Of the predominant gynecologic cancers, cancer of the uterine cervix is the least common, with only 11,270 new cases anticipated in the United States in 2009. Nevertheless, approximately 4,070 women die of cancer of the uterine cervix annually in the United States.

Epidemiology

Age The peak age of developing cervical cancer is 47 years. Approximately 47% of women with invasive cervical cancer are < 35 years old at diagnosis. Older women (> 65 years) account for another 10% of patients with cervical cancer. Although these older patients represent only 10% of all cases, they are more likely to die of the disease due to their more advanced stage at diagnosis.

Socioeconomic class Carcinoma of the uterine cervix primarily affects women from the lower socioeconomic class and those with poor access to routine medical care.

Geography Although invasive cervical carcinoma is relatively uncommon in the United States compared with the more common cancers in women (breast, endometrial, and ovarian cancers), it remains a significant health problem for women worldwide. In many developing countries, not only is cervical carcinoma the most frequently occurring cancer among middle-aged women, but also it is a leading cause of death. This is due, in part, to poor access to medical care and the unavailability of routine screening in many of these countries.

Etiology and risk factors

Sexual activity Invasive cervical carcinoma can be viewed practically as a sexually transmitted disease. Human papillomavirus Molecular and epidemiologic evidence clearly indicates that certain types of human papillomavirus (HPV), which is sexually transmitted, are the principal causes of invasive cervical cancer and cervical intraepithelial neoplasia (CIN). More than 100 HPV types have been identified, and about 40 infect the genital tract. HPV-16 and HPV-18 are the types most commonly linked with cancer, present in 70% of cervical cancers and high-grade CINs. Two vaccines to prevent cervical cancer were approved by the FDA and became available in 2006 and 2009, respectively. Age of onset of sexual activity Population studies of women with invasive cervical carcinoma have demonstrated that early age of onset of sexual activity also plays a role in the later development of the cancer. It is postulated that during the time of menarche in early reproductive life, the transformation zone of the cervix is more susceptible to oncogenic agents, such as HPV. Women who began sexual activity before 16 years of age or who are sexually active within 1 year of beginning menses are at particularly high risk of developing invasive cervical carcinoma.

Other risk factors include multiple sexual partners, a history of genital warts, and multiparity. Gardasil, a quadrivalent vaccine to prevent cervical cancer, is approved by the FDA to be used in girls and women aged 9 to 26. The vaccine uses virus-like particles to induce immunity to HPV types 16 and 18, which cause approximately 70% of cervical cancers and more than 50% of precancerous lesions of the cervix, vulva, and vagina. It is also reported to be protective against HPV types 6 and 11, which cause more than 90% of genital wart cases. Overall, more than 50,000 women have participated in the phase III trials worldwide. With follow-up ranging from 1 to 4 years, the vaccine has been reported to be 90% to 100% effective in preventing infection and precancerous lesions (Prescribing information, US FDA. Issued June 2006. No. 9682300). Further, Cervarix, a bivalent vaccine, was recently approved by the FDA to prevent cervical cancer and precancerous lesions caused by HPV types 16 and 18. It is indicated for use in girls and women ages 10 to 25 years.
Cigarette smoking has been identified as a significant risk factor for cervical carcinoma. It is thought to increase risk by two-fold to five-fold. The mechanism may be related to diminished immune function secondary to a systemic effect of cigarette smoke and its by-products or a local effect of tobacco-specific carcinogens.

Oral contraceptives may also play a role in the development of invasive cervical carcinoma, although this theory is controversial. Given that most women who use oral contraceptives are more sexually active than women who do not, this may represent a confounding factor rather than a true independent risk factor. The exception may be adenocarcinoma of the cervix; this relatively uncommon histologic subtype may be related to previous oral contraceptive use.

Immune system alterations In recent years, alterations in the immune system have been associated with an increased risk of invasive cervical carcinoma, as exemplified by the fact that patients who are infected with the human immunodeficiency virus (HIV) have increased rates of both preinvasive and invasive cervical carcinomas. These patients also are at risk for other types of carcinoma, including Kaposi's sarcoma, lymphomas, and other squamous cell carcinomas of the head and neck and the anogenital region. (For further discussion of AIDS-related malignancies, see chapter 24).

Data suggest that patients who are immunocompromised due to immunosuppressive medications also are at risk for both preinvasive and invasive cervical carcinomas. This association is probably due to the suppression of the normal immune response to HPV, which makes patients more susceptible to malignant transformation. An exciting recent development in the prevention of carcinoma of the cervix is the increasing use of HPV vaccines; if used on a timely basis in young women (ideally before they are exposed to the HPV virus), they can decrease this infection and eventually the incidence of cervical cancer.

Signs and symptoms

A symptom of advanced cervical carcinoma is intermenstrual bleeding in a premenopausal patient. Other commonly reported symptoms include heavier menstrual flow, menorrhagia, and/or postcoital bleeding. With effective screening, cervical cancer is generally asymptomatic. Less frequently, patients with advanced cancer will present with signs of advanced disease, such as bowel obstruction and renal failure due to urinary tract obstruction. Only rarely are asymptomatic patients with a normal screening Pap smear found to have a lesion on the cervix as their only sign or symptom of cervical cancer. Foul-smelling vaginal discharge, pelvic pain, or both are occasionally observed.

Screening and diagnosis

Screening

Pap smear The paradigm for a cost-effective, easy-to-use, reliable screening test is the cervical cytology screen, or Pap smear. The introduction of the Pap smear has resulted in a significant reduction in the incidence of invasive cervical carcinoma, as well as a shift toward earlier stages at the time of diagnosis. The success of cervical cytology, as measured by the lowered incidence of cervical cancer, ironically has led to some controversy regarding the most effective application of this screening tool. With the marked reduction in the incidence of cervical carcinoma, more patients are screened and greater costs incurred to detect each additional case of cervical carcinoma.

Current screening recommendations The current recommendation of the American College of Obstetricians and Gynecologists (ACOG) is that all women who are 18 years of age or older and are sexually active be screened. If the patient has three consecutive annual cervical cytology smears that are normal, she may be safely screened at a less frequent interval of perhaps 2 to 3 years. There are no data to support screening patients on a less frequent basis. Any patient who has a history of cervical dysplasia should be screened at least on a yearly basis. The current American Cancer Society (ACS) revised guidelines for cervical cancer screening follow: Cervical cancer screening should begin ~3 years after the onset of vaginal intercourse but no later than age 21. Cervical screening should be performed every year with conventional cervical cytology smears, or every 2 years using liquid-based cytology until age 30. After age 30, as an alternative to annual routine cytology, HPV DNA testing may be added to cervical cytology for screening. After this initial dual testing, women whose results are negative by both HPV DNA testing and cytology should not be rescreened before 3 years. Women whose results are negative by cytology but who are high-risk HPV DNA positive (type 16, 18, most commonly) are at a relatively low risk of having
high-grade cervical neoplasia, and colposcopy should not be performed routinely in this setting. Instead, HPV DNA testing along with cervical cytology should be repeated in these women at 6 or 12 months. If test results of either modality are positive, colposcopy should then be performed. A randomized study of more than 10,000 women confirmed the evolving role of HPV testing as an accurate screening tool. In this study, women were randomized to undergo either conventional Pap testing or HPV testing as a screening method to identify high-grade CIN. The sensitivity and specificity for CIN 2/3 was 94.6% and 94.1% with HPV testing vs 55.4% and 96.8% for Pap tests. The sensitivity reached 100% when the tests were combined together.

Women who are > 70 years old with an intact cervix and who have had three or more documented, consecutive, technically satisfactory normal cervical cytology tests and no abnormal cytology tests within the 10-year period prior to age 70 may elect to cease cervical cancer screening. Women with a history of cervical cancer, in utero exposure to diethylstilbestrol (DES), and/or who are immunocompromised (including HIV-positive) should continue cervical cancer screening for as long as they are in reasonably good health and do not have a life-limiting chronic condition. Women > 70 years old should discuss their need for cervical cancer screening with a health care professional and make an informed decision about continuing screening based on its potential benefits, harms, and limitations.

Women who have had a supracervical hysterectomy should continue cervical cancer screening as per current guidelines. Cervical cancer screening following total hysterectomy (with removal of the cervix) for benign gynecologic disease is not indicated. Women with a history of CIN 2/3 or for whom it is not possible to document the absence of CIN 2/3 prior to or as the indication for hysterectomy should be screened until three documented, consecutive, technically satisfactory normal cervical cytology tests and no abnormal cytology tests (within a 10-year period) are achieved. Women with a history of in utero DES exposure and a history of cervical carcinoma should continue screening after hysterectomy for as long as they are in reasonably good health and do not have a life-limiting chronic condition.

Techniques designed to improve the sensitivity of the Pap smear have been approved by the FDA. Liquid-based cytologies such as ThinPrep and SurePath are commercially available techniques. Computer-based analysis of these techniques has been developed but is still under evaluation.

**Diagnosis**

The diagnosis of invasive cervical carcinoma can be suggested by either an abnormal Pap smear or an abnormal physical finding.

**Colposcopy** In the patient who has an abnormal Pap smear but normal physical findings, colposcopy is indicated. Colposcopic findings consistent with invasive cervical carcinoma include dense white epithelium covering the ectocervix, punctuation, mosaicism, and especially, an atypical blood vessel pattern.

**Biopsy** If the colposcopic findings are suggestive of invasion, biopsies are obtained from the ectocervix and endocervix. If these biopsies demonstrate only precancerous changes but not an invasive carcinoma, the patient should undergo an excisional biopsy of the cervix. In most current clinical settings, the loop electrosurgical excision procedure (LEEP) is the most expedient method for performing an excisional biopsy. This can be easily accomplished in the office with the patient under local anesthesia and provides adequate tissue for diagnosis. Once the diagnosis of either microinvasive or invasive carcinoma has been established, the patient can be triaged accordingly.

**Patient with signs/symptoms of advanced disease** The patient with signs/symptoms of advanced invasive cervical carcinoma requires a cervical biopsy for diagnosis and treatment planning. In this setting, a Pap smear is superfluous and may be misleading.

**Pathology**

**Squamous cell carcinoma** The most common histology associated with invasive cervical carcinoma is squamous cell carcinoma, which accounts for approximately 80% of all carcinomas of the uterine cervix. For the most part, the decline in the annual incidence of invasive cervical carcinoma has been seen primarily among patients with this subtype.

**Adenocarcinoma** In the past, adenocarcinoma was relatively uncommon as a primary histology of cervical cancer. As a result of the decrease in the overall incidence of invasive squamous cell cancer and, probably, an increase in the baseline incidence of adenocarcinoma of the uterine cervix, this histology now accounts for approximately 20% of all cervical cancers. There is controversy over whether patients with adenocarcinoma of the cervix have a worse
prognosis than those with the more common squamous cell histology. The poorer prognosis associated with adenocarcinoma may be due to the relatively higher frequency of late stage at the time of diagnosis among patients with this histologic type. In several series in which patients were stratified by stage and tumor size, the outcome of cervical adenocarcinoma appeared to be similar to that of squamous lesions of the cervix.

Among the various subtypes of adenocarcinoma, certain types are particularly aggressive and are associated with a poor prognosis. Among them are the small cell or neuroendocrine tumors, which have a poor prognosis even when diagnosed at an early stage.

**Rare tumor types** More rare lesions of the cervix include lymphoma, sarcoma, and melanoma. These histologic subtypes account for < 1% of all cervical cancers.

**Staging and prognosis**

**Clinical staging: Suspected early disease**

When a diagnosis of invasive cervical cancer has been established histologically, an evaluation of all pelvic organs should be performed to determine whether the tumor is confined to the cervix or has extended to the adjacent vagina, parametrium, endometrial cavity, bladder, ureters, or rectum. According to the International Federation of Gynecology and Obstetrics (FIGO) guidelines for clinical staging (Table 1), diagnostic studies may include intravenous urography (IVU), cystoscopic examination of the bladder and urethra, a proctosigmoidoscopic study, a barium enema (BE), and in the case of early-stage disease, a colposcopic study of the vagina and the vaginal fornices. Colposcopic findings may be used for assigning a stage to the tumor (for instance, FIGO stage IIA), but the results must be confirmed by biopsy.

A pelvic examination must be performed as part of the staging process, and the procedure is best done with the patient completely relaxed by general anesthesia. In up to 20% of patients, the initial
clinical classification of the disease has proved to be incorrect at the time of pelvic examination. Such an examination can reveal a more advanced stage of the disease than was originally found; additional biopsies (if indicated) or fractional curettage can be performed as well as colposcopy, cystoscopy, and proctosigmoidoscopy.

Clinical staging: suspected advanced disease
When studies detect ureteral obstruction, a tumor is classified as a stage IIB lesion, regardless of the size of the primary lesion. Ureteral obstruction, either hydronephrosis or nonfunction of the kidneys, is well established as an indicator of poor prognosis, as recognized in the FIGO classification. In women with bulky or advanced-stage tumors, the bladder mucosa also should be inspected cystoscopically for possible bullous edema, which indicates lymphatic obstruction within the bladder wall. Evidence of tumor in the bladder must be confirmed by biopsy before the lesion can be classified as stage IVA. Rectal mucosal lesions also require a biopsy via proctosigmoidoscopy, because they can be related to an inflammatory process rather than to the cervical tumor.

Surgical experience from pelvic lymphadenectomy has confirmed an error rate of 15% to 25% in the clinical staging of patients with stage IB or II lesions. In 10% to 30% of cases with stage II/III tumors, in addition to positive findings of occult pelvic lymph nodes, other metastases may be found in the para-aortic nodes. Unfortunately, pelvic examinations and clinical staging as defined by FIGO cannot detect such metastases.

Consequently, there is a growing body of literature showing the superiority of cross-sectional imaging (CT and MRI) over clinical staging in delineating the extent of disease in patients with cervical cancer. As stated previously, official FIGO guidelines do not incorporate the use of either CT or MRI findings into the staging of cervical cancer. However, as knowledge of prognostic factors and the value of cross-sectional imaging has accumulated, its use in treatment planning has increased without changing the official FIGO clinical staging guidelines. Similarly, although the benefits of laparoscopic extraperitoneal surgical staging have also been reported in this setting, this approach has not been incorporated into the FIGO staging system.

The value of CT scanning in the pretreatment evaluation of patients with cervical cancer is in the assessment of advanced disease (stage IIB and greater) and in the detection and biopsy of suspected lymph node metastasis. The treatment plan for patients with locally advanced disease must be modified if upper abdominal tumor masses and/or distant metastasis is discovered. The soft-tissue contrast resolution of CT scanning does not allow for consistent tumor visualization at the primary cervical site, and, therefore, neither tumor size nor early parametrial invasion can be evaluated reliably. However, T2-weighted MRI allows consistent tumor visualization and has been reported to be over 90% accurate in determining tumor size to within 5 mm of measurements of surgical specimens. Nevertheless, a recent study by the American College of Radiology Imaging Network (ACRIN) in 208 patients with invasive cervical cancer evaluated with CT scans or MRI before radical hysterectomy showed that MRI was superior to CT and clinical exam in evaluating uterine body involvement and in measuring tumor size, but neither method was accurate in evaluating the cervical stromal depth of tumor invasion.

Recent reports show the value of positron emission tomography (PET) scanning in the pretreatment evaluation, treatment planning, and post-therapy assessment of response in patients with higher-risk invasive carcinoma of the cervix. In a prospective study of 103 patients who were successfully treated initially with concurrent chemotherapy and radiation therapy, a surveillance FDG-PET (fluorodeoxyglucose-PET) detected asymptomatic recurrent disease earlier, which may be potentially amenable to salvage therapy.

Noteworthy, in 60 patients with stage IA2–IIA cervical cancer up to 4 cm with MRI-negative nodes, preoperative FDG-PET scanning detected 1 para-aortic node metastasis, but only 1 of 10 pelvic node metastases, which led to the conclusion that PET scanning is of little value in evaluating patients with stage IA2–IIA cervical cancer up to 4 cm. A second study showed 3 of 38 patients with no para-aortic uptake on FDG-PET/CT imaging had histologically proven para-aortic node involvement. PET/CT imaging without histologic examination of the para-aortic area used to determine radiation therapy fields in stage IB2/II cervical cancer would overlook 8% of patients with histologic para-aortic nodal involvement.

Surgical staging
Clinical staging of cervical carcinoma, although widely utilized, is not without controversy. When compared with surgical staging performed by large cooperative groups, clinical staging is frequently inaccurate in predicting locoregional tumor spread. For many cooperative groups, including the Gynecologic Oncology Group (GOG), surgical staging may be required for patients who are entering
prospective, randomized clinical protocols. However, because of the controversy of risk and benefit, the GOG considers surgical staging optional.

The most common method used to stage patients with advanced disease is extraperitoneal sampling of the pelvic and para-aortic lymph nodes. This approach minimizes the risk of subsequent radiation injury to the small bowel due to surgical adhesions and, in patients with advanced disease, allows for individualized treatment planning. Another approach is sentinel lymph node detection in the pelvis, which is still an active area of research.

**Pros and cons of surgical staging** The advantage of surgical staging is that patients with microscopic disease in the para-aortic lymph nodes can be treated with extended-field radiation therapy (EFRT) and, possibly, chemotherapy and potentially benefit in terms of long-term survival. The controversy regarding surgical staging stems from the fact that a small number of patients will actually benefit from the procedure; the majority of patients who undergo it will be found not to have metastatic disease and will receive the same treatment as planned prior to surgical staging; if they are found to have metastatic disease, they will be unlikely to benefit from EFRT. Because of this controversy, GOG considers surgical staging to be optional for patients with advanced-stage cervical cancer.

Loft et al reported the diagnostic value of PET/CT scanning in 120 patients with newly diagnosed cervical cancer FIGO stage ≥ IB. Regarding the para-aortic lymph nodes, the positive predictive value (PPV) was 94%, the negative predictive value (NPV) was 100%, the sensitivity was 100%, and the specificity was 99%. Regarding the distant metastases, the PPV was 63%, the NPV was 100%, the sensitivity was 100% and the specificity was 94% (Loft A et al: Gynecol Oncol 106:29-34, 2007).

**Workup for advanced disease** The standard workup of a patient with advanced cervical carcinoma who is not considered a candidate for radical surgery includes an abdominopelvic CT scan with both IV and GI oral contrast. If there is evidence of para-aortic lymph node metastases, the patient should undergo fine-needle aspiration (FNA) of these enlarged lymph nodes. If FNA confirms that there is para-aortic lymph node metastasis, treatment should be individualized, and EFRT should be considered part of the primary treatment regimen.

If the scalene lymph nodes are negative on clinical examination and the patient is known to have positive metastatic disease to the para-aortic lymph nodes, consideration can be given to performing a scalene lymph node biopsy; the incidence of positive scalene nodes when para-aortic lymph nodes are known to be positive ranges from 0% to 17%. The rationale for biopsying the scalene nodes is that if there is disease outside the radiation therapy field, chemotherapy may be appropriate.

If the result of FNA is negative, or if the abdominopelvic CT scan does not demonstrate enlarged para-aortic lymph nodes, the patient can be considered for surgical staging.

Recent data reported the comparison of accuracy between PET and PET/CT for detecting lymph node metastasis in cervical cancer. In a series of 86 patients with stages IB–IVA cervical cancer, a total of 688 lymph node regions were evaluated. PET/CT was more sensitive than PET for detecting small (<5 mm) lymph node metastases (ASCO 2007).

**Laparoscopic surgery** In more recent years, the introduction of minimal-access surgery has allowed surgeons to accurately stage patients via the laparoscope prior to initiation of radiation therapy. However, the safety and efficacy of laparoscopic surgical staging are areas of ongoing investigation.

**Workup for early-stage disease** For patients who have early-stage disease for which surgery is contemplated, only a minimal diagnostic work-up is indicated prior to surgery. At most institutions, this would include a two-view chest x-ray. Patients who have stage IA cervical carcinoma (microinvasive carcinoma) do not require preoperative CT scanning prior to hysterectomy. For patients with a small stage IB carcinoma of the cervix, a CT scan of the abdomen and pelvis has a low yield and is unlikely to change the treatment plan.

**Prognostic factors**

**Clinical stage** The most important determinant of prognosis remains clinical stage, which is defined by tumor volume and extent of disease spread. The overall 5-year survival rate ranges from 95% to 100% for patients with stage IA cancer and from 75% to 90% for those with stage IB disease. Patients with stage IV disease have a ≤ 5% chance of surviving 5 years after diagnosis.

**Patients with early disease** For patients with early invasive carcinoma (stage IB), the size of the lesion, percentage of cervical stromal invasion, histology, tumor grade, and lymphovascular space involvement are important local factors that predict prognosis. In general, good prognostic signs are lesions that are ≤ 2 cm in diameter, superficially invasive, and well differentiated with no
lymphovascular space involvement. In a study of 1,067 patients treated with surgery, HPV-16 was detected in 63.8% and HPV-18 in 16.5% of samples. With a median follow-up of 77 months, HPV was not found to be a significant prognostic factor.

For patients who have undergone radical hysterectomy for early cervical carcinoma, poor prognostic factors, in addition to the local factors previously mentioned, include positive vaginal or parametrial margins and metastasis to the pelvic lymph nodes. For patients with stage IB disease and positive pelvic nodes, the 5-year survival rate drops from approximately 75%-85% to 50%.

**Patients with advanced disease** For patients with advanced-stage disease (stages IIB–IV), the primary determinants of prognosis are histology and size of the primary lesion. Survival is significantly longer for patients with small stage IIB cervical carcinomas and minimal parametrial involvement than for patients with large bulky tumors and bilateral parametrial involvement. Disease extension beyond the pelvis to the para-aortic nodes is associated with a significant decrease in overall survival rate. With regard to histology, a better prognosis is associated with a large-cell nonkeratinizing squamous cell cancer of the cervix, as opposed to a poorly differentiated adenocarcinoma.

**Other prognostic factors** Other factors that may predict outcome include the patient’s general medical and nutritional status. Patients who are anemic may respond poorly to radiation therapy, as compared with those with normal hemoglobin levels. Patients with significant alterations in their immune system may not respond as well; this result is becoming increasingly apparent with regard to patients who are HIV-seropositive.

A retrospective review of 605 patients from seven institutions in Canada treated with irradiation for cervical cancer described average weekly nadir hemoglobin levels as significant prognostic factors for survival, second only in importance to tumor stage. Interestingly, Winter et al reported that hemoglobin levels during treatment were independent predictors of treatment outcome through a recent retrospective study of 494 patients from two consecutive prospective GOG trials. The pretreatment level was not a significant predictor of outcome in the multivariate regression model. Hemoglobin levels in the last part of treatment were the most predictive of disease recurrence and survival. However, erythropoietin should not be given outside a clinical trial, as thrombosis is a significant complication and cause/effect has not been proven.

PET scanning is being used to determine response and outcome after therapy. In 152 patients with cervical cancer treated with irradiation alone or in combination with chemotherapy, Grigsby et al reported cause-specific survival of 80% in 114 patients without post-therapy PET abnormalities, 32% in 20 patients with persistent abnormal scans, and no survivors in 18 patients who developed new sites of abnormal uptake.

**Treatment**

**Surgical treatment of early-stage disease**

The standard management of patients with early cervical carcinoma is surgical removal of the cervix. The extent of resection of surrounding tissue depends on the size of the lesion and the depth of tumor invasion.

**Stage IA1 disease**

**Simple hysterectomy** Patients who have a microinvasive squamous carcinoma of the cervix with ≤ 3 mm of tumor invasion, ≤ 7 mm of lateral extent, and no lymphovascular space involvement (stage IA1) can be treated with a simple hysterectomy. Vaginal, abdominal, and laparoscopic hysterectomies are equally effective.

**Cone biopsy** Although simple hysterectomy is considered the standard therapy for patients with microinvasive cervical carcinoma, there are some patients in whom preservation of future fertility is a strong consideration. A cone biopsy entails removal of the cervical transformation zone. Provided that the biopsy margins are free of dysplasia and microinvasive carcinoma, cone biopsy is probably a safe treatment for such patients who meet the criteria of having superficial invasion < 3 mm, minimal lateral extension, and no lymphovascular space involvement.

Since there is a small risk of recurrence among this population of patients treated by cone biopsy alone, they should be followed closely. Follow-up includes a Pap smear and pelvic examinations every 3 months for 2 years, every 6 months for 4 years, and then yearly thereafter. An abnormal Pap smear is an indication for a repeat colposcopy. If such patients are successful in achieving pregnancy and have no evidence of recurrent squamous cell carcinoma, there is no need to proceed with hysterectomy at the completion of planned childbearing.
Stages IA2, IB1, and nonbulky IIA disease

Radical hysterectomy A standard treatment for patients with small cervical carcinomas (≤ 4 cm) confined to the uterine cervix or with minimal involvement of the vagina (stage IIA) is radical hysterectomy (removal of the uterus, cervix, and parametrial tissue), pelvic lymphadenectomy, and para-aortic lymph node sampling. The overall success of this treatment is similar to that of radiation therapy, and for patients with early lesions, radical hysterectomy may provide an improved quality of life. The benefits of surgical excision include rapid treatment, less time away from normal activities, and preservation of normal ovarian and vaginal function.

A randomized trial for patients with early-stage cervical cancer reported no difference in survival between radical hysterectomy and definitive radiation therapy. Because a significant percentage of patients following radical hysterectomy required postoperative pelvic radiotherapy, the morbidity was increased in the surgery arm. Therefore, patients selected for radical hysterectomy should have small-volume disease so adjuvant pelvic radiation therapy is unnecessary.

Currently, there are no specific contraindications to radical hysterectomy. Several studies have demonstrated that patients ≥ 65 years old tolerate this procedure well, and age alone should not be considered a contraindication. Obesity also is not a contraindication to radical hysterectomy. Studies addressing fertility-sparing surgeries such as radical abdominal trachelectomy vs radical vaginal trachelectomy are ongoing. A prospective study included 43 women with stage IB1 cervical cancer; the vaginal approach was performed on 28 patients and the abdominal approach on 15 patients. There was no statistical difference in average blood loss or the number of lymph nodes removed between the two approaches. There was the possibility that the abdominal approach would provide a wider margin of resection of the parametria, but overall, both the radical abdominal and vaginal approaches are potential fertility-sparing options for women with early-stage cervical cancer (Einstein MH et al: Gynecol Oncol 112:73-77, 2009). Another study has compared outcomes associated with radical trachelectomy as a fertility-sparing option vs radical hysterectomy for stage IB1 cervical cancer. Radical trachelectomy was performed in 40 women, and radical hysterectomy was performed in 110 patients. After 5 years, the recurrence-free survival was 96% for those patients undergoing radical trachelectomy and 86% for those undergoing radical hysterectomy. Therefore, there are potential radical surgeries that can be utilized as fertility-sparing options for women with early-stage cervical cancer (Diaz JP et al: Gynecol Oncol 111:255-260, 2008).

Alternatives to radical hysterectomy Reports have described laparoscopically assisted radical vaginal hysterectomy, laparoscopic abdominal radical hysterectomy, laparoscopy-assisted radical vaginal hysterectomy, and robotic-assisted surgery as less invasive alternatives to traditional radical hysterectomy. Robotic-assisted surgery, in particular, has become an area of interest; it may be associated with less estimated blood loss as well as shorter postoperative hospital stays than traditional radical hysterectomy. However, more studies need to be conducted in terms of potential intraoperative and postoperative complications with robotic-assisted surgery in comparison to other types of radical hysterectomy. Although these procedures are not performed in all centers, the results from centers that have the surgical expertise are promising. The use of fertility-preserving surgery by means of pelvic lymphadenectomy combined with radical vaginal trachelectomy (removal of the uterine cervix) has also been evaluated in selected women with early cervical cancer. Successful pregnancies after this procedure have been reported. However, further data are needed to assess the safety and efficacy of fertility-preserving surgery. There is a lack of long-term follow-up data and survival rates between conservative and radical treatment. These techniques should be performed by fully trained surgeons. The role of laparoscopic sentinel lymph node dissection is an area of active investigation. Several studies addressing the utility of intraoperative lymphatic mapping with the use of blue dye and technetium are being conducted in patients with early-stage cervical cancer undergoing radical hysterectomy. Although studies are ongoing, the role of sentinel node detection appears promising.

Complications Due to improved surgical techniques, as well as the use of prophylactic antibiotics and prophylaxis against deep vein thrombosis, the morbidity and mortality associated with radical hysterectomy have declined significantly over the past several decades. The currently accepted complication rate for radical hysterectomy includes approximately a 0.5% to 1.0% incidence of urinary tract injury, a 0.5% to 1.0% incidence of deep vein thrombosis, and an overall mortality of < 1.0%.

The increased awareness of the risks associated with blood transfusion is reflected in the fact that, in many cases, no transfusions are administered. The need for heterologous blood transfusion also can be decreased by encouraging autologous blood donation prior to radical hysterectomy or by using...
intraoperative hemodilution. The average hospital stay for patients undergoing radical hysterectomy is between 4 and 7 days. Follow-up should include a vaginal Pap smear with pelvic examination every 3 months for 2 years, twice a year for 3 years, and yearly thereafter.

**Stages IB2 and bulky IIA disease**

Numerous studies have demonstrated that patients with early-stage “bulky” lesions (> 4 cm) have a worse prognosis than those with nonbulky tumors. Therefore, patients who have undergone radical hysterectomy and pelvic lymphadenectomy for early-stage bulky cervical cancer have traditionally received postoperative adjuvant pelvic radiation therapy. However, a randomized trial from Italy demonstrated that radical hysterectomy plus radiotherapy does not improve overall or disease-free survival in patients with early-stage bulky tumors, as compared with radiation therapy alone, but does significantly increase morbidity. In selected 92 patients with bulky stages IB2, IIA, and IIB disease, without pelvic or para-aortic nodes, preoperative external-beam radiation therapy (EBRT) (40 Gy in 4.5 weeks), low-dose-rate (LDR) brachytherapy (20 Gy), and cisplatin/5-FU (fluorouracil) were administered, followed by class II modified radical hysterectomy. Pathologic residual tumor was observed in 43 patients (47%), and 5-year disease-free survival was 72%. Two severe ureteral complications were noted.

![Figure 1: Relative risk estimate of survival from five phase III randomized, controlled clinical trials of chemoradiation therapy in women with cervical cancer. A relative risk of 1 indicates no difference in outcome between the treatment arms. A relative risk of < 1 indicates a benefit for the experimental treatment. A relative risk of 0.6, for example, indicates that the treatment has reduced the risk of death by 40%. The relative risks of survival for all five trials, with 90% confidence intervals shown, range from 0.70 to 0.50, indicating that the concurrent chemotherapeutic decrease the risk of death by 30% to 50% (Rose PG, Bundy BN: J Clin Oncol 20:891-893, 2002).](image)

Furthermore, GOG 123 demonstrated the benefit of the addition of cisplatin chemotherapy to pelvic radiation therapy followed by extrafascial hysterectomy in this group of patients (Figure 1). Therefore, many experts believe that patients with stages IB2 and bulky IIA cervical cancer should be treated initially with chemoradiation therapy instead of radical hysterectomy. Others argue that treatment decisions should not be based on tumor size alone, because some studies have demonstrated that significant independent predictors of disease-free survival are lymphovascular space involvement and outer two-thirds depth of invasion. Overall, there are still conflicting data in terms of efficacy on utilizing chemoradiation therapy alone vs chemoradiation therapy followed by surgery for bulky stage IB2 cervical disease. The role of curative surgery diminishes once cervical cancer has spread beyond the confines of the cervix and vaginal fornices. Intracavitary irradiation for central pelvic disease and EBRT for lateral parametrial and pelvic nodal disease are typically combined to encompass the known patterns of disease spread with an appropriate radiation dose while sparing the bladder and rectum from receiving full doses. The addition of intracavitary irradiation to external-beam irradiation is associated with improved pelvic tumor control and survival over external irradiation alone, as the combination can achieve high central doses of radiation. In some patients, when intracavitary brachytherapy cannot be performed, it is possible to deliver additional irradiation to the central tumor after whole pelvis radiation therapy. In 44 patients with various clinical stages treated in this fashion, recurrent tumor was noted in 48%. Central recurrence was observed in 16 of 21 patients with recurrent disease. Late grade 3 sequelae were seen in 2% of the patients.
Radiation therapy

**Intracavitary brachytherapy**  Radioactive isotopes, such as cesium-137, can be introduced directly into the uterine cavity and vaginal fornices with special applicators. The most commonly used applicator is the Fletcher-Suit intrauterine tandem and vaginal ovoids.

*Calculating dose rates* With the advent of computerized dosimetry, the dose rate to a number of points from a particular source arrangement can be calculated. Adjustments in the strength or positioning of the sources can then be made to yield a selected dose rate to one or more points. Quantification of acceptable implant geometry has been described by Katz and Eifel after review of 808 implants performed in 396 patients with cervical cancer treated with irradiation at M. D. Anderson Cancer Center. These guidelines set the standard for high-quality tandem and ovoid insertions.

Points of interest usually include the maximal rectal and bladder dose, as well as the dose to three standard pelvic points: A, B, and P (see Figure 2). Point A is located 2 cm cephalad from the cervical os and 2 cm lateral to the uterine canal. Anatomically, it represents the medial parametrium/lateral cervix, the approximate point at which the ureter and uterine artery cross. Point B is 5 cm lateral to the center of the pelvis at the same level as point A and approximates the region of the obturator nodes or lateral parametrium. Point P is located along the bony pelvic sidewall at its most lateral point and represents the minimal dose to the external iliac lymph nodes. Recent publications have advocated the use of imaging (CT or MRI) to delineate tumor/target volumes and to specify more precisely the doses of brachytherapy administered to patients with carcinoma of the cervix (Potter et al).

*LDR vs HDR brachytherapy* Standard dose rates at point A are typically 50 to 70 cGy/hour; this level is considered low-dose-rate (LDR) brachytherapy. The applicator is placed into the uterus while the patient is under anesthesia in the operating room, and the patient must stay in the hospital for 2 to 3 days during the procedure. One or two implants are usually placed. Despite the fact that two insertions may allow time for regression of disease between placements, there are no data indicating that two insertions improve pelvic tumor control or survival rates over one insertion.

Whereas LDR brachytherapy has been used successfully for decades in the treatment of carcinoma of the cervix, the use of high-dose-rate (HDR) brachytherapy has been increasing in the United States over the past decade. Dose rates are typically 200 to 300 cGy/minute, with short treatment times allowing for stable position of the applicator.

The major benefit of HDR brachytherapy is that the procedure can be performed on an outpatient basis with less radiation exposure to personnel. The major disadvantage is biologic: large single fractions of radiation (5 to 10 Gy) are used with 3 to 10 insertions per patient, which may increase the rate of late complications.

Several series have cited comparable disease control and complication rates with HDR and LDR.
A total of 237 patients with previously untreated invasive cervical cancer were enrolled into one randomized study to compare the clinical outcome between HDR and LDR intracavitary brachytherapy. The median follow-up for LDR and HDR groups was 40.2 and 37.2 months, respectively. The 3-year overall and relapse-free survival rates for all patients were 69.6% and 70.0%, respectively. There was no significant difference in the following clinical parameters between LDR and HDR groups: the 3-year overall survival rate was 70.9% and 68.4% ($P = .75$), the 3-year pelvic control rate was 89.1% and 86.4% ($P = .51$), and the 3-year relapse-free survival rate in both groups was 69.9% ($P = .35$). Considering patient convenience, the small number of medical personnel needed, and the decreased radiation exposure to health care workers, HDR intracavitary brachytherapy is an alternative to conventional LDR brachytherapy and is in current GOG and RTOG advanced cervical cancer trials.

Guidelines have been published for HDR brachytherapy for cervical cancer by the American Brachytherapy Society (see Suggested Reading).

**Pelvic EBRT** is used in conjunction with intracavitary radiotherapy for stage IA2 disease and above when the risk of pelvic lymph node involvement is significant. The amount of EBRT delivered and the timing of its administration relative to intracavitary radiation are individualized. For example, the presence of a large exophytic cancer that distorts the cervix would initially preclude successful placement of intracavitary brachytherapy. EBRT would be administered first, and after significant regression of disease, it could be followed by intracavitary radiotherapy. Various techniques have been developed to optimize EBRT, including CT simulation, conformal blocking, and, more recently, intensity-modulated radiation therapy (IMRT). These techniques reduce the volume of normal tissue having full-dose irradiation while not compromising coverage of the target. MRI has been shown to enhance the accuracy of tumor delineation and design of treatment portals, to avoid geographic misses, particularly in the posterior margin of the lateral pelvic fields. Recently, PET scanning (FDG) has been used to more accurately identify the tumor volume in the cervix and optimize the radiation dose administered with intracavitary brachytherapy (to point A), without increasing the dose delivered to the bladder or the rectum. Several preliminary reports have been published describing highly conformal dose distributions for patients with carcinoma of the cervix in IMRT. Tumor control has been about 80% for various stages, and no patient has developed $> \text{grade 2 GI or genitourinary toxicity.}$ Advanced tumors require relatively more external irradiation due to the inability of central radioisotope sources to effectively irradiate disease in the lateral parametrium. Typically, external pelvic doses of 4,000 to 5,000 cGy are followed by 4,000 to 5,000 cGy to point A with intracavitary LDR brachytherapy, for a total dose of 8,000 to 9,000 cGy to point A. A parametrial boost completes treatment to the lateral pelvis, for a total dose to point B or P of 6,000 cGy from EBRT and brachytherapy, depending on the extent of disease.

With HDR brachytherapy, equivalent doses are prescribed using the linear quadratic equation. The HDR/LDR dose ratio ranges from .5 to .8 depending on the number of HDR fractions. Deep hyperthermia (administered once weekly) has been combined with pelvic external beam and intracavitary brachytherapy to treat patients with bulky tumors of the cervix. In 378 patients, overall complete tumor response was 77%; at 5 years, the tumor control rate was 53% and disease-free survival was 47%. Late toxicity was observed in 12% of the patients.

**Para-aortic EBRT** may be used in addition to pelvic EBRT when para-aortic disease is confirmed or suspected. An RTOG trial found that para-aortic EBRT conferred a survival benefit in patients with advanced cervical cancer (stages IB > 4 cm, stage IIA, and stage IIB) over external-beam pelvic therapy alone. Although external-beam radiation therapy can successfully sterilize microscopic disease, its value in the treatment of gross para-aortic disease is limited, as the tolerance of surrounding organs (bowel, kidneys, spinal cord) precludes the delivery of sufficiently high doses to the para-aortic region. In multivariate analysis, treatment factors associated with improved pelvic control for cervical cancer include the use of intra-cavitary brachytherapy, total point A dose $> 8,500 \text{ cGy (stage III only)}$, and overall treatment time $< 8$ weeks.

**Definitive radiation therapy**

**CIS, stage IA disease** Carcinoma in situ (CIS) and microinvasive cervical cancer (stage IA) are not associated with lymph node metastases. Therefore, intracavitary LDR brachytherapy alone, delivering approximately 5,500 cGy to point A, can control 100% of CIS and stage IA disease and is an acceptable alternative to surgery for patients who cannot undergo surgery due to their medical condition.
Stage IB disease The most important prognostic factor associated with pelvic tumor control and survival following radiation therapy for stage IB cervical cancer is tumor size. The central pelvic control rate with radiotherapy alone is excellent for tumors < 8 cm (97%), with total pelvic control and survival rates of 93% and 82%, respectively. Therefore, many experts have argued that adjuvant hysterectomy following chemoradiation therapy is unnecessary for cervical cancer < 8 cm. For bulky cervical cancers ≥ 8 cm, pelvic control and survival rates decrease to 57% and 40%, respectively, with irradiation alone, and adjuvant hysterectomy may potentially improve local tumor control and survival rates (Table 2).

CHEMORADIATION THERAPY FOR LOCALLY ADVANCED DISEASE

An updated RTOG trial (RTOG 90-01) for advanced cervical cancer (stage IB or IIA with tumor ≥ 5 cm or with biopsy-proven pelvic lymph node involvement and stages IIB–IVA disease) compared external-beam pelvic irradiation plus concurrent 5-FU and cisplatin with pelvic and para-aortic EBRT in both arms; these therapies were followed by intracavitary irradiation. The addition of chemotherapy to irradiation improved 5-year survival from 55% to 79% and disease-free survival from 46% to 74% for stage IB/IIA disease by reducing the rates of both local recurrence and distant metastases. For stage III/IVA disease, chemoradiotherapy improved 5-year survival from 45% to 59% and disease-free survival from 37% to 54% (Figures 1 and 3).

GOG 123 randomized patients with stage IB bulky cervical cancer to receive either local treatment alone (external and intracavitary irradiation followed by hysterectomy) or local therapy plus weekly cisplatin. The combination of concurrent weekly cisplatin and irradiation significantly reduced the relapse rate and improved survival by 50%. The 3-year survival rate was significantly improved from 74% to 83% with the use of chemotherapy; this improvement was primarily due to a reduced risk of local recurrence (21% vs 9%).

On the other hand, an Australian gynecologic group randomized study with 76 patients and a Canadian randomized study with 127 patients with stages IB–IIB carcinoma of the cervix treated with chemotherapy and irradiation or irradiation alone showed no significant difference in tumor control or survival. A possible explanation for the discrepancy in the results between the five US trials and the National Cancer Institute of Canada (NCIC) study has been analyzed by Lehman.
and Thomas. A review of 4,069 patients with invasive carcinoma of the cervix treated in Ontario, Canada, between 1992 and 2001 documented a significant increase in 3-year survival in patients treated with concurrent chemotherapy-radiotherapy (CT-RT; 75.9%) compared with those treated with irradiation alone (71.1%; see Suggested Reading). Current treatment recommendations Concurrent CT-RT (usually cisplatin-based) with or without adjuvant hysterectomy is standard treatment for bulky IB2 cervical cancer. An alternative approach is radical hysterectomy followed by tailored postoperative CT-RT. The use of adjuvant hysterectomy is controversial for stage IB2 cervical cancer, since dose-intense external pelvic and intracavitary irradiation plus chemotherapy may obviate the need for adjuvant surgery. The GOG trial suggests that adjuvant hysterectomy reduces the recurrence rate but does not affect survival. The use of weekly cisplatin for 6 cycles or 5-FU and cisplatin every 3 weeks concurrently with radiotherapy is the standard treatment approach for bulky stage IB2 cervical cancer.

Stages IIA–IVA disease The most important prognostic factor associated with pelvic tumor control and survival is the bulk of pelvic disease within each stage. For stage IIB, bulky disease is variously defined as bilateral or lateral parametrial infiltration or central bulky disease > 4 cm. For stage IIIB, bulky disease is defined as bilateral sidewall involvement, lower-third vaginal involvement, or hydronephrosis. In the previous GOG experience, in which para-aortic lymph node staging had been mandated, multivariate analysis testing revealed para-aortic lymph node involvement to be the most powerful negative prognostic factor, followed by pelvic lymph node involvement, larger tumor diameter, young age, advanced stage, and lower performance status for patients with negative para-aortic lymph nodes. Five-year survival rates for radiotherapy alone vary from 80% for stage I, 60% for stage II, and 45% for stage III disease, with corresponding pelvic control rates of 90%, 80%, and 50%, respectively. CT-RT A GOG phase III trial (GOG 120) compared standard pelvic EBRT/intracavitary brachytherapy plus hydroxyurea vs weekly cisplatin versus hydroxyurea, 5-FU, and cisplatin. Both the weekly cisplatin and the 5-FU-cisplatin-hydroxyurea arms produced significantly improved survival and relapse rates compared with hydroxyurea alone. Two-year progression-free survival rates were
significantly improved from 47% to 67% and 64% with weekly cisplatin-irradiation and 5-FU-cisplatin-hydroxyurea-irradiation compared with hydroxyurea and radiotherapy (Figure 1). The improved outcome was due to the reduced rates of pelvic failure and lung metastases. Because of an improved therapeutic ratio, weekly cisplatin is the favored regimen. Updated results of this trial confirm the original observations.

GOG 165 compared standard radiation therapy plus concurrent weekly cisplatin vs concurrent protracted venous infusion of 5-FU (225 mg/day over 5 weeks) as radiation sensitizers. In a randomized trial 294 patients with advanced cervical cancer were enrolled to compare cisplatin and cisplatin + topotecan (Hycamtin). Patients receiving topotecan had statistically superior outcomes to those receiving cisplatin alone, with median overall survival of 9.4 and 6.5 months (P = .017), median progression-free survival of 4.6 and 2.9 months (P = .014), and response rates of 27% and 13%, respectively. This recently reported study confirms the efficacy of pelvic radiotherapy with weekly cisplatin. The study was closed prematurely when a planned interim analysis indicated that the 5-FU arm had a 35% higher rate of treatment failure. An editorial published with the article highlighted the future difficulties with randomized trials for this population.

A recent randomized study of patients with stages IIIB–IVA cervical cancer was presented at ASCO 2009. The study had two arms: 1) a standard regimen of weekly cisplatin with pelvic radiation therapy vs 2) concurrent radiation therapy and weekly cisplatin (40 mg/) plus weekly gemcitabine (Gemzar, 125 mg/), followed by 2 additional cycles of higher-dose cisplatin and gemcitabine after radiation therapy was completed. This study enrolled more than 500 patients worldwide, most notably in developing countries. There was a significant survival advantage with the addition of gemcitabine and post-radiation therapy chemotherapy (3-year progression-free survival rate, 65% vs 74%; overall survival HR = .68). Neutropenia and anemia rates were higher in the gemcitabine group. This study did not clarify whether the addition of gemcitabine or the post-radiation chemotherapy, or both, was the reason for the survival improvements.

**Current treatment recommendations** In view of the multiple randomized trials documenting a survival benefit with concurrent CT-RT, the use of concurrent weekly cisplatin or cisplatin-5-FU every 3 weeks with irradiation is standard therapy for stages IB2–IVA cervical cancer (Figure 1). Further prospective studies should be explored to determine the role of gemcitabine and post-radiation therapy chemotherapy.

Five of six large randomized clinical trials demonstrated a significant survival benefit for patients treated with concurrent CT-RT, using a cisplatin-based regimen, with a 28% to 50% relative reduction in the risk of death. In addition, the results of a meta-analysis of 19 randomized clinical trials of concurrent CT-RT involving 4,580 patients showed that concurrent CT-RT significantly improved overall survival (HR = 0.71; P < .001), as well as progression-free survival (HR = .61; P < .0001). In line with these results, concurrent CT-RT is currently recommended as standard therapy (Table 3).

A meta-analysis from all randomized trials was recently published and reaffirms the benefits of concurrent CT-RT. On the basis of 13 trials that compared CT-RT vs the same radiation therapy, there was a 6% improvement in 5-year survival with CT-RT (HR = .81; P < .001). A larger survival benefit was seen for the two trials in which CT was administered after CT-RT. There was a significant survival benefit for both the group of trials that used platinum-based (HR = .83; P < .017) and non-platinum-based (HR = .77; P < .009) CT-RT, but no evidence of a difference in the size of the benefit by radiation therapy or chemotherapy dose or scheduling was seen. CT-RT also reduced local and distant recurrence and disease progression and improved disease-free survival. There was a
suggestion of a difference in the size of the survival benefit with tumor stage, but not across other patient subgroups. Acute hematologic and GI toxicities were increased with CT-RT, but data were too sparse for an analysis of late toxicity. This meta-analysis clearly demonstrates the benefit of concurrent CT-RT and suggests further exploration should continue with additional adjuvant chemotherapy and non-platinum-based CT-RT.

Based on the promising responses and acceptable toxicity reported in the phase I/II study, a phase III GOG trial for advanced cervical cancer (stages IB2–IVA) is randomizing patients to undergo pelvic radiotherapy plus cisplatin weekly or pelvic radiotherapy, cisplatin, and tirapazamine (a hypoxic cell sensitizer).

For patients without para-aortic lymph node metastases, pelvic external irradiation (4,000 to 5,000 cGy) should be used, followed by intracavitary LDR brachytherapy (4,000 to 5,000 cGy) to point A, for a total dose of 8,000 to 9,000 cGy to point A. Noteworthy, in a study at the Norwegian Radiumhospital, in 147 patients, the estimates of physician-assessed intestinal, bladder, and vaginal grade 3/4 morbidity were 15%, 13%, and 23%, respectively, whereas the prevalence of patient-reported severities of the same symptoms were 45%, 23%, and 58%, respectively. The study underscores the importance of incorporating patient assessment in the analysis of treatment morbidity.

**Adjuvant radiotherapy following radical hysterectomy**

**Node-negative disease** Local failure rates approach 20% following radical hysterectomy and pelvic lymphadenectomy when pelvic lymph nodes are not involved but the primary tumor has high-risk characteristics (primary tumor > 4 cm, outer-third cervical stromal invasion, and capillary-lymphatic space invasion). A GOG trial randomized these intermediate-risk patients with node-negative disease to receive pelvic EBRT (5,100 cGy/30 fractions) or no further therapy following radical hysterectomy-pelvic lymphadenectomy. Postoperative irradiation produced a significant 44% reduction in recurrence; the recurrence-free rate at 2 years was 88% with irradiation vs 79% without it. Survival analysis awaits further follow-up.

**Node-positive disease** For patients with positive pelvic lymph nodes following radical hysterectomy-pelvic lymphadenectomy, pelvic radiotherapy reduces the pelvic failure rate from approximately 50% to 25% but does not affect survival, since distant metastases are still seen in 30% of patients. GOG/SWOG 8797 randomized these high-risk patients with node-positive disease (or patients with positive surgical margins) to undergo pelvic EBRT (4,930 cGy/29 fractions) vs pelvic EBRT plus concurrent 5-FU and cisplatin for 4 cycles following radical hysterectomy-pelvic lymphadenectomy. A significant improvement in disease progression-free and overall survival was seen for concurrent 5-FU–cisplatin and radiation therapy compared with radiation therapy alone (4-year survival, 81% vs 71%). A prospective study comparing the accuracy of PET scan with that of CT and/or MRI scans has been presented. Eighteen patients underwent PET scans with CT or MRI scans prior to surgical exploration for pelvic exenteration. PET scan was reported to be the most accurate method of detecting extrapelvic metastasis, with a sensitivity of 100% and a specificity of 73% (Husain A et al: Gynecol Oncol 106:177-180, 2007).

Current treatment recommendations At present, the use of adjuvant pelvic radiotherapy should be considered for patients with negative nodes who are at risk for pelvic failure and remains the standard postoperative treatment for patients with positive lymph nodes. Treatment consists of external pelvic irradiation (45 to 50 Gy), with specific sites boosted with further external-beam or intracavitary irradiation as needed. Since the combination of radical surgery and irradiation has greater morbidity than either modality alone, complete preoperative assessment is crucial to minimize the need for both. Since concurrent CT-RT following radical hysterectomy provides a significant benefit in node-positive high-risk cervical cancer, it should be part of the postoperative treatment plan. Postoperative CT-RT following radical hysterectomy should be strongly considered for patients with negative nodes but positive margins or parametria, ≥ middle-third stromal invasion, and lymphovascular space invasion for tumors ≥ 5 cm.

**Surgical management of recurrent or metastatic disease**

**Recurrent advanced disease**

**Pelvic exenteration** For patients whose disease fails to respond to primary radiation therapy or for those with early invasive cervical carcinoma whose disease recurs after surgery or radiation therapy, pelvic exenteration offers the possibility of cure. Patients should be considered for pelvic
exenteration only if they have locoregional disease that can be completely removed by this radical surgical procedure. In most cases, patients will require surgical removal of the bladder, uterus, cervix, vagina, and rectum.

Of all patients who are considered candidates for pelvic exenteration, only about half will be found to have resectable disease at the time of exploratory laparotomy. For patients who successfully undergo pelvic exenteration, 5-year survival rates range from 25% to 50%.

When the patient has central recurrence of squamous cell or adenocarcinoma of the cervix, the initial evaluation includes a complete physical examination, as well as a CT, MRI, or PET/CT scan. Evidence of extrapelvic disease is a contraindication to pelvic exenteration. If no evidence of disease beyond the pelvis is found, the patient can be prepared for pelvic exenteration.

Preparation for exenteration includes complete bowel preparation, a visit with the stomal therapy nurse, and counseling regarding the radical nature of the surgery and the anticipated changes in body image after the operation. In most cases, we counsel the patient that vaginal reconstruction should be performed at the time of pelvic exenteration, both for maintenance of body image and improved healing.

Surgical procedure During surgery, a careful exploration is carried out to confirm that there is no evidence of unresectable disease beyond the pelvis. The pelvic sidewall spaces are opened and resectability is determined. An en bloc resection is usually performed; in some cases, especially when the recurrent tumor involves the lower vagina, a two-team approach can expedite the procedure. The actual exenterative portion of the procedure may take several hours and is usually accompanied by significant blood loss. In cases where surgical margin status may be questionable, the use of intraoperative radiation therapy is considered.

Reconstruction Following the exenterative procedure, the reconstructive portion of the procedure begins. We currently recommend to nearly all patients that they consider a continent urinary diversion. Although this step may add approximately 30 to 60 minutes to the surgical procedure, the improvement in quality of life is significant.

In patients who have undergone a supralevator pelvic exenteration, we frequently attempt a stapled reanastomosis of the colon. Unless there is excessive tension on the anastomosis or other problems, a diverting colostomy is not routinely indicated. About one-third of these patients suffer anastomotic breakdown in the postoperative period. At that time, a diverting colostomy can be performed. Unfortunately, Hatch et al found no benefit to the earlier use of colostomy.

Lung metastasis For the rare patient who presents with a single isolated lung metastasis after treatment of invasive cervical carcinoma, pulmonary resection may offer the possibility of long-term disease-free survival or even cure in selected cases. For patients who have multiple lung metastases or unresectable pelvic disease, surgery offers little or no hope and produces significant morbidity and mortality.

therapy for recurrent or metastatic disease

Local recurrence after radical hysterectomy Local recurrence confined to the pelvis following radical hysterectomy for cervical cancer can be treated with radiotherapy with curative intent. An experience with 5-FU–based chemotherapy and concurrent pelvic EBRT resulted in a 58% complete response rate and a 45% no-evidence-of-disease rate, at a median follow-up of 57 months. The total pelvic EBRT dose was 5,280 cGy plus a boost to sites of recurrence with twice-daily 160-cGy fractions during the 5-FU infusion. Therefore, radiotherapy, with or without chemotherapy, can provide durable local tumor control, with better results attainable for small, central recurrences, for which brachytherapy is possible.

Local recurrence after definitive radiation therapy Local recurrence confined to the pelvis following definitive radiation therapy rarely can be cured with exenteration. In a series of patients treated with definitive radiotherapy, 21% of recurrences (80 of 376) were isolated to the pelvis. Only 29% of these localized pelvic recurrences (23 of 80) were explored for curative exenteration, and for the 43% of patients (10 of 23) deemed operable, the 5-year survival rate was 16%. Para-aortic lymph node recurrences are also observed in some of these patients, and some are successfully treated with aggressive irradiation and chemotherapy. Of 758 patients, 42 (6%) had isolated and nonisolated para-aortic lymph node failures. The 5-year survival in the above group was 28%. Careful follow-up, early detection, and aggressive treatment of para-aortic lymph node recurrences may increase the probability of salvage for some of these patients.

Palliation of metastatic disease Palliative radiation therapy to sites of metastatic cervical cancer is effective. The most common sites
of metastasis are distant lymph nodes, bone, and lungs. Reirradiation of the pelvis is possible in selected patients to control local symptoms, such as bleeding, but carries an increased risk of bowel complications. For previously unirradiated sites of metastatic disease, 3,000 cGy in 10 fractions provides palliation of symptoms in the majority of patients.

Chemotherapy for advanced/recurrent disease

Chemotherapy has traditionally been used for the palliative management of advanced or recurrent disease that can no longer be managed by surgery or radiation therapy (see Table 3). Various factors complicate the use of chemotherapy in such patients, however. Prior radiation treatment can affect the blood supply to the involved field, which may result in decreased drug delivery to the tumor site. Pelvic irradiation also reduces bone marrow reserve, thus limiting the tolerable doses of most chemotherapeutic agents. Moreover, irradiation may produce its cytotoxic effect, in part, through a mechanism similar to that of alkylating agents; thus, it is thought to be cross-resistant with some chemotherapeutic agents. A significant number of patients with advanced disease may also have impaired renal function, further limiting the use of certain chemotherapeutic regimens.

Single agents

Among the chemotherapeutic agents used for cervical cancer, cisplatin and ifosfamide have shown the most consistent activity as single agents (Table 4). The duration of response with any single agent is brief, ranging from 4 to 6 months, with survival ranging from 6 to 9 months.

**Cisplatin** has been the most extensively evaluated single agent for cervical carcinoma. A dose of 100 mg/ was shown to have a higher response rate than a dose of 50 mg/ (31% vs 21%), but the higher dose was associated with increased toxicity, and overall survival did not differ significantly between the two groups. A 24-hour infusion of cisplatin was tolerated better than a 2-hour infusion, with no difference in therapeutic efficacy.

**Ifosfamide** produces response rates ranging from 33% to 50% in various dose schedules. A dose of
1.5 g/over 30 minutes for 5 days (with mesna [Mesnex]) produced an overall response rate of 40% and a complete response rate of 20%.

Lower response rates are generally seen in patients who have had prior chemotherapy. Responses also are decreased in previously irradiated sites.

**Taxanes** Paclitaxel and docetaxel (Taxotere) have been reported to be active in cervical cancer. A study of paclitaxel (170 mg/over 24 hours) showed an objective response rate of 17%, and another study of paclitaxel (250 mg/over 3 hours) demonstrated an objective response rate of 27%.

Docetaxel (100 mg/over 1 hour) has yielded a response rate of 19%.

**Camptothecins** Irinotecan and topotecan (Hycamtin), semisynthetic camptothecins, have shown activity in patients with cervical cancer, even in patients who did not respond to prior chemotherapy and prior radiation therapy. The reported objective response rates were 21% and 19%, respectively.

**Targeted therapies** Newer biologic agents are being actively studied. Two important receptors in cervical cancer include vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR). VEGF is a key promoter of tumor progression in cervical cancer. A GOG phase II study of 46 patients with metastatic cervical cancer explored the role of bevacizumab (Avastin), a recombinant humanized anti-VEGF monoclonal antibody. Eleven patients (24%) survived progression free for at least 6 months, and five patients (11%) had objective radiographic responses. This finding compared favorably with results of historic phase II studies in this population. GOG227E is testing cetuximab (Erbitux), a monoclonal antibody to the EGFR, in patients with metastatic disease.

**Combination regimens**

Various combination chemotherapy regimens have been evaluated in phase II trials, and high response rates (> 50%) were noted, even in patients who had received prior radiation therapy. The results of some of these trials are summarized in Tables 5 and 6. In one study, a subset analysis showed a response rate of 72% with the combination
of bleomycin, ifosfamide, and cisplatin as treatment for tumors located in previously irradiated sites. Neoadjuvant regimens of cisplatin combined with gemcitabine in patients with locally advanced cervical cancer demonstrated very high activity, with a clinical response rate of 95%. Neoadjuvant ifosfamide and cisplatin, with or without paclitaxel, produced 87% and 82% response rates, respectively, among 146 evaluable patients in a randomized study. A randomized trial was reported by Long et al. A total of 146 patients with advanced persistent or recurrent cervical cancer were treated with cisplatin (50 mg/IV every 21 days), and 147 patients were treated with topotecan (.75 mg/IV during 30 minutes on days 1, 2, and 3 followed by cisplatin (50 mg/on day 1) repeated every 21 days. All regimens were administered for a maximum of 6 cycles for nonresponders or until disease progression or unacceptable toxicity prohibited additional chemotherapy. The complete response rate was 3% for cisplatin and 10% for the cisplatin-topotecan combination, and the complete and partial remission rates were 13% and 27%, respectively; the median progression-free survival was 2.9 and 4.6 months, respectively. Chemotherapy remains palliative, with no longevity prolongation of survival in recurrent or metastatic disease. The most recent phase III GOG randomized trial was presented; it explored four cisplatin-containing doublet combinations in stage IVB, recurrent or persistent cervical carcinoma. A total of 434 evaluable patients received cisplatin (50 mg/on day 1), combined with either paclitaxel (135 mg/) or vinorelbine (30 mg/on days 1 and 8) or gemcitabine (1,000 mg/on days 1 and 8) or topotecan (Hycamtin, 0.75 mg/on days 1, 2, and 3). Each cycle was repeated every 21 days. In the analysis, the cisplatin and paclitaxel regimen was considered the standard arm, and a 33% death reduction was considered to be a significant endpoint. In the final results, there was no survival difference seen among the four groups. Cisplatin-paclitaxel had the highest radiographic response rate (29.1%) and slightly higher survival rates (2.6 months longer), but still these results were not statistically better than those of the other treatment groups.

Palliative care

Palliation of the dying cervical cancer patient is difficult. Pain due to recurrent pelvic disease can be extreme and requires skillful use of combinations of narcotics, sedatives, and anxiolytics. Fistula from the bladder or rectum demands meticulous local skin care and occasionally surgical diversion procedures in patients with reasonable expected longevity. This patient population often has limited resources, with dependent children requiring careful social service planning. A small percentage has concurrent HIV infection, making the infectious disease specialist part of the palliative care team. The tripod of care in advanced cervical cancer is the judicious use of chemotherapy and radiation therapy, palliation of the symptoms of advancing disease, as well as emotional and social support for the patient and family members. In the follow-up of patients treated for carcinoma of the cervix, it is important to keep in mind that they are at risk for the development of secondary malignant tumors. In a study of more than 85,000 patients with squamous cell carcinoma and 10,280 with adenocarcinoma, treated in Scandinavian countries and the United States, there were 10,559 second cancers (standardized incidence ratio [SIR], 1.31) in the squamous cell carcinoma and 920 (SIR, 1.29) in the adenocarcinoma patients. Risk of lung cancer was increased in both groups of patients. SIRs for second cancers of the colon, soft tissues, melanoma, and non-Hodgkin lymphoma were
significantly higher among the adenocarcinoma survivors than the squamous cell carcinoma survivors.

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SUGGESTED READING


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Acknowledgment
The authors would like to thank Dr. Xipeng Wang, Dr. Hye-Sook Chon, Dr. Xi Cheng, and Lora Lothringer for their assistance.

Abbreviations in this chapter
GOG = Gynecologic Oncology Group; RTOG = Radiation Therapy Oncology Group; SWOG = Southwest Oncology Group

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