, some may require the help of assisted reproductive technologies. In two recent series, 70–79% of all women attempting to conceive succeeded spontaneously [15-17]. The main concern with pregnancies following radical vaginal trachlectomy is the higher rate of premature labor and delivery.

Current literature supports the feasibility and safety of radical trachelectomy

It has been estimated that 10–15% of patients may develop cervical stenosis following vaginal radical trachelectomy [18]. The lack of cervical mucus during pregnancy may cause cervical incompetence and ascending infections, leading to prematurity and/or fetal death.

There are no guidelines for the management of pregnancies following radical vaginal trachelectomy. Routine genital tract infection screening, prophylactic antibiotics, bed rest and routine administration of steroids for fetal lung maturation have been suggested. Most authors agree that a specialist in fetal-maternal medicine should be involved in the early care of these patients.

Table 3. Obstetric outcomes after radical vaginal trachelectomy

Author [ref]	Cases	Pregnancies	Live births	< 32 weeks	Term
Milliken & Shepherd [17]	790	320	24%	9%	–
Plante [19]	256	256	40%	12%	65%

Milliken and Shepherd [17] published a review in 2008 on the obstetric outcomes in 790 radical vaginal trachelectomy procedures with 302 pregnancies and 190 live births described in the literature. Nine percent (27 patients) were significantly premature. It has been estimated that 63% of pregnancies following radical vaginal trachelectomy will result in live births. According to another review, performed by Plante [19], of 256 pregnancies following vaginal radical trachelectomy 65% of pregnancies will reach term.

As reported by Dornhofer and Hockel [20] in a more recent review, the most important obstetric outcome parameter is the rate of very premature infants related to the overall number of babies born, which is 15%. Despite major medical progress, children born at 24–28 weeks of gestation are still at significant risk to develop cognitive and motoric deficiencies, and the treatment costs for these infants are very high. In order to minimize the rate of very premature infants after radical trachelectomy, the authors propose the preservation of at least 1 cm of residual cervical tissue. Table 3 summarizes the obstetric outcome following radical trachelectomy.

RADICAL ABDOMINAL TRACHELECTOMY

Far fewer cases of abdominal trachelectomy have been reported in the literature. Technically, abdominal trachelectomy is very similar to the abdominal radical hysterectomy, making this surgery a viable option for the gynecologic oncologist with limited experience in vaginal radical surgery [21].

Abdominal radical trachelectomy is the technique of choice in pediatric patients, and in cases of distorted vaginal anatomy, bulky exophytic tumor, or cervical cancer in the first half of pregnancy [22].

The results of 10 abdominal radical trachelectomies performed in the Massachussetts General Hospital from 1999 to 2008 were published by Olawaiye et al. [23]. A high infertility rate in patients after abdominal radical trachelectomies was reported by the authors. They concluded that the high infertility rate may merely be secondary to the small sample size, but may also be attributed to a larger amount of cervix taken during the abdominal approach, leading to cervical factor as a cause of infertility. It should be noted that no cancer recurrences were found in this group after abdominal radical trachelectomy.

Einstein and co-authors [22] reported that radical abdominal trachelectomy provides similar surgical and pathological outcomes with a wider parametrial resection in comparison with the radical vaginal approach.

Although premature deliveries are the main obstetric complication of radical trachelectomy, abundant successful pregnancies have been reported

Another disadvantage of the radical abdominal trachelectomy is the necessity for laparotomy. Most authors consider that an abdominal approach is preferable in units with limited experience with vaginal surgical procedures.

ROBOTIC RADICAL TRACHELECTOMY

The advantages of minimally invasive surgery have been well documented and include decreased blood loss, decreased pain medication requirements, reduced length of hospital stay, quicker return of bowel function, and faster return to daily activities. Ramirez et al. [24] reported their experience in performing four cases of robotic radical trachelectomy. The robot offers excellent visualization of the vasculature and parametrial tissues, which must be isolated during this procedure, while still offering a minimally invasive technique that has a quick recovery and is likely to help preserve fertility [25]. The use of robotic surgical systems has allowed surgeons to perform complex gynecologic oncology procedures using a minimally invasive approach.

The first to report on robotic radical trachelectomy was Geisler et al. [26] from St. Vicente Hospital in Indianapolis, USA. They described a patient with stage IB1 adenosarcoma of the cervix. Persson et al. [27] from the Lund University Hospital in Sweden presented two patients who underwent robotic radical trachelectomy. One patient was diagnosed with stage IB1 adenocarcinoma of the cervix and the other with a stage IA2 squamous carcinoma of the cervix. This group of investigators was the first to describe robotic radical trachelectomy in conjunction with lymphatic mapping and sentinel identification. Ramirez and co-scientists [24], from the M.D. Anderson Cancer Center in Houston, USA, recently reported a case series of four patients who underwent robotic radical trachelectomy. The authors of these case reports agree that robotic surgery is a feasible and safe option for gynecologic oncology procedures with reasonable operative times, low blood loss, and short hospital stays [24-26].

FOLLOW-UP AFTER TRACHELECTOMY

Contraception is recommended for 6 months before colposcopic assessment + vaginal vault and isthmic smear are carried out. Magnetic resonance imaging is performed and if there is no evidence of recurrent disease then the patient is free to conceive. MRI assessment with colposcopy and smears are performed at 6, 12 and 24 months [17].

COMPLICATIONS

The typical complications reported in patients undergoing radical trachelectomy include dysmenorrhea (24%), dysplastic Pap smears (24%), irregular or intermenstrual bleeding (17%), problems with cerclage sutures (14%), excessive vaginal discharge (14%), isthmic stenosis (10%), and amenorrhea (7%). Another potential complication unique to this procedure is occasional reports of deep dyspareunia. Deep dyspareunia occurs because the uterus and the ovaries are much lower in the pelvis; this, accompanied by cervical stenosis, causes deep dyspareunia [18].

CONCLUSIONS

The accumulating data in the literature support the notion that radical trachelectomy is a safe option for the treatment of carefully selected women diagnosed with early cervical cancer who want to preserve their fertility. In view of the series reported in the literature, we believe that it is safe to claim that the oncologic outcome of radical trachelectomy is not inferior to radical hysterectomy in well-selected cases.

The data comparing the two main surgical approaches – radical vaginal trachelectomy versus radical abdominal trachelectomy – are not sufficient to determine which surgical approach is superior, and the decision will usually be made by the surgeon's preference and experience. It has yet to be proven whether the use of a robot carries any advantage over the traditional surgical approaches. Until more data are published, we contend that robotic radical trachelectomy should be considered an experimental procedure.

With regard to fertility, it appears that conception rates after radical trachelectomy are high, and the main obstetric obstacle remains premature delivery. Due to the relatively high premature birth rates, it is prudent to follow pregnancies after radical trachelectomies as high risk pregnancies.

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