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Conservative Surgery for Early Cervical Cancer in Young Women- A Review

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Published Date: December 10, 2015

ABSTRACT

Cervical cancer is the third most common cancer in women worldwide with 500,000 new cases and 250,000 deaths annually. Persistent Human Papilloma Virus **(HPV)** infection is accepted as the leading aetiological agent for cervical cancer. Up to 42 percent of all cervical cancers are diagnosed in women before the age of 45 years, and up to 40% of early cervical cancers are diagnosed in young women desirous of preserving fertility and potentially interested in a fertility-preserving surgery. The high incidence rate and progressiveness of cervical cancer has led researchers to continually examine and pursue better diagnosis, prognosis, and treatment techniques to decrease mortality rates and comorbidity. While radical hysterectomy is an effective treatment in women with early stage cervical cancer (Stages IA1–IIA), with 5-year overall survival rates of 73.4%–97.5%, this procedure is not without morbidity. Although traditionally patients have received radical surgery for all but the smallest squamous cervical lesions, there is a movement towards less radical surgery in patients with 1A and small 1B cervical carcinoma. Non-radical surgery can be considered in such patients desirous of fertility preservation in whom tumor size <2 cm, limited depth of invasion, absence of LVSI and negative pelvic lymph nodes on frozen section when the risk of parametrial involvement is approximately 1% or less. Recent studies have explored less radical surgical options for early-stage cervical cancer, including simple

hysterectomy, simple trachelectomy and cervical conization with or without sentinel lymph node biopsy and pelvic lymph node dissection. Such options may be available for patients with low-risk early-stage cervical cancer. More conservative surgical approaches have therefore been suggested. Ongoing research efforts are especially being made in properly identifying the patient subset suitable for a conservative/less radical approach. This report provides a review of the existing literature on the conservative surgical management of early cervical cancer.

INTRODUCTION

Cervical cancer is the third most common cancer in women worldwide with 500,000 new cases and 250,000 deaths annually [1]. A total of 80% of these cases are diagnosed in developing countries. Additionally, 99% of these cases are due to Human Papilloma Virus **(HPV)** infection. An estimated 12,200 new cases of cervical cancer and 4210 deaths occurred in USA in 2010 [2]. As the fourth leading cause of female cancer deaths, cervical cancer is a key research area [3,4]. Up to 42 percent of all cervical cancers are diagnosed in women before the age of 45 years, and up to 40% of early cervical cancers are diagnosed in young women desirous of preserving fertility and potentially interested in a fertility-preserving surgery [5-7].

Cervical cancer refers to any malignant neoplasm arising from the uteri cervix. Its most common onset site is the cellular junction or transformation zone, where the stratified squamous epithelium of the ectocervix meets the columnar mucus-secreting epithelium of the endocervix. The most frequent types of cervical cancer are thus Squamous Cell Carcinoma **(SCC)** and Adenocarcinoma **(ADC)** [8-10].

While radical hysterectomy is an effective treatment in women with early stage cervical cancer (Stages IA1–IIA), with 5-year overall survival rates of 73.4%–97.5% [11-14], this procedure is not without morbidity. The risk of blood loss and transfusion, nerve or vascular injury, bladder and bowel dysfunction, fistula formation, lymphedema, and sexual dysfunction are significant [11,15-19]. Although traditionally patients have received radical surgery for all but the smallest squamous cervical lesions [11,20]. There is a movement towards less radical surgery in patients with 1A and small 1B cervical carcinoma. Of late, a number of studies have explored less radical surgical options for early-stage cervical cancer, including simple hysterectomy, simple trachelectomy, and cervical conization with or without sentinel lymph node biopsy and pelvic lymph node dissection. Such options may be available for patients with low-risk early-stage cervical cancer [21]. More conservative surgical approaches have therefore been suggested. This report provides a review of the existing literature on the conservative surgical management of early cervical cancer.

ROLE OF HPV AS A CAUSATIVE FACTOR IN CERVICAL CANCER

Persistent Human Papilloma Virus (**HPV)** infection is accepted as the leading aetiological agent for cervical cancer [3,22]. HPV is a circular double-strand DNA virus of almost 8000 bp belonging to the Papillomaviridae family. From more than 150 different genotypes, only 40 are

reported to infect the anogenital tract, typically classified as high- or low-risk according to their ability to cause a recurrent infection [3,23]. After HPV infection, dysplasia usually develops in the transformation zone. Low grade dysplasia can spontaneously regress without leading to cervical cancer. Cervical cancer is postulated as a progressive disease as some lesions progress to moderate and subsequently severe dysplasia, finally progressing to invasive cancer [3,9,24].

CAUSES FOR INCREASED INCIDENCE OF CERVICAL CANCER IN YOUNG WOMEN

Cervical cancer screening programs have improved detection of early invasive cervical carcinomas in women of childbearing age [25-27]. Cervical cancer is still a major problem in developing countries where approximately 80% of the cases occur. The implementation of coordinated and organized cytology screening programmes in developed countries has resulted in a marked decrease of the disease over the past decades [28]. The high incidence rate of cervical cancer as well as its progressiveness has led researchers to continually examine and pursue better diagnosis, prognosis, and treatment techniques to decrease mortality rates and comorbidity from the disease [8].

Criteria that define this low-risk group include: squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma, tumor size <2 cm, stromal invasion <10mm, and no lymph-vascular space invasion. The GOG is currently evaluating physical function and quality of life in patients following non-radical surgery for early stage cervical cancer patients (IA1 with Lymph-Vascular Space Invasion **(LVSI)**, IA2–IB1 ≤2 cm) [11].

For women with early stage disease undergoing surgical management, the standard treatment consists of a radical hysterectomy and pelvic lymph node dissection [29,30]. Although radical hysterectomy results in excellent local tumor control, it is also associated with significant morbidity [19,31-35]. Much of this morbidity is due to removal of the parametrium, which contains autonomic nerve fibers associated with bladder, bowel and sexual function. The utility of parametrial resection in women with early stage cervical cancer is controversial.

WHY CONSERVATIVE SURGERY FOR EARLY CERVICAL CANCER?

In patients with favourable pathologic characteristics such as tumor size <2 cm and absence of lymphovascular space invasion, the rate of parametrial involvement is very low. Non-radical surgery can be considered in such patients desirous of fertility preservation in whom tumor size <2 cm, limited depth of invasion, absence of LVSI and negative pelvic lymph nodes on frozen section when the risk of parametrial involvement is approximately 1% or less. In a study by Covens et al, the incidence of parametrial involvement in patients with negative lymph nodes, tumor size 2 cm or smaller, and stromal invasion 10 mm or less was 0.6% [36]. In the treatment of microinvasive squamous cell carcinoma, for instance, cone biopsy or simple hysterectomy has become an acceptable alternative [11,37,38].

ROLE OF PRE-OPERATIVE MRI IN DETERMINING THE RADICALITY OF SURGERY

Preoperative Magnetic Resonance **(MR)** imaging allows for noninvasive evaluation of the tumor size, cranial extent, and parametrial involvement. Cervical carcinoma was diagnosed if a lesion is found that had higher T2 Signal Intensity **(SI)** than the adjacent cervical stroma. The presence of tumor was scored as follows: 1, Definitely absent; 2, Probably absent; 3, Indeterminate (ie, impossible to distinguish residual tumor from postprocedural inflammation); 4, Probably present; and 5, Definitely present. Tumor, if present, was measured in three orthogonal planes by analyzing T2-weighted and, if available, contrast agent material–enhanced images. The largest tumor dimension was recorded [25,39,40]. Although pretrachelectomy MR imaging is considered mandatory by many, few studies have evaluated the diagnostic value of MR imaging and its ability to help predict what surgical procedure will ultimately be performed [41-43]. Pretrachelectomy MR imaging can help identify high-risk patients likely to need radical hysterectomy or confirm the absence of residual tumor in the cervix after a cone biopsy with negative margins.

EVOLUTION OF CONSERVATIVE SURGICAL TREATMENT OPTIONS IN EARLY CERVICAL CANCER

Traditionally, treatment for International Federation of Gynecology and Obstetrics **(FIGO)** stage IB disease has been radical hysterectomy and pelvic lymphadenectomy with en bloc removal of the uterus and parametria. In the late 1980s, radical trachelectomy with pelvic lymph node dissection was introduced as an alternative for young women with early stage cervical carcinoma who wanted to preserve their fertility [25,44]. This procedure involves radical removal of the uterine cervix, adjacent parametria, and a cuff of the vagina. Ideally, a 1-cm disease-free margin is achieved and healthy upper endocervical stroma of 1 cm or larger is preserved to increase the chance of the patient maintaining pregnancy [25,39]. Both transabdominal and transvaginal forms of radical trachelectomy are effective for treatment of early stage cervical cancers and result in acceptable rates of successful pregnancies [25,45]. Evidence demonstrates there is a reduction in tumour size in patients receiving neoadjuvant chemotherapy as well as a reduction in poor prognostic factors such as LVSI, parametrial invasion and lymph node metastases [46,47].

DIFFERENT SURGICAL TREATMENT OPTIONS [5,11]

- Simple Trachelectomy/ Cervical conization with or without sentinel lymph node biopsy and pelvic lymph node dissection.
- NACT prior to Fertility-Preserving Surgery
- Radical Trachelectomy

A. Vaginal approach

B. Abdominal approach

i. Open Radical Trachelectomy

ii. Laparoscopic Radical Trachelectomy

iii. Robotic Radical Trachelectomy

Simple Trachelectomy/Cone Biopsy

Cone biopsy, if proven to be oncologically safe, could be considered for patients desiring fertility preservation, since it may be associated with fewer obstetrical complications than trachelectomy. Obtaining negative cone margins is crucial to ensuring the safety of conisation for the treatment of invasive carcinoma [11,48]. Eligibility for conisation was determined using Rainer's system, which combines depth of invasion, LVSI, host defense reaction, pathologic pattern on invasion, mitotic activity and cell type [11,49]. The use of cone biopsy alone is common practice for stage 1A1 SCC of the cervix without LVSI [11,50]. This is based on a risk of pelvic nodal metastases of approximately 1%, and a very low rate of recurrence in these patients [11,38]. Studies generally reported conisation using a cold-knife technique [11,51] although some investigators reported the use of laser conisation [52-54]. Use of Loop Electrosurgical Excision Procedure **(LEEP)** is discouraged due to the difficulty in confirming negative margins [11,52]. 62%–67% of patients who have had a diagnostic cone biopsy have no residual carcinoma in the final trachelectomy specimen [55-57]. The chances of finding residual cancer are further reduced when cone biopsy margins are negative. Lakhman et al found that six of six patients with negative cone biopsy margins and no tumor at postconization MR imaging had no tumor at final trachelectomy pathologic examination. Further studies are needed to determine whether a less radical procedure (eg, a simple trachelectomy or a large cold knife cone combined with sentinel lymph node sampling) may effectively treat the cancer and spare fertility in this group of low-risk patients. The concept of simple trachelectomy and node assessment is an interesting emerging concept. Clearly, careful patient selection is of paramount importance. Abundant retrospective recent literature has shown that in small-volume, low-risk, early-stage cervical cancer (primarily defined as measuring G2 cm with G50% stromal invasion), the probability of parametrial extension is very low. Larger series are necessary to confirm the safety of this ultraconservative approach [26].

Procedure of simple trachelectomy

A tenaculum is placed on the cervix, followed by cervical injection of lidocaine solution containing a vasoconstrictor. The vaginal wall is incised circumferentially just above the cervix, paying close attention to carry the incision through the full thickness of the wall. Similar to a radical trachelectomy, the peritoneum is entered posteriorly and anteriorly. The uterosacral ligaments are clamped, cut, and ligated. Unlike a radical trachelectomy, the parametrium is not excised. The cervix is amputated just distal to the internal os. The specimen is removed, and the cervical stump is sutured to the vaginal mucosa [58].

Sentinel Lymph node biopsy in determining the lymph node status

Conceptually, the sentinel node is the first lymph node in a basin of lymph nodes draining a particular anatomical location. Therefore, if the sentinel node is free of metastatic disease, the other lymph nodes in the regional basin will also be negative for metastasis, and a full lymphadenectomy can be avoided [11,59]. In a systematic review, the sensitivity of SLNB in early cervical cancer was 92% (95% CI 84–98%) and the detection rate was 97% (95% CI 95–98%) when the combined technique of technetium-99 radiotracer and blue dye was used [11,60]. The sensitivity of SLNB is improved in small tumors measuring 2 cm or less compared to larger tumors [11,61].

NACT prior to Fertility-Preserving Surgery

Maneo et alpioneered this approach and proposed 3 cycles of chemotherapy followed by lymph node dissection and simple conisation [11,62]. There are no randomized studies to date exploring the use of NACT to allow for non-radical surgery, and insufficient patient numbers and follow-up preclude statements of safety in this setting. While the use of NACT prior to non-radical surgery (conisation or simple trachelectomy) for fertility preservation has been reported, [11,63,64] its safety is only supported by small case series and can only be considered experimental. This concept is currently being explored by the Gynecologic Oncology Group (CVM 1201, personal communication).

Radical Trachelectomy

Fertility preservation through the use of radical vaginal trachelectomy in patients with early cervical carcinoma was first described by Dargent [65]. A radical trachelectomy with pelvic lymphadenectomy is a reasonable fertility-sparing approach for treating selected patients with stage I cervical cancers. This operation is a major innovation in the surgical therapy of early cervical cancer [66,67]. Over the last 20 years, radical trachelectomy has also been performed abdominally through open [11,39] laparoscopic [11,68,69] and robotic [11,70-72] approaches. Regardless of approach, radical trachelectomy removes the cervix with contiguous parametria and upper vaginal cuff, and preserves the uterine corpus and adnexae. It is combined with an assessment of the pelvic lymph nodes.

Vaginal Radical Trachelectomy

The radical vaginal approach to trachelectomy was developed and popularized in France in the 1980s and 1990s [66,67]. It is a modification of the radical vaginal hysterectomy (Schauta) to treat early cervical cancer and preserve uterine morphology and reproductive function. The general eligibility criteria for radical vaginal trachelectomy include the following: women less than 40 years of age who have a strong desire to preserve fertility, no clinical evidence of impaired fertility, lesion size less than 2 cm, International Federation of Gynecology and Obstetrics **(FIGO)** stages IA–IB1, no involvement of the upper endocervical canal, and negative regional lymph nodes [44]. Vaginal radical trachelectomy is the most commonly reported procedure and has

resulted in the highest number of successful pregnancies. Obstetrical results following vaginal radical trachelectomy for early-stage cervical cancer are very encouraging [5].

Procedure of Vaginal radical trachelectomy consists of 5 steps [73]:

(1) Vaginal cuff preparation,

(2) Posterior phase,

(3) Anterior phase,

(4) Lateral phase and

(5) Excision of the specimen and closure

The procedure is begun by defining approximately 2 cm of the vaginal mucosa and grasping the vaginal margin with 5-8 straight clamps. A local anesthetic containing a vasoconstrictor is then injected followed by a circumferential incision along the vaginal mucosa. Then, the posterior phase is developed by opening the posterior cul-de-sac. The paracolpos are excised, and the pararectal space is opened. The uterosacral ligaments are isolated and divided. By releasing the posterior attachments, there is greater uterine descent to help with the anterior phase [74]. The anterior phase is developed by opening the vesicouterine space followed by the paravesical spaces. The ureter is localized and mobilized by dissecting the bladder pillar off the cardinal ligament. After the ureter has been dissected and identified, the uterine vessels will be visible over the ureter. Subsequently, the lateral phase is performed by excising the parametrium. Unlike in vaginal hysterectomy, only the descending branch of the uterine artery is excised. It is important to leave optimal vascularization of the uterus, since the procedure is being performed to preserve fertility. The cervicovaginal artery is clamped, ligated, and cut. Lastly, the cervix is transected approximately 1 cm below the internal cervical os. The specimen should be 1-2 cm wide, with a 1-cm vaginal mucosa and 1-2 cm of parametrium. The final step is the reconstruction phase. A prophylactic cerclage is placed at the level of the isthmus using a nonresorbable suture such as Prolene. In order to avoid cervical stenosis, a rubber catheter is inserted into the remaining cervical canal. The final step involves approximating the edge of vaginal mucosa to the new exocervix [73].

Abdominal Radical Trachelectomy

Although the concept of a uterine fundus-sparing radical abdominal trachelectomy (Colpohisterectomia largita subfundica) for microcarcinoma and *in situ* carcinoma of the cervix was described by Aburel [67,75,76] in Romania in the 1950s, this abdominal procedure did not initially become popular; and until recently, fertility-sparing surgical options in cervical cancer remained limited to cervical conization in selected women with very early lesions (stage IA1) and a strong desire to retain reproductive function. The intent of the radical abdominal trachelectomy was to resect the cervix, upper 1–2 cm of the vagina, parametrium, and paracolpos in a similar

manner to a type III radical abdominal hysterectomy but sparing the uterine fundus or corpus [68]. The abdominal radical trachelectomy may possibly be an option for highly selected women with stage IB1 lesions and a clinical diameter of 2–4 cm who desire fertility preservation and may be excluded from the radical vaginal approach. Moreover, Ungar, who reported the largest abdominal trachelectomy experience to date, described cases performed in stage IB2 disease [77].

Smith et al pioneered this approach. Indications and advantages of the abdominal approach include patients with distorted vaginal anatomy, pediatric patients, bulky exophytic lesions, and the need for increased radicality [5,78]. Initial description of the procedure involved the sacrifice of the uterine artery bilaterally. However, recent improvements in the surgical technique allow for preservation of the main uterine artery. New advances in the surgical technique allow for nerve-sparing radical trachelectomy in the hope of reducing the morbidity of the procedure [5,79].

Procedure of Abdominal Radical Trachelectomy: Abdominal radical trachelectomy can be approached multiple ways. The surgery can be performed with a low transverse (with either a Cherney or Maylard) or a vertical incision.

Upon entry into the abdominal cavity, an intra abdominal survey is performed by paying close attention to the abdominal viscera and parietal peritoneum for possible evidence of metastasis. A self-retaining or Bookwalter retractor is used to provide better exposure into the abdominal cavity. The liver, diaphragm, spleen, small and large bowel and omentum are evaluated for evidence of metastasis.

A bilateral complete pelvic lymphadenectomy is performed. Any suspicious lymph nodes are sent for frozen-section evaluation. Upon evidence of metastasis, the radical trachelectomy procedure is abandoned. If there is no evidence of metastasis, the procedure is started by developing the paravesical and pararectal spaces. The retroperitoneal space is opened through the round ligament. Clamps are placed on the medial round ligaments to assist with uterine manipulation. Care is taken to avoid injury to the infundibulopelvic and tuboovarian ligaments. Once the ureter and bladder are dissected, the uterine arteries at transected at their origin bilaterally. After mobilizing the ureter off the broad ligament, the parametria and paracolpos are dissected in a fashion similar to a radical hysterectomy. At this point, the posterior cul-de-sac is incised and the uterosacral ligaments are divided. Finally, clamps are placed on the lower uterine segment at the level of the internal os followed by transection of the specimen. The vaginal mucosa is sutured to the remaining cervical stump, followed by a prophylactic cerclage [58].

Recent data indicate that ART does not appear to affect ovarian function with respect to ovarian reserve and response to ovarian stimulation, which is reassuring [5,80].

Laparoscopic Radical Trachelectomy [5]: The laparoscopic radical trachelectomy was adapted from the laparoscopic radical hysterectomy technique. There are variations in the technique, in that some groups do parts of the surgery laparoscopically and complete the rest vaginally,

whereas others do the entire procedure laparoscopically. Caution regarding patient selection is of paramount importance, and it should primarily be performed in patients with small-volume disease.

Robotic Radical Trachelectomy [5]: Surgeons have adapted the technique of the ART to the robot, claiming to obtain as radical a trachelectomy specimen as with ART but with the benefits of a minimally invasive approach. . Refinement in the technique allows for uterine artery preservation and nerve-sparing procedure. It is currently too early to tell if the obstetrical and oncologic outcomes will be comparable to other techniques, but in theory, they should be. Obviously, the main limitation for the approach is access to the robot.

SHORTCOMINGS AND FERTILITY ISSUES WITH RADICAL TRACHELECTOMY

Despite careful preoperative patient evaluation, 10%–12% of patients are found to have more extensive than expected endocervical disease or positive lymph nodes during attempted fertility-sparing surgery, which results in the abandonment of radical trachelectomy in favor of radical hysterectomy or adjuvant radiation therapy [25,40,57,81,82].

Fertility rates vary after radical trachelectomy, but have been reported to be between 41% and 70% [56,83,84]. Fertility may be impaired after trachelectomy secondary to cervical stenosis, absence of cervical mucus, or occult tubal disease, although women attempting to conceive after radical trachelectomy may be older than other women attempting pregnancy, which may partially account for the lower rates of fertility observed [85]. Premature birth and PPROM are the most important complications of pregnancy after VRT. Ma LK et al observed the pregnancy rate of 36.4% and the rate of preterm delivery rate was 25%-28%, which represents an increased risk of four-fold as compared with the normal population [86]. The mechanism is likely to be due either to cervical incompetence or to increased incidence of infection. The impaired production of mucus can facilitate the access of microorganisms to the choriodecidual space and the uterine cavity, leading to preterm birth and PPROM [87]. There is an increased occurrence of preterm delivery after VRT. Caesarean section after full term pregnancy through a high transverse incision should be considered as a suitable and safe procedure.

ADENOCARCINOMA AND RADICALITY

Approximately 15–25% of cases of cervical carcinoma are histologically adenocarcinoma [37,88,89] and the incidence appears to be increasing, particularly in younger women [90]. Women with adenocarcinoma receive more radical and aggressive treatment than those with SCC due to the difficulty in the diagnosis and measurement of early invasive adenocarcinoma [91]. Studies support the safety of conisation and follow-up of FIGO stage IA1 cervical adenocarcinomas [91-98].

PROSPECTIVE TRIALS OF CONSERVATIVE SURGICAL MANAGEMENT OF LOW-RISK CERVICAL CANCER

Currently, 3 prospective trials are evaluating a conservative approach in patients with lowrisk early-stage cervical cancer.

1. Prospective trial lead by Schmeler and colleagues at The University of Texas MD Anderson Cancer Center [99]

2. Gynecologic Cancer Intergroup trial led by Plante and colleagues. The study is known as the SHAPE Trial [100]

3. Gynecologic Oncology Group protocol 278, a multiinstitutional trial, led by Alan Covense, entitled "Evaluation of physical function and quality of life before and after non-radical surgical therapy (extrafascial hysterectomy or cone biopsy with pelvic lymphadenectomy) for stage IA1 (LVSI+) and IA2-IB1 (≤2 cm) cervical cancer" [101].

CONCLUSION

Ongoing research efforts are especially being made in properly identifying the patient subset suitable for a conservative/less radical approach and prospectively confirming the oncological safety of the proposed clinical-pathological algorithms. VRT is an effective fertility-preserving treatment for young patients with early-stage cervical cancer ((Table 1) Staging of Cervical Cancer) and has reasonable oncology and fertility outcomes [102].

The American Joint Committee on Cancer **(AJCC)** TNM classification and the International Federation of Gynecology and Obstetrics **(FIGO)** staging system for cervical cancer are provided below [103,104,105].

Table 1: TNM and FIGO Classifications for Cervical Cancer.

Primary tumor (T)

TNM	FIGO	Surgical-Pathologic Findings
Categories	*Stages*	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma *in situ* (preinvasive carcinoma)
T1	I	Cervical carcinoma confined to the cervix (disregard extension to the corpus)
T1a	IA	Invasive carcinoma diagnosed only by microscopy; stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less; vascular space involvement, venous or lymphatic, does not affect classification
T1a1	IA1	Measured stromal invasion ≤ 3.0 mm in depth and ≤ 7.0 mm in horizontal spread
T1a2	IA2	Measured stromal invasion > 3.0 mm and ≤ 5.0 mm with a horizontal spread ≤ 7.0 mm
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
T1b2	IB2	Clinically visible lesion > 4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2a1	IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
T2a2	IIA2	Clinically visible lesion > 4.0 cm in greatest dimension
T2b	IIB	Tumor with parametrial invasion
T3	III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctional kidney
T3a	IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctional kidney
T4	IV	Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)
T4a	IVA	Tumor invades mucosa of bladder or rectum (bullous edema is not sufficient to classify a tumor as T4)
T4b	IVB	Tumor extends beyond true pelvis
Regional lymph nodes (N)		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
Distant metastasis (M)		
M0	No distant metastasis	
M1	Distant metastasis (including peritoneal spread; involvement of supraclavicular, mediastinal or para-aortic lymph nodes; and lung, liver or bone)	

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