Cervical Cancer

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KEYWORDS

- Cervical cancer • Human papillomavirus • Radical hysterectomy
- Cervical cancer treatment

KEY POINTS

- Squamous cell cervical cancer incidence and mortality have been reduced dramatically as a result of successful screening in many countries.
- Cervical cancer is staged clinically, and stage is the most important indicator of long-term survival.
- Treatment is typically dictated by clinical staging.
- Improvements in radiation techniques and molecular targeted therapy are the current research venues in cervical cancer.

Cervical cancer is the most common gynecologic cancer in women. High-risk human papillomavirus (HPV) is implicated as the major etiologic agent. Most invasive cervical cancers are preceded by a severe cervical dysplasia or carcinoma-in-situ.

Common symptoms associated with cervical cancer are postcoital and irregular vaginal bleeding; watery vaginal discharge; and physical signs associated with venous, lymphatic, neural, or ureteral compression. Diagnosis of cervical cancer usually follows a physical examination and histologic evaluation of cervical biopsies.

Cervical cancer is staged clinically, and stage is the most important indicator of long-term survival. Treatment is typically dictated by clinical staging. In general, early-stage disease is treated effectively with either surgery or chemoradiation. Advanced-stage disease is treated primarily with chemoradiation.

Prevention lies mainly in early detection. For this reason, regular Papanicolaou test (Pap smear) screening is recommended by the American College of Obstetricians and Gynecologists (2003) and the U.S. Preventative Task Force (2003). More recently, HPV vaccines have been developed and marketed for cervical cancer prevention.

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EPIDEMIOLOGY

Cervical cancer is the third most common cancer and the fourth leading cause of cancer death in women worldwide. In 2008, 529,800 women were diagnosed with cervical cancer and 275,100 died from the disease, accounting for 9% of the total new cancer cases and 8% of total care deaths among women.[1] In the United States, approximately 12,710 women are diagnosed with invasive cervical cancer and 4290 will die from the disease in 2011. The majority of cervical cancer now occurs in developing countries and medically underserved populations due to the lack of Papanicolaou smear screening.[2–5] The incidence and mortality are higher among minorities. The incidence of cervical cancer is 30% higher in African Americans than in whites, and mortality is twice as high.[2–5] The disparity of cervical cancer burden in the developing counties and in medically underserved populations reflects a lack of screening for cervical cancer. Screening for cervical cancer and its premalignant lesions by Pap smear has led to a decrease in the incidence of cervical cancer in the United States.

RISK FACTORS

HPV

HPV can be detected in more than 99% of cervical cancers and is essential for the malignant transformation. More than 40 subtypes of HPV have been identified, of which at least 15 are known to be oncogenic. The most common subtypes, HPV 16 and 18, account for about 70% of cervical cancer in the United States.[6]

HPV infection is common. Most HPV infections are transient. When persistent HPV infection does occur, it has been estimated that it takes an average of 15 years from initial infection to the development of cervical intraepithelial neoplasia (CIN) and ultimately invasive cervical cancer.

Lower Socioeconomic Predictors

Lower educational attainment, older age, obesity, smoking, and neighborhood poverty are independently related to lower rates of cervical cancer screening. Specifically, those living in impoverished neighborhoods have limited access to screening and may benefit from outreach programs to decrease rates of cervical cancer.[7]

Cigarette Smoking

Cigarette smoking, both active and passive, increases the risk of cervical cancer. Among HPV-infected women, current and former smokers have a two- to threefold incidence of high grade squamous intraepitheliel lesion (HSIL) or invasive cancer. Passive smoking is also associated with increased risk, but to a lesser extent.[8] Of cervical cancer types, current smoking has been associated with a significantly increased rate of squamous cell carcinoma, but not of adenocarcinoma. Interestingly, squamous cell and adenocarcinomas of the cervix share most risk factors with this exception of smoking. Although the mechanism underlying the association between smoking and cervical cancer is unclear, smoking may alter HPV infection in those who smoke. For example, “ever smoking” was associated with reduced clearance of high-risk HPV infection.[9,10]

Reproductive Behavior

Parity and combination oral contraceptive (COC) pill use has a significant association with cervical cancer. Pooled data from case-control studies indicate that high parity

increases the risk of developing cervical cancer. Specifically, women with seven prior full-term pregnancies have an approximately fourfold increased risk, and those with one or two full-term pregnancies have a twofold increased risk compared with nulliparas.[11]

In addition to parity, long-term COC use may be a cofactor. In women who are positive for cervical HPV DNA and who use COCs, risks of cervical carcinoma increase by up to fourfold compared with women who are HPV positive and never users of COC.[12] In addition, current COC users and women who are within 9 years of use have a significantly higher risk of developing both squamous cell and adenocarcinoma of the cervix.[13]

Sexual Activity

An increased number of sexual partners and early age at first intercourse have been shown to increase cervical cancer risks. Having more than six lifetime sexual partners imposes a significant increase in the relative risk of cervical cancer compared with controls.[13] Similarly, early age at first intercourse, before age 20, confers a significantly increased risk of developing cervical cancer, whereas intercourse after age 21 shows only a trend toward an increased risk. Moreover, abstinence from sexual activity and barrier protection during sexual intercourse has been demonstrated to decrease cervical cancer incidence.[13]

SCREENING AND PREVENTION

Pap Smear

Screening for cytologic abnormality by Pap smear has led to significant reduction in the incidence of cervical cancer in the United States. Pap smear has a sensitivity of 55% to 80% on any given test and does not always detect cervical cancer.[14] In addition, in women with stage I cervical cancer, only 30% to 50% of Pap smears are interpreted as positive for malignancy.[14] Therefore, serial screening as prescribed by the clinical guidelines is important.

HPV Vaccines

The advent of HPV vaccines holds promise of reducing the incidence of cervical cancer. The current HPV vaccines provide protection against HPV types 16 and 18, which account for about 70% of cervical cancers. Vaccines are most effective when administered in sexually naïve individuals. The vaccines are indicated for females 9 to 26 years of age for prevention of cervical and other lower genital tract cancers. However, women who have received HPV vaccines must continue to receive Pap smear screening because present vaccines do not provide protection for other high-risk HPV subtypes that can cause cervical and other lower genital tract cancers. Recent U.S. Food and Drug Administration (FDA) approval has been obtained for vaccination of males in the similar age group for prevention of anal cancers and other HPV-mediated dysplasias; however, downstream effect for preventing subsequent infection in women is unknown.

PATHOPHYSIOLOGY

Squamous cell carcinoma of the cervix typically arises within the squamocolumnar junction from a preexisting dysplastic lesion, which in nearly all cases follows infection with high risk HPV.[15] In general, progression from dysplasia to invasive cancer requires several years, but wide variations exist. The molecular alterations involved with cervical carcinogenesis are complex and not fully understood. Carcinogenesis is

suspected to result from the interactive effects between environmental insults, host immunity, and somatic cell genomic variations.[16–19]

Lymphatic Spread

Traditional teaching implies that the pattern of tumor spread typically follows cervical lymphatic drainage. The cervix has a rich network of lymphatics, which follow the course of the uterine vein. These channels drain principally into the paracervical and parametrial lymph nodes. From the parametrial and paracervical nodes, lymph subsequently flows into the obturator lymph nodes and the internal, external, and common iliac lymph nodes. In contrast, lymphatic channels from the posterior cervix course through the rectal pillars and the uterosacral ligaments to the rectal lymph nodes.

More recently, sentinel lymph node data in cervical cancer, pursued with the impetus to understand further the lymphatic trafficking of the cervix, indicate that the external iliac region just distal to the common iliac bifurcation was the most common sentinel lymph node location.[20] Para-aortic lymph nodes have also been identified as the sentinel node in a very small percentage of patients with cervical cancer.[21]

Local Tumor Extension

As primary lesions enlarge and lymphatic involvement progresses, local invasion increases and will eventually become extensive. With extension through the parametria to the pelvic sidewall, ureteral blockage frequently develops. In addition, the bladder and rectum may be invaded by direct tumor extension through the vesicouterine ligaments.

Distant metastasis results from hematogenous dissemination and the lungs, ovaries, liver, and bone are the most frequently affected organs.

HISTOLOGIC SUBTYPES

Squamous Cell Carcinoma

The two most common histologic subtypes of cervical cancer are squamous cell and adenocarcinoma (**Table 1**). Squamous cell carcinoma of the cervix typically arises at the squamocolumnar junction. Squamous cell carcinoma comprises more than 70% of cervical cancer. Over the last 30 years, there has been a decline in the incidence of squamous cell carcinoma and an increase in the incidence of adenocarcinoma. This trend is likely due to screening for premalignant and malignant diseases of the cervix through Pap smear.[6]

Adenocarcinoma

Adenocarcinoma comprises 25% of cervical cancers and arises from the mucus-secreting glandular cells of the endocervix. Because of this origin within the endocervix, adenocarcinomas are often occult and may be advanced before becoming clinically evident. The traditional Pap smears are not reliable for screening for adenocarcinomas of the cervix. The Gynecologic Oncology Group (GOG) is currently conducting a study to determine if a tumor-associated transmembrane glycoprotein (MN), which has demonstrated powerful discriminatory capacity to identify atypical glandular cells associated with high-grade squamous or glandular cervical cells, can be used as a biomarker to identify cervical adenocarcinoma.

There is controversy regarding whether squamous cell carcinoma or adenocarcinoma is associated with a worse prognosis. When adjusted for stage, some series found similar outcomes between squamous cell carcinoma and adenocarcinoma.[22–25]

Table 1
Histologic subtypes of cervical cancer

Squamous Cell Carcinoma	
Adenocarcinoma	Endocervical type adenocarcinomas Endometrioid adenocarcinomas Minimal deviation adenocarcinoma Papillary villoglandular adenocarcinoma Serous adenocarcinoma Clear cell adenocarcinoma Mesonephric adenocarcinoma
Mixed cervical carcinomas	Adenosquamous carcinoma Glassy cell carcinoma Adenoid cystic carcinoma Adenoid basal epithelioma
Neuroendocrine tumors of the cervix	Large cell neuroendocrine Small cell carcinoma
Other malignant tumors	Sarcomas of the cervix Malignant lymphomas Metastatic cancers

However, most studies have shown that adenocarcinoma has a worse prognosis and that the difference is more pronounced in the advanced stage.[26–32]

Neuroendocrine/Small Cell Carcinoma

Neuroendocrine tumors account for 2% to 5% of cervical cancers. There are four types of neuroendocrine tumors in the cervix: small cell, large cell, carcinoid, and atypical carcinoid tumors, with the small cell neuroendocrine carcinoma (SCNEC) being the most common variant. SCNEC is considered an extrapulmonary variant of small cell lung cancer and has a worse prognosis than squamous cell carcinoma or adenocarcinoma.[33,34]

Other Less Common Subtypes

Adenosquamous carcinoma exhibits both glandular and squamous differentiation and may be associated with a worse prognosis than squamous cell carcinoma or adenocarcinoma. Other subtypes include adenoid cystic carcinoma, adenoid basal epithelioma, glassy cell carcinoma, sarcoma, and lymphoma.

DIAGNOSIS

Presenting Symptoms

Early stage

Many women with cervical cancer are asymptomatic initially. For those with symptoms, early-stage cervical cancer may present with a watery, blood-tinged vaginal discharge or postcoital bleeding.

Late stage

With the enlargement of cervical mass, the vaginal discharge may become mucoid, purulent, and malodorous as the cervical mass becomes necrotic. With parametrial invasion and extension to the pelvic side wall, the tumor may compress pelvic organs to produce symptoms such as pelvic pain, lower back pain, or lower extremity edema.

With ureteral obstruction, hydronephrosis and renal failure can result. Tumor invasion into the bladder or rectum can result in hematuria, hematochezia, or rectal bleeding.

Diagnosis and Workup

Physical examination

A thorough external genital and vaginal examination should be performed during gynecologic examination to search for concomitant lesions. On speculum examination, the cervix may appear grossly normal if the cancer is microinvasive. Visible cancer may appear as an ulcerated lesion, granular or papillary tissue, exophytic growth, polypoid mass, or barrel-shaped cervix. Large lesions may become necrotic and friable. A watery, purulent, or bloody discharge may be present.

A rectovaginal examination is performed to evaluate the extent of tumor and is the only way to adequately assess parametrial involvement. An enlarged uterus may be palpated, as the result of tumor growth. Obstruction of cervical canal by the tumor can result in hematometra or pyometra and lead to an enlarged uterus. Vaginal extension of the tumor can be appreciated on bimanual and rectovaginal examination as obliteration of the vaginal fornices or a thick, firm, irregular rectovaginal septum. Parametrial extension and involvement of pelvic sidewall and uterosacral ligaments can also be palpated on rectovaginal examination. With the parametrial involvement, the tissue feels firm, irregular, and less mobile.

Most women with cervical cancer have normal general physical examination findings. However, with advanced disease, enlarged inguinal or supraclavicular lymph nodes and lower extremity edema may be found.

Colposcopy and biopsy

Evaluation of the cervix with colposcopy is necessary when a Pap smear reveals abnormal cytology including atypical squamous cells cannot rule out high grade lesion (ASC-H), low grade squamous intraepitheliel lesion (LSIL), HSIL, or atypical glandular cells of undetermined significance (AGUS). During colposcopic evaluation, the entire transformation and all lesions must be visualized for the procedure to be considered adequate. The appearance of the cervix is recorded and a biopsy performed for any suspicious lesion with a Tischler biopsy forceps. Endocervical curettage should also be performed. The biopsies of the lesions should explain the abnormal cytology.

Cervical biopsy and endocervical curetting may reveal invasive cancer, premalignant lesions, or benign tissue. Premalignant lesions such as CIN II and III and carcinoma-in-situ need to be evaluated further with cervical conization to evaluate for the possibility of microinvasive disease. By obtaining the entire lesion on conization, maximum depth of invasion can be evaluated properly. Conization also needs to be performed if colposcopy is inadequate. Either cold knife conization or loop electrosurgical excision is acceptable. However, cold knife conization is preferred because thermal artifact can make interpretation of surgical margins difficult.

Staging

Clinical staging

Cervical cancer is staged by clinical criteria, whereas most other gynecologic malignancy is staged by surgical and pathologic findings. The FIGO system for cervical cancer staging was established by the International Federation of Gynecology and Obstetrics (FIGO), in conjunction with World Health Organization (WHO) and the Union for International Cancer Control (UICC). The FIGO staging system for cervical cancer was modified most recently in 2009 to define prognostic groups more

accurately. The FIGO Committee on Gynecologic Oncology decided that clinical staging should be continued, while lymph nodal assessment during staging is not necessary because surgical staging cannot be employed worldwide, especially in low-resource countries. Thus, the aforementioned two changes have been approved in the new staging system as follows. First, the subdivision of the tumor size (with a 4 cm cutoff in maximum diameter) has been applied for previous stage IIA. Second, the previous stage 0 has been deleted from the new clinical staging system because it is a preinvasive lesion.[35]

In addition to physical examination, studies and procedures that are allowed for staging include colposcopy, endocervical curettage, conization, hysteroscopy, cystoscopy, proctoscopy, intravenous pyelogram, and radiography of the lungs and skeleton.[36] Other imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) cannot be used for FIGO staging. The rationale is to provide a basis for resource-rich and resource-poor countries to compare data.

The limitations of clinical staging may led to understaging of some patients.[37] For this reason, additional imaging modality such as CT scans and more recently positron emission tomography (PET)/CT scans are frequently employed in the United States for treatment planning purposes. See **Table 2** for the revised 2009 FIGO staging of cervical cancer.

Radiologic Modalities

CT scan

A CT scan is frequently used to supplement physical examination and studies performed for clinical staging. It can help evaluate the tumor size and identify the extent of disease spread, lymph node involvement, and hydronephrosis.

MRI

The utility of MRI lies in its ability to evaluate in greater accuracy the extent of disease spread in early-stage cervical cancer. MRI has been found to be superior to CT scan and clinical examination for measuring tumor size and determining involvement of uterine corpus or parametrium for evaluation of early-stage cervical cancer.[38,39]

PET

PET scan may provide more accurate assessment of metastatic disease than other imaging modalities. This nuclear medicine scan utilizes radioisotope-tagged substrates such as glucose ([^{18}F]-fluoro-2-deoxy-D-glucose [FDG]) and generates images based on the uptake and metabolism of the substrate in the tissues. PET scan with FDG is now increasingly being used as part of initial staging and monitoring of the response to therapy of different types of cancers, including cervical cancer.[40,41] FDG–PET is highly sensitive and specific for the detection of para-aortic lymph nodes in locally advanced disease.[42–44] However, its ability to detect pelvic lymph node metastasis is more limited, especially for early-stage disease.[43,45–47]

Integrated PET/CT is a technique in which both PET and CT are performed sequentially on a hybrid PET/CT scanner. The PET and CT images are then combined using computer software, allowing the physiologic data from the PET imaging to be better localized based on the anatomic information from the CT scan. Integrated PET/CT might be more sensitive than PET alone or MRI for detection of lymph node metastasis.[48]

Table 2
Staging of cervical cancer

FIGO Stage	Definition
I	Cervical carcinoma confined to the cervix.
IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a depth of ≤5 mm and a horizontal spread of ≤7 mm.
IA1	Stromal invasion ≤3 mm in depth and horizontal spread ≤7 mm.
IA2	Stromal invasion >3 mm but ≤5 mm in depth and horizontal spread ≤7 mm.
IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2.
IB1	Clinically visible lesion ≤4 cm in greatest dimension.
IB2	Clinically visible lesion >4 cm in greatest dimension.
II	Cervical carcinoma invades beyond the uterus but not to pelvic wall or the lower third of vagina.
IIA1	Clinically visible lesion ≤4 cm or less with involvement of less than the upper two thirds of the vagina.
IIA2	Clinically visible lesion >4 cm with involvement of less than the upper two thirds of the vagina.
IIB	Tumor with parametrial invasion.
III	Tumor involves lower third of vagina, extends to the pelvic wall, or causes hydronephrosis or nonfunctioning kidney.
IIIA	Tumor involves lower third of vagina, but no extension to pelvic wall.
IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney.
IV	Tumor has extended beyond the true pelvis or has involve the mucosa of the bladder or rectum.
IVA	Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis.
IVB	Distant metastasis (including peritoneal spread; involvement of supraclavicular, mediastinal, or para-aortic lymph nodes; lung; liver; or bone).

TREATMENT

Microinvasive Cervical Cancer

Stage IA

The term microinvasive cervical cancer refers to this group of early-stage, small tumors. Criteria by FIGO staging for stage IA tumor limits stromal invasion to no greater than 5 mm and lateral spread to no wider than 7 mm. Microinvasive cervical cancer carries a minor risk of lymph node involvement and excellent prognosis after appropriate treatment.

Stage IA1

These tumors have stromal invasion no deeper than 3mm and horizontal spread no more than 7 mm and are associated with low risk for lymph node involvement. Squamous cervical cancer with stromal invasion less than 1 mm have a 1% risk of nodal metastasis, and patients with 1 to 3 mm of stromal invasion carry a 1.5% risk or nodal metastases. Of 4098 women studied with stage IA1, fewer than 1% died of the disease.[49] Findings such as this provide the basis for less aggressive management

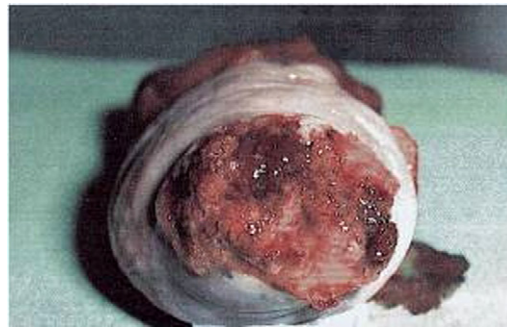

Fig. 1. Stage IB cervical cancer: visible lesion confined to cervix.

of stage IA1 squamous cell carcinoma, if lymphovascular space invasion (LVSI) is absent. Acceptable treatment options include cervical conization or a simple hysterectomy.

The presence of LVSI in stage IA1 cervical cancer increases the risk of lymph node metastasis and cancer recurrence to approximately 5%. Therefore, some gynecologic oncologists manage these cases with modified radical hysterectomy (type II hysterectomy) and pelvic lymphadenectomy.

Stage IA2

Cervical lesions with 3 to 5 mm of stromal invasion have a 7% risk of lymph node metastasis and a greater than 4% risk of cancer recurrence. Therefore, modified radical hysterectomy and pelvic lymphadenectomy are indicated. Alternatively, patients with microinvasive carcinoma (stages IA1 and IA2) and who are poor surgical candidates can be treated with intracavitary brachytherapy alone with excellent results.

Stage IB to IIA1

Cervical stage IB to IIA1 cancer can be treated with either surgery or chemoradiation[50] (**Fig. 1**). In a prospective study of primary therapy, 393 women were randomly assigned to undergo radical hysterectomy and pelvic lymphadenectomy or receive primary radiation therapy. Five-year overall survival and disease-free survival were statistically equivalent (83% and 74%, respectively). Surgical patients, however, had significantly greater severe morbidity rates compared with the radiotherapy group.[50]

Because radiotherapy and surgery are both viable options, the optimum treatment for each woman ideally should assess clinical factors such as menopausal status, age, concurrent medical illness, tumor histology, and cervical diameter. In general, radical hysterectomy for stage IB to IIA tumors is usually selected for young women with low body mass index (BMI) who wish to preserve ovarian function and have concerns about altered sexual functioning following radiotherapy. Surgery is contraindicated in patients with severe cardiac or pulmonary disease or prior thromboembolism. Age and weight are not contraindications to surgery; although in general, older women may have longer hospital stays and heavier women can have longer operative time, greater blood loss, and higher rates of wound complication.

In those electing surgery, oophorectomy may be deferred in younger women. A GOG study evaluated tumor spread to the ovary in those with IB tumors electing radical hysterectomy without adnexectomy. Ovarian metastases were identified in

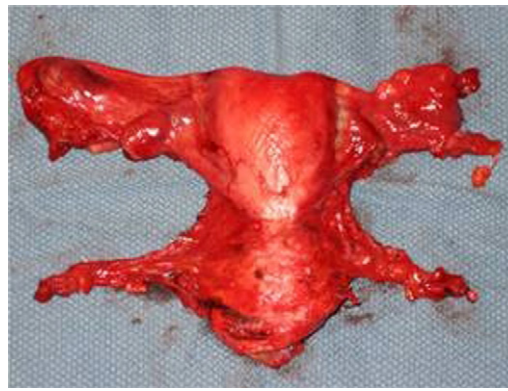

Fig. 2. Radical hysterectomy specimen.

only 0.5% of 770 women with stage IB squamous cell cancers and in 2% of those with adenocarcinomas.[51]

Modified radical hysterectomy (type II)

Modified radical hysterectomy removes the cervix, proximal vagina, and parametrial and paracervical tissue. The ureters are unroofed from the paracervical tunnel until their point of entry into the bladder. They are then retracted laterally to enable removal of the parametrial and paracervical tissue medial to the ureter. This hysterectomy is well suited for tumors with 3- to 5-mm depths of invasion and for smaller stage IB tumors.[52]

Radical hysterectomy (type III)

This hysterectomy requires greater resection of the parametria, and excision extends to the pelvic sidewall (**Fig. 2**). The ureters are completely dissected from their beds and the bladder and rectum are mobilized to permit this more extensive removal of tissue. In addition, at least 2 to 3 cm of proximal vagina is resected. This procedure is performed for larger IB lesions, on patients with relative contraindications to radiation such as diabetes, pelvic inflammatory disease, hypertension, collagen disease, or adnexal masses.

Radical trachelectomy

Some authors have reported management of stage IA2 and IB1 cervical cancer with radical trachelectomy, lymphadenectomy, and placement of cerclage for fertility preservation. These procedures have high cure rates, and successful pregnancies have been reported. Preoperative MRI is recommended for these cases; if the tumor has extended beyond the internal cervical os, then trachelectomy is contraindicated. For selected patients with stage IB1 cervical cancer, fertility-sparing radical trachelectomy appears to have an oncologic outcome similar to that of radical hysterectomy. Lymph vascular space invasion and deep stromal invasion appear to be valuable predictors of outcome.[53,54] The majority of patients can undergo the operation successfully; however, nearly 32% of all selected cases will require hysterectomy or postoperative chemoradiation for oncologic reasons.[55]

Surgical and radiotherapy complication

Complications for early-stage cervical cancer surgery include ureteral stricture, bladder dysfunction, constipation, wound breakdown, lymphocyst, and lymphedema. In addition, adjuvant radiotherapy increases complication risks.

Radiation therapy is also associated with long-term complications. Altered sexual function secondary to shortened vagina, dyspareunia, psychological factors, and vaginal stenosis are often encountered. Late urinary and bowel complications such as fistula formation, enteritis, proctitis, and bowel obstruction may also develop.

Adjuvant treatment after radical hysterectomy

Intermediate risk of recurrence The GOG has defined recurrence risk factors that would identify women who undergo radical surgery for early-stage cervical cancer. Intermediate risk describes those who on average would have a 30% risk of cancer recurrence within 3 years. Factors included in this model are depth of tumor invasion, tumor diameter, and LVSI.

To determine appropriate treatment of these at-risk women, patients with these intermediate-risk factors have been studied. In one study, women were randomly assigned to receive pelvic radiation therapy after radical hysterectomy or radical hysterectomy and observation. A nearly 50% reduced risk of recurrence was found in those who received postoperative adjuvant radiation therapy.[56] However, this adjuvant radiation does not prolong overall survival. In our practice, these intermediate-risk patients are counseled regarding their risk of recurrence and offered the option of adjuvant radiation therapy.

High risk of recurrence A high-risk category of patients who undergo radical surgery for early-stage cervical cancer has also been described. High risk is defined as a 50% to 70% risk of recurrence within 5 years. These women have positive lymph nodes, positive surgical margins, or microscopically positive parametria.[57]

This group is routinely offered adjuvant radiation therapy. Moreover, the GOG recently demonstrated that the addition of concurrent chemotherapy consisting of cisplatin and 5-fluorouracil would be beneficial in significantly prolonging disease-free and overall survival in this group of women with high-risk early-stage cancer.[57]

Stage IIA2 to IVA

Advanced-stage cervical cancers extend past the confines of the cervix and are often found to involve adjacent organs and retroperitoneal lymph nodes (**Fig. 3**). As such, treatment for these tumors must be individualized to maximize patient outcome. The vast majority of advanced-stage tumors have poor prognosis, with 5-year survival rates of less than 50% (**Table 3**). Advanced-stage tumors represent a large proportion

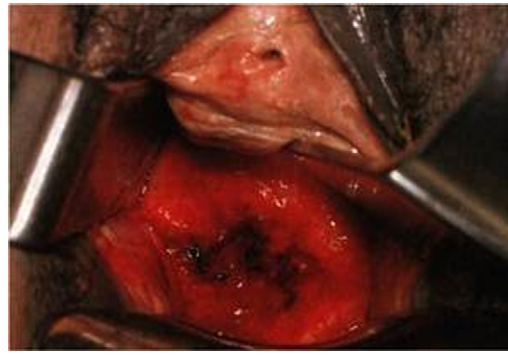

Fig. 3. Advanced-stage cervical cancer: large, ulcerative lesion involving cervix and vagina.

Table 3
Cervical cancer survival rates according to stage

Stage	5-Year Survival (%)
IA	100
IB	88
IIA	68
IIB	44
III	18–39
IVA	18–34

Data from Refs.[79–81]

of invasive cervical cancers treated, depending on the geographic area studied. Untreated, these tumors progress rapidly.

Radiation therapy

This modality forms the cornerstone of advanced-stage cervical cancer management. Both external pelvic radiation and brachytherapy are typically delivered. Of these, external-beam radiation usually precedes intracavitary radiation, which is one form of brachytherapy. External-beam radiation is commonly administered in 25 fractions during 5 weeks. To limit bladder and rectal doses during brachytherapy, bowel and bladder are packed away from the intracavitary source during tandem insertion, using vaginal packing. During staging, if para-aortic nodal metastasis is found, then extended field radiation can be added to treat these affected lymph nodes.

Chemoradiation

Current evidence indicates that concurrent chemotherapy significantly improves overall and disease-free survival of women with advanced cervical cancer. Thus, most patients with stage IIA2-IVA cervical cancer are best treated with chemoradiation. Cisplatin-containing regimens have been associated with the best survival rates.[58,59] For patients without proven para-aortic nodal metastases, a study reported in 1999 demonstrated that pelvic radiation and concurrent chemotherapy was superior to prophylactic extended-field radiation without chemotherapy.[60] Extended-field radiation is used when there is proven common iliac nodal or para-aortic nodal disease, although the dose of concurrent chemotherapy may have to be reduced to manage toxicity. At our institution, cisplatin is given weekly for 5 weeks and is administered concurrently with radiotherapy. Additional doses of chemotherapy, administered after chemoradiation, have also been shown to improve survival outcomes in patients with advanced-stage cervical cancer.[61]

Surgery for advanced stage cervical cancer

Surgical evaluation of retroperitoneal lymph nodes offers accurate detection of pelvic and para-aortic metastasis. In addition, debulking of tumor-laden nodes is also achieved. As a result, lymph node dissection may enhance management of and improve survival rates in patients with advanced-stage cervical cancer. Retrospective studies have suggested a statistically significant survival benefit to extended chemotherapy and/or extended-field radiation therapy if positive pelvic/para-aortic nodes are identified.[62,63]

In addition to its diagnostic power, surgical staging also permits debulking of grossly positive nodes. Evidence supporting a survival benefit from debulking macroscopic para-aortic nodes is contradictory. Although some retrospective studies have shown disease-free survival rates for patients whose macroscopic nodal disease has been resected is similar to that of women with microscopic nodal disease, this benefit does not extend to overall survival rates.[62,64]

Despite these suggested benefits, routine operative staging for advanced-stage cervical cancer has failed to achieve its intended goal of substantially increasing survival. Studies estimate only a 4% to 6% survival benefit.[65,66] These patients often have systemic disease, and failure to control pelvic disease has contributed to the poor overall survival in this group of patients.

Coexistent pelvic mass in advanced-stage cervical cancer

A pelvic mass maybe identified on CT or other imaging. Before radiation, any suspicious adnexal masses should be explored and a histologic diagnosis obtained. Coexistent pyometra or hematometra should be drained and broad-spectrum antibiotics utilized to treat the infection. Active infection may decrease the response to radiation therapy and may exacerbate into a systemic infection when radiation rods are placed for purposes of brachytherapy.

Stage IVB

Patients with stage IVB disease have poor prognosis and are treated for palliative purposes only. Pelvic radiation may be administered for vaginal bleeding or pain. Systemic chemotherapy is offered to palliate symptoms.

SURVEILLANCE

Eighty percent of recurrences are detected within the subsequent 2 years. In addition to pelvic examination, a thorough manual nodal survey should include neck, supraclavicular, infraclavicular, axillary, and inguinal lymph nodes. In addition, a chest radiograph can be obtained yearly. Cervical or vaginal cuff Pap smear should also be collected every 3 months for 2 years and then every 6 months for 3 years. Abnormal Pap smears should prompt further evaluation for recurrent disease. During patient surveillance, identification of an abnormal pelvic mass or abnormal pelvic examination, pain radiating down the posterior thigh, or new-onset lower extremity edema should prompt CT scanning of the abdomen and pelvis.

RECURRENT CERVICAL CANCER DISEASE

Disease recurrence is defined as a new lesion after completion of primary therapy. Cervical cancer that has not completely regressed within 3 months of radiotherapy is considered persistent.

Treatment of persistent or recurrent disease depends on its location and extent. The intent in these cases is usually palliative. However, in certain instances, a woman may qualify for pelvic radiation if she previously had not received this treatment or for a curative-intent surgical procedure. All chemotherapy-based treatments of metastatic disease are administered with a goal of palliation. In these cases, the primary focus is to maximize existing patient quality of life.

Pelvic Exenteration for Secondary Disease

When curative-intent surgery is contemplated, local disease should be biopsy proven. Clinically, a woman may be considered for pelvic exenteration if lower extremity

Table 4
Combination chemotherapy regimens and response rates of cervical cancer

Study	Chemotherapy Agents	Response Rates (%)	PFS	OS
Moore et al[75]	Cisplatin vs cisplatin and taxol (phase III)	19 vs 36	2.8 vs 4.8 mo	No difference
Long et al[76]	Cisplatin vs cisplatin and topotecan (phase III)	13 vs 27	2.9 vs 4.6 mo	6.5 vs 9.4 mo
Morris et al[77]	Cisplatin and vinorelbine (phase II)	30	5.5 mo	
Brewer et al[78]	Cisplatin and gemcitabine (phase II)	22	2.1 mo	

Abbreviations: OS, overall survival; PFS, progression-free survival.

edema, back pain, and hydronephrosis are absent. If present, these suggest disease extension to the pelvic side walls, which would contraindicate surgery. In addition, regional and distant metastasis should be excluded by both physical examination and radiologic imaging.

Pelvic exenteration begins with exploratory laparotomy, biopsies of suspicious lesions and pelvic and para-aortic lymph node evaluation. Exenteration is completed only if there is no disease in frozen section specimens sampled during surgery. A total pelvic exenteration involves enbloc removal of bladder, uterus, rectum, vagina, and at times vulva, depending on the exact site and extent of the recurrent lesion. The reported 5-year survival is approximately 40%, ranging from 18% to 70% in the literature. As part of the total pelvic exenteration, reconstruction can involve diversion of urine utilizing a segment bowel, termed “conduit,” a descending colostomy and vaginal reconstruction with placement of flaps or omental pedicle graft.

Alternatively, in highly selected patients radical hysterectomy may be considered an alternative to pelvic exenteration.[67] In these circumstances, women should have small cervical recurrences measuring less than 2 cm and have disease-free pelvic lymph nodes both before and during surgery. With either surgical procedure, intraoperative and postoperative complications can be significant.

Radiotherapy for Recurrent Disease

Patients with central or limited peripheral recurrences who are radiotherapy naive are candidates for curative-intent radiation treatment. In these groups, survival rates of 30% to 70% have been reported.[68–71] Radiotherapy can occasionally be used as salvage treatment after definitive primary radiation in patients with small-volume pelvic disease when there has been a long disease-free interval.

Chemotherapy for Secondary Disease

Antineoplastic drugs are used to palliate both disease and symptoms of advanced, persistent, or recurrent cervical cancer (**Table 4**). Cisplatin is considered the single most active cytotoxic agent in this setting.[72] Overall, response duration to cisplatin is 4 to 6 months, and survival in such women approximates only 7 months.[73] Cisplatin is also combined with paclitaxel or topotecan to offer a survival advantage to this group of patients (see **Table 4**). Ongoing GOG studies aim to determine the best combination cytotoxic chemotherapy for patients with recurrent or persistent cervical cancer.

PALLIATIVE CARE

Palliative chemotherapy is administered only if this treatment does not cause significant decline in patient quality of life. Pain management forms the basis of palliation. Any decision for treatment of cervical cancer in a palliative care setting should be assessed against the benefits of supportive care. We recommend discussion of medical directives if a patient has adequate mental capability. Home hospice is an invaluable part of terminal care for most of these women, who require intense pain management and 100% assistance with daily living activities.

MANAGEMENT DURING PREGNANCY

There is no difference in survival between pregnant and nonpregnant women with cervical cancer when matched by age, stage, and year of diagnosis. As with nonpregnant women, clinical stage at diagnosis is the single most important prognostic factor for cervical cancer during pregnancy. Overall survival is slightly better for cervical cancer in pregnancy because an increased proportion of patients have stage I disease.

Diagnosis

A Pap smear is recommended for all pregnant patients at the initial prenatal visit. In addition, clinically suspicious lesions should be directly biopsied. If Pap test results reveal suspected HSIL or malignancy, then colposcopy is performed and biopsies are obtained. However, endocervical curettage is excluded. If Pap testing indicates malignant cells and colposcopic-directed biopsy fails to confirm malignancy, then diagnostic conization may be necessary. Conization is recommended only during the second trimester and only in patients with inadequate colposcopic findings and extremely strong cytologic evidence of invasive cancer. Conization is deferred in the first trimester, as this surgery is associated with abortion rates of 30% in this part of pregnancy.

Stage I Cancer in Pregnancy

Women with microinvasive squamous cell cervical carcinoma measuring 3 mm or less and containing no LVSI may deliver vaginally and be reevaluated 6 weeks postpartum. Moreover, for those with stage IA or IB disease, studies find no increased maternal risk when treatment is intentionally delayed to optimize fetal maturity regardless of trimester during which cancer was diagnosed. Given the outcomes, a planned treatment delay is generally acceptable for women who are 20 or more weeks gestational age at diagnosis with stage I disease and who desire to continue their pregnancy. However, a patient may be able to delay from earlier gestational ages if she wishes.

Advanced Cervical Cancer in Pregnancy

Women with advanced cervical cancer diagnosed before fetal viability are offered primary chemoradiation. Spontaneous abortion of the fetus tends to follow whole-pelvis radiation therapy. If cancer is diagnosed after fetal viability is reached and a delay until fetal pulmonary maturity is elected, then a classic cesarean delivery is performed. A classic cesarean incision minimizes the risk of cutting through tumor in the lower uterine segment, which can cause serious blood loss. Chemoradiation is administered after uterine involution. For patients with advanced disease and treatment delay, pregnancy may impair prognosis. Women who elect to delay treatment,

to provide quantifiable benefit to their fetus, will have to accept an undefined risk of disease progression.

INVASIVE CERVICAL CANCER FOUND AFTER SIMPLE HYSTERECTOMY

Simple hysterectomy for invasive cervical cancer is not curative. The treatment options include either chemoradiation or radical surgery with radical parametrectomy, upper vaginectomy, and pelvic and para-aortic lymphadenectomy. In an exhaustive review of the literature comparing the two options, the weighted average 5-year survival favored radiation therapy over further surgery (68.7% vs 49.2%).[74] Complication rates of either treatment modality after a simple hysterectomy are high. Concurrent cisplatin-based chemoradiation is recommended for gross residual disease, positive imaging, disease in the lymph nodes and/or parametrium, and/or a positive surgical margin.

Survival for patients with no residual cancer after simple hysterectomy is favorable, although the treatment complication rate may be higher than that reported for patients undergoing primary irradiation. Survival for patients with gross disease at the start of posthysterectomy treatment is poor.

SUMMARY

Squamous cell cervical cancer incidence and mortality have been reduced dramatically as a result of successful screening in many countries. The incidence of cervical adenocarcinoma continues to increase. There has been concentrated effort toward improving early detection and screening by utilizing molecular biomarker assays. The FIGO staging system for cervical cancer was revised in 2009. Fertility preservation can be offered to patients with early-stage cervical cancer through radical trachelectomy, although radical hysterectomy remains the surgical standard of care. Concurrent chemotherapy with radiation has been shown to have a survival advantage in patients with advanced-stage disease. Improvements in radiation techniques and molecular targeted therapy are the current research venues in cervical cancer.

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