CHAPTER 14.

Surgical management of early invasive cervical cancer

Wertheim described the principles of surgical management of invasive cervical cancer more than 100 years ago in his treatise on 500 cervical cancers operated by radical hysterectomy (Wertheim, 1912). Wertheim's radical hysterectomy included removal of the uterus, upper vagina, and adjacent supporting tissues medial to the ureters, along with the metastatic lymph nodes. In the 1940s, Meigs introduced the concept of routine systematic pelvic lymphadenectomy along with extended parametrial dissection up to the lateral pelvic wall. With his improved technique, he demonstrated a high survival rate (Meigs, 1951). By that time, the surgical practice had become much safer with the use of antibiotics, thromboprophylaxis, and administration of blood products. As a result, Meigs could also demonstrate significantly lower morbidity, including intra-operative deaths, in his case series. Radical vaginal hysterectomy was initially described by Schauta (1908) and was subsequently combined with extraperitoneal lymphadenectomy by Mitra (1959). Over the past decades, two major developments have taken place in the surgical management of early cervical cancer: the increasing use of minimal access techniques for radical surgery, and tailoring the radicality of surgery to the extent of the disease. With the increasing popularity of minimal access surgeries, there has been a renewed interest in radical vaginal hysterectomy.

Because of the effective screening programmes, early-stage cervical cancers are increasingly being detected in younger women. These women have a long life expectancy after treatment, and the management strategies are increasingly focusing on improvement in quality of life, free of long-term treatment sequelae. Like for any other malignancies, involvement of a multidisciplinary team comprising gynaecological oncologists, radiation and medical oncologists, pathologists, and radiologists can optimize the patient care.

The management of microinvasive cancer (stage IA1) has been described in Chapter 13. In this chapter, the discussion is restricted to principles of surgical management of more advanced cervical cancers. Detailed descriptions of the steps of radical surgeries are beyond the scope of this manual.

14.1 Diagnosis and staging

Diagnosis of cervical cancer should be confirmed by histology before treatment is planned. Like for cancers of other sites, the management of

cervical cancer is essentially based on the extent of the disease. Cervical cancer spreads through direct extension to the paracervical tissues, the vagina, and the parametrium, and can invade the urinary bladder and rectum in more advanced stages. Although spread to the endometrium/body of the uterus is uncommon, such involvement has been shown to increase the risk of distant metastasis. However, involvement of the endometrium/body of the uterus is not taken into account in staging and does not alter stage. For instance, in a patient with stage I cancer, stromal involvement of the endometrium/body of the uterus does not alter the stage.

The disease spreads to the pelvic lymph nodes, which comprise the paracervical, obturator, internal iliac, external iliac, presacral, and common iliac nodes. The extension of the disease to the para-aortic nodes is considered distant metastasis. Other common sites of distant metastasis are bone (particularly the spine), lungs, and liver.

The staging of cervical cancer by FIGO was last updated in 2009 and is described in Table 14.1 (Wiebe et al., 2012). The FIGO staging is essentially clinical, backed by a limited number of investigations, like chest X-ray, ultrasonography, and cystoscopy and proctosigmoidoscopy if indicated. For cervical cancer, the pre-treatment staging is the most clinically relevant staging, on which therapeutic decisions are based. Although CT scans and MRI – and even positron emission tomography (PET) scans, in advanced healthcare settings – are increasingly used to define pre-treatment staging in many settings, these are not mandatory investigations for clinical staging of cervical cancer.

Ideally, the clinical examination required for staging should be performed under anaesthesia, although this is not mandatory. In LMICs, the majority of cervical cancers present at advanced stages and can be staged clinically in the outpatients department with reasonable accuracy. Every patient should have a thorough pelvic examination that includes inspection and palpation to note the position and size of the cervical growth, as well as extension to the vagina and the parametrial tissues. Colposcopy is useful to note the extent of the tumour in the vagina and the presence of vaginal

Table 14.1. FIGO staging for cervical cancer (last updated in 2009)

FIGO stage (2009)	Description
I	Cervical carcinoma confined to uterus (extension to body of uterus should be disregarded)
IA	Only microscopically visible lesion with stromal invasion not exceeding 5.0 mm and horizontal extension not exceeding 7.0 mm
IA1	Stromal invasion no greater than 3 mm in depth and no wider than 7 mm in diameter
IA2	Stromal invasion greater than 3 mm but does not exceed 5 mm in depth and no wider than 7 mm in diameter
IB	Microscopic lesion exceeding stage IA2 or clinically visible lesion confined to the cervix
IB1	Size of lesion 4.0 cm or less in the greatest dimension
IB2	Size of lesion exceeds 4.0 cm in the greatest dimension
II	Tumour extends beyond the cervix but not to the pelvic wall or to the lower third of the vagina (extension to corpus should be disregarded)
IIA	No parametrial invasion
IIA1	Size of lesion 4.0 cm or less in the greatest dimension
IIA2	Size of lesion exceeds 4.0 cm in the greatest dimension
IIB	Parametrial invasion present
III	Tumour extends to the pelvic wall and/or involves the lower third of the vagina and/or causes hydronephrosis or non-functioning kidney
IIIA	Extends to the lower third of the vagina without any spread to the lateral pelvic wall
IIIB	Extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney
IV	Tumour involves the bladder or rectal mucosa and/or extends beyond the true pelvis
IVA	Tumour involves the bladder or rectal mucosa
IVB	Distant metastases

FIGO, International Federation of Gynecology and Obstetrics.

intraepithelial neoplasia. Vesical involvement should be suspected if there is extensive involvement of the anterior vaginal wall by a large growth with induration of the bladder base. Rectal examination is very valuable to diagnose the nature and extent of parametrial involvement and infiltration of the disease to the rectal mucosa. Pelvic and abdominal ultrasonography has replaced routine intravenous urography to exclude hydroureter and hydronephrosis. Ultrasonography provides additional information, such as the size of the growth, possible invasion of the bladder and rectum, metastasis to the liver, and so forth. Cystoscopy and proctosigmoidoscopy should be performed if there are clinical and/or radiological suspicions of bladder and rectal involvement, respectively. Bladder or rectal mucosal involvement has to be proven by histology. Bullous oedema of the bladder epithelium does not, by itself, confirm malignant infiltration of the bladder wall. Additional information may be obtained from CT scans, MRI, and PET scans. MRI (thin-section T2-weighted images perpendicular to the cervix) is more accurate than other imaging modalities in assessing the tumour volume and the extent of spread to the vagina or parametrium and is useful in selecting cases for more conservative surgery. Involvement of pelvic and para-aortic nodes can be best assessed by PET-CT scan. However, the results of these specialized diagnostic procedures should not alter the initial clinical FIGO staging.

14.2 Principles of surgical treatment of early cervical cancer

The management of cervical cancer depends on the age of the patient, the stage of the disease, whether fertility preservation is required, co-morbidities, and availability of and access to different treatment options. Radical surgery for early cervical cancer requires good surgical skills and operative facilities. Definitive surgical management is feasible only in early stages of the disease, such as stages IA, IB1, and IIA1, when the vaginal involvement does not extend beyond 2 cm. Radiotherapy can be equally effective at the early stages, although surgical treatment is preferred. The major advantages of surgery are preservation of ovarian function, better preservation of sexual function (by avoiding radiation-induced stenosis and shortening of the vagina), accurate assessment of the lymph node status, and avoidance of long-term radiation sequelae, such as vaginal atrophy, stenosis, and bladder and rectal morbidity. Fertility can also be preserved by specialized surgical procedures. Radiation-induced long-term complications, especially cystitis and proctitis, can be very distressing to the patient and difficult to treat. Radiotherapy may be the treatment of choice for early cervical cancer in women with co-morbid conditions that may make surgical interventions more risky. For small-volume early disease, survival outcomes are similar for surgery and radiotherapy. As a general principle, surgery should be avoided if there is a need for adjuvant radiotherapy or chemoradiotherapy.

From stages IB2, IIA1 with vaginal involvement of more than 2 cm, and IIA2 onward, radiotherapy (with or without concomitant cisplatin-based chemotherapy) is the treatment of choice, because the incidence of lymph node metastasis increases significantly (> 35%) if the size of the lesion exceeds 4 cm (stage IB2 or stage IIA2). It is important to understand that the combination of surgery and radiotherapy increases the risk of post-treatment morbidities several-fold and should be avoided as much as possible. Surgery should not be attempted or may be abandoned if there is any suspicion that the patient would require radiotherapy in spite of surgery. Patients with bulky tumour volume and radiological evidence of lymph node involvement should not be scheduled for surgery and should be referred directly for radiotherapy.

14.3 Radical hysterectomy for cervical cancer

The most common surgery for early invasive cervical cancer is a combination of radical hysterectomy and bilateral pelvic lymphadenectomy. Radical hysterectomy involves en bloc removal of the uterus with the cervix, the upper vagina, and the parametrium. Ovaries can be preserved in younger women with squamous cell cancers, because the risk of the tumour spreading to the ovaries is very low in these patients. During surgery, the ovaries are trans-positioned retroperitoneally above the pelvic brim so that they escape radiation-induced damage in case the patient requires postoperative radiotherapy.

The extent of radicality of the surgery depends on the size and the nature of the tumour. Piver et al. (1974) classified radical hysterectomy into five types, ranging from extrafascial hysterectomy (type I) to partial resection of the ureter and bladder along with the uterus and vagina (type V). Each class requires progressively more radical resection than the previous one and is associated with increased morbidity (Fig. 14.1). Querleu and Morrow (2008) modified Piver's classification and included paracervical lymph node dissection and nerve-sparing radical hysterectomy. The comparison between the two classifications is shown in Table 14.2. Piver type V has become obsolete, because the

majority of the patients requiring this grade of radical surgery are treated by radiotherapy with or without chemotherapy.

As described in Chapter 13, all cases of microinvasive cancer (stage IA1) should have a large type 3 excision of the TZ, preferably with a scalpel (cold-knife conization). Patients who have LVSI and/or positive cone margin and who do not desire future fertility should have an extrafascial (type A) hysterectomy after cone biopsy. The rest of the patients need careful monitoring through annual screening. For a stage IA1 tumour, the risk of lymph node metastasis is less than 1% unless there is LVSI. Bilateral pelvic lymphadenectomy is indicated along with hysterectomy only in the presence of LVSI, because the likelihood of lymph node involvement is higher.

For patients with stage IA2 and small (< 2 cm) stage IB1 disease, parametrial dissection up to the lateral pelvic wall (as originally proposed by Meigs) is not required. The spread of disease through the pelvic lymphatics is an embolic phenomenon. In these early cancers, disease is found in the lateral parametria very rarely, especially when the lymph nodes are also negative for any metastasis. For these stages, the surgery is less radical, including only medial parametrectomy, and is called modified radical hysterectomy (type B1). Type C1 or C2 radical hysterectomy is appropriate for more advanced (> 2 cm) stage IB1 or stage IIA1 disease.

Some recent publications suggest that even less radical surgery for small (< 2 cm) stage IB1 disease has a similar oncological outcome with significant reduction in immediate and late morbidities and improved quality of life (Reade et al., 2013). The risk of parametrial infiltration is less than 1% if the cancer is less than 2 cm in diameter, does not have LVSI or lymph node metastasis, and has a maximum depth of infiltration less than 10 mm (Gemer et al., 2013). In carefully selected cases of stage IA2 or stage IB1 disease with a cancer that is smaller than 2 cm, non-radical surgeries may be performed. A Gynaecologic Oncology Group trial is currently evaluating this. Several case series and case–control studies evaluating simple hysterectomy or simple trachelectomy in such cases observed no increase in recurrence or mortality. A randomized case–control study by Landoni et al. (2012) found the same results in tumours smaller than 3 cm. However, this approach should be practised in centres with high-quality pathology services after adequately counselling the women about the need for regular follow-ups.

Many oncologists are hesitant to recommend conservative treatment of adenocarcinomas, because pathological interpretation of adenocarcinoma is more complicated due to lack of concordance in assessing the tumour volume, depth of infiltration, and LVSI. This is in spite of the fact that the majority of the studies showed no difference in outcome (Al-Kalbani et al., 2012).

Protection of the autonomic pelvic nerve plexus from injury during surgery results in faster recovery of bladder function and reduced incidence of bladder dysfunction after surgery (Ceccaroni et al., 2012; Fujii et al., 2007). This technique, originally described by Okabayashi, is known as nerve-sparing radical hysterectomy (Fujii et al., 2007). The hypogastric nerves originating from the superior hypogastric plexus and the upper part of the inferior hypogastric plexus are exposed along the lateral border of the mesorectum. The inferior hypogastric plexus, which comprises the hypogastric nerve and the pelvic splanchnic nerve, is mobilized and protected before transection of the uterosacral ligaments. The vesical branch of the plexus is also preserved. Studies have also reported better preservation of sexual function after nerve-sparing surgery (Jarruwale et al., 2013).

Fig. 14.1. Sagittal section of female pelvis showing the different pelvic spaces and extent of dissection in different classes of radical hysterectomy.

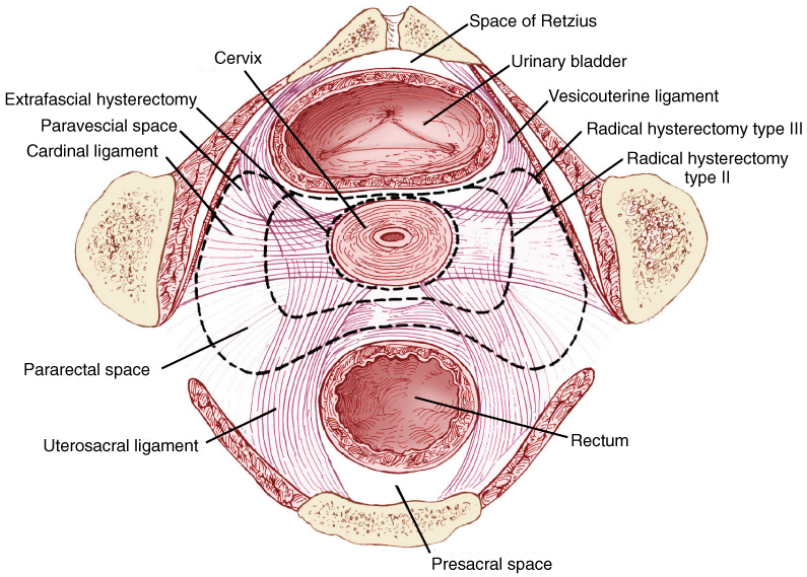

Table 14.2. Comparison between the classifications of radical hysterectomy by Piver et al. (1974) and Querleu and Morrow (2008)

Piver–Rutledge classification		Querleu–Morrow classification		Indications
Class I	Extrafascial hysterectomy Ureter not dissected Cardinal and uterosacral ligaments resected as close as possible to uterus Vagina not excised	Type A	Extrafascial hysterectomy Cardinal and uterosacral ligaments resected as close as possible to uterus Removal of < 1 cm of vagina	Stage IA1 with LVSI
Class II	Modified radical hysterectomy Uterine artery ligated medial to the ureters Ureter freed from paracervical tissues but not mobilized from pubovesical ligament Cardinal ligament resected up to medial half Uterosacral ligament resected midway from sacral insertion	Type B1	Ureters mobilized laterally Partial resection of vesico-uterine and uterosacral ligaments Resection of paracervical tissue at ureteric tunnel At least 1 cm of vagina from cervix or tumour excised Lateral paracervical lymph nodes not removed	Stage IA2
		Type B2	All resections as per type B1 Removal of lateral paracervical lymph nodes	Stage IB1 (≤ 2 cm)
Class III	Radical hysterectomy Complete mobilization of ureter including from pubovesical ligament Uterine artery ligated at origin Cardinal ligament resected close to pelvic wall Uterosacral ligament excised near sacral insertion Upper half of vagina removed	Type C1	Complete mobilization of ureter Complete resection of paracervical tissue Sectioning of uterosacral ligaments at the level of the rectum 1.5–2 cm of vagina from cervix or tumour resected with paracolpos Autonomic nerve supply preserved	Stage IB1 (> 2 cm); stage IIA1
		Type C2	All resections as per type C1 Autonomic nerve supply not preserved	
Class IV	Complete dissection of ureter Umbilical-vesical artery sacrificed Three quarters of upper vagina excised	Type D1	Ureter fully mobilized Complete resection of paracervical tissues up to lateral pelvic wall Internal iliac vessels tied Sciatic nerve roots exposed	Recurrent (central, < 4 cm) cervical cancer
		Type D2	All resections as per type D1 Resection of muscles and adjacent fascia	
Class V	Class IV along with partial excision of ureter and/or bladder	—	—	—

LVSI, lymphovascular space involvement.

14.4 Pelvic lymphadenectomy for cervical cancer

Pelvic lymphadenectomy includes removal of all the lymph nodes along with the fibro-fatty tissues from the external iliac, internal iliac, and common iliac vessels and also from the obturator fossa. The distal extent of nodal dissection is the crossing of the deep circumflex iliac vein over the external iliac artery, and the proximal extent is the aortic bifurcation or at least the middle of the length of the common iliac artery. The obturator nodes should be collected from below the obturator nerve up to the level of the pelvic diaphragm.

Identification of the sentinel node and tailoring of the subsequent management based on the histology of the node is widely practised in breast cancer, vulvar cancer, and so forth. The sentinel lymph node is the first node involved in case of lymphatic spread, and if the sentinel node is negative, the remainder of the nodes in the nodal basin are considered to be free of disease. In early cervical cancer, the sentinel node can be detected either by injecting 1% isosulfan blue dye around the tumour or by injecting ^{99m}Tc-nanocolloid into the tumour after anaesthesia (van de Lande et al., 2007). Sometimes both are used, for more accurate detection. The sentinel node is detected mostly in the internal iliac, obturator, or external iliac group of nodes, in that order of frequency, and has a high negative predictive value. If the frozen-section histopathology of the sentinel node is negative, further systematic lymphadenectomy and the consequential risk of

lymphocysts and lymphoedema can be avoided (Gortzak-Uzan et al., 2010). Sentinel node biopsy does not have any value in more advanced disease (tumour size > 2 cm or stage IIA) or if there are already grossly enlarged lymph nodes. Systematic lymphadenectomy is always recommended in those cases, along with radical hysterectomy. Sentinel node detection is not yet recommended for routine practice, because long-term follow-up data are still awaited.

Para-aortic lymphadenectomy is not recommended for the management of early cervical cancer. If suspicious nodes are seen in the para-aortic region during surgery, they should be removed and sent for frozen-section histopathology. A positive para-aortic lymph node is an indication for abandoning the radical hysterectomy and referring the patient for radiotherapy.

14.5 Fertility preservation in cervical cancer

Hysterectomy can be avoided in stage IA1 cervical cancer by performing cold-knife conization if the woman desires preservation of fertility. In more advanced cases (stage IA2 or stage IB1), the surgical technique of choice for fertility preservation is radical trachelectomy, which can be performed by both vaginal and abdominal routes. Radical vaginal trachelectomy is practised more commonly and was first described by Dargent more than 20 years ago (Dargent, 1994). In this surgery, the cervix along with the contiguous upper 1–2 cm of the vagina and the medial parts of the Mackenrodt's and uterosacral ligaments are resected through the vaginal approach. A prophylactic cerclage suture is applied after transection of the cervix near the isthmus. Radical trachelectomy must be preceded by bilateral pelvic lymphadenectomy (usually by laparoscopic approach) and frozen-section histopathology of all the nodes.

The criteria for selection of cases for radical trachelectomy are:

- stage IA1 (with LVSI), IA2, or IB1;
- tumour size less than 2 cm;
- limited endocervical extension;
- histology other than clear cell carcinoma, neuroendocrine tumour, or sarcoma;
- no deep stromal infiltration (greater than 10 mm);
- pelvic lymph nodes free of metastasis;
- patient desires preservation of fertility; and
- no known infertility problem.

The excised specimen after radical trachelectomy should be sent for frozen-section histopathology to assess the proximity of the tumour to the resected margin. If the gap is less than 5 mm, the surgery has to be converted into radical hysterectomy. A preoperative MRI is very useful to assess the tumour volume and the extent of the cervical growth to the parametrium or inside the endocervical canal. Studies that compared radical hysterectomy with radical trachelectomy and controlled for age, tumour size, histology, grade, depth of invasion, LVSI, pelvic node metastasis, and adjuvant therapy observed similar 5-year recurrence-free or overall survival. A meta-analysis of 346 patients treated with radical trachelectomy reported a recurrence rate of 4.1% after a median follow-up of 44 months (Plante et al., 2004). Fertility rates after radical trachelectomy vary between 40% and 70%, with a live birth rate of about 70%. The delivery has to be by Caesarean section (Pareja et al., 2013).

14.6 Minimal access surgery in cervical cancer

The laparoscopic pelvic lymphadenectomy for cervical cancer was first performed by Querleu et al. (1991). Soon after that, Nezhat et al. (1992) performed the radical hysterectomy and pelvic lymphadenectomy laparoscopically. Minimal access surgery by laparoscopy has been proven to have similar surgical and oncological outcomes to those of open surgery. The major benefits of minimally invasive surgery are better visualization, less blood loss, fewer wound-related problems, increased patient comfort, decreased analgesic requirements, a shorter hospital stay, and earlier recovery. Laparoscopic lymphadenectomy combined with radical vaginal hysterectomy or laparoscopic lymphadenectomy combined with laparoscopic radical hysterectomy have become acceptable alternatives to open surgery.

Robotic technology, an advanced innovation aimed at overcoming the shortcomings of conventional laparoscopy, offers stable, three-dimensional, high-resolution vision, surgical dexterity, and precision. It is now being increasingly used for minimally invasive surgery in cervical cancer.

14.7 Adjuvant therapy after surgery

The excised specimen should be carefully assessed for the size of the primary tumour, the depth of stromal invasion, the presence or absence of LVSI, the proximity of the tumour to the vaginal and parametrial margins, and the presence of intraepithelial neoplasia at the vaginal margin. The lymph nodes should be counted, and all of them should be examined microscopically. A total pelvic lymph node count of less than 10 indicates a suboptimal lymphadenectomy.

Patients with the following high-risk features should undergo postoperative radiotherapy (with or without concomitant chemotherapy):

- tumour size > 4 cm;
- lymph node metastasis;

- deep stromal invasion (greater than 10 mm);
- LVSI;
- parametrial infiltration;
- positive or close vaginal or parametrial margin.

For these high-risk cases, postoperative pelvic irradiation substantially reduces the local recurrence rate, at the cost of a high incidence of some of the distressing side-effects, like lymphoedema, increased urinary frequency, bladder dysfunctions, diarrhoea, radiation cystitis, and radiation proctitis. Radiotherapy involves a combination of external beam radiotherapy and brachytherapy.

14.8 Survival after treatment of early-stage cervical cancer

The survival rate after radical hysterectomy and pelvic lymphadenectomy in appropriately selected cases is high. Rates of 5-year disease-free survival have been reported to be between 80% and 95% (Ware and van Nagell, 2010). The survival rate decreases significantly with the involvement of lymph nodes and the parametrium, in spite of the adjuvant radiotherapy. Although there is concern about the prognostic significance of adenocarcinoma, large prospective and retrospective studies have not found any difference in survival between early-stage patients with squamous cell carcinoma and those with adenocarcinoma.

14.9 Surgical management of early cervical cancer during pregnancy

The treatment of cervical cancer during pregnancy is determined by the clinical extent of disease and the gestational age. A biopsy is mandatory to confirm diagnosis, and it may be necessary to resort to MRI to establish the stage of disease. In patients with stage IA2 or stage IB disease, waiting for viability of the fetus may be an option if there is no evidence of lymphatic spread. Patients with stage IA2 or stage IB disease and with lymph node spread should undergo immediate treatment.

Patients with stage II and greater disease should undergo radiotherapy or chemoradiotherapy. If possible, fetal evacuation should be performed before radiotherapy is initiated. If evacuation is not feasible, radiation will result in spontaneous abortion 4–5 weeks after initiation of radiotherapy.

Key points

- Radical hysterectomy with lymph node dissection is the classic surgical option for the treatment of early cervical cancer, up to stage IIA1.
- Radiation may be used for every treatable stage of cervical cancer.
- Radical trachelectomy is increasingly popular as fertility-preserving surgery for stage IA2 or stage IB1 disease.
- Laparoscopic access is the preferred access method for treatment, where adequate training and equipment are in place.