

REVIEW ARTICLES

MEDICAL PROGRESS

CANCER OF THE UTERINE CERVIX

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INVASIVE cervical cancer is uncommon in the United States, with an incidence of 15,800 cases and 4800 deaths in 1995.¹ This relatively low incidence is largely due to the effectiveness of screening programs that assess cervical cytology by Pap smear. On a global scale, however, cancer of the cervix is a major cause of death, especially in Third World countries, where such screening is often not routinely performed. Pap-smear screening is designed to detect precursor lesions in cervical epithelium, which may antedate the development of invasive cancer by several years. In contrast to other screening strategies, such as mammography, which improves survival by detecting malignant disease at an early stage, the Pap test is a central part of a strategy designed to prevent the development of invasive cancer.

Because cervical cancer is a potentially preventable disease, it is important to be aware of the risk factors, screening techniques, and available diagnostic options, with special attention to the management of preinvasive disease. This review concentrates on the pathogenesis and management of squamous-cell carcinoma of the cervix, which accounts for the majority of cases of cervical cancer in the United States.

EPIDEMIOLOGY AND RISK FACTORS

Although cervical cancer is associated with a broad age range, it usually occurs in the fifth or sixth decade, at a mean age of 54 years.² In contrast, intraepithelial lesions, which are the precursors of invasive disease, frequently occur in younger women (often under 40 years of age).³ These precursor lesions, known as cervical intraepithelial neoplasia (CIN), are characterized by dysplastic changes confined to the cervical epithelium and showing varying degrees of disordered maturation.⁴ The observation that CIN occurs at a younger age than does invasive disease is consistent with the notion that the malignant transformation of squamous epithelial cells requires a long latency period.

Several risk factors for cervical cancer have been identified, including sexual intercourse at an early age, multiple male sexual partners, male sexual partners

who themselves have had multiple sexual partners, and smoking.⁵⁻⁸ It has been suggested that the risk of cervical cancer is also increased in patients who are immunosuppressed as a consequence of renal-allograft transplantation or Hodgkin's disease.⁹⁻¹¹ Although the immunosuppression caused by human immunodeficiency virus (HIV) infection is a risk factor for the development of CIN, the relation between HIV and the risk of cervical cancer is less clear.¹²⁻¹⁴

ROLE OF HUMAN PAPILLOMAVIRUS IN THE DEVELOPMENT OF CERVICAL CANCER

Both intraepithelial lesions (i.e., CIN) and cervical-cancer specimens frequently harbor the human papillomavirus (HPV), an agent known for its ability to immortalize cells *in vitro*.¹⁵⁻¹⁹ Infection with HPV is highly prevalent, being detected in approximately one third of American female college students and in 8 percent of men between the ages of 15 and 49 years.²⁰⁻²² There are several types of HPV, which vary in their ability to transform the cervical epithelium. Low-risk varieties, such as types 6 and 11, are commonly associated with either viral condyloma or mild dysplastic changes in cervical epithelium (CIN I), which do not usually progress to invasive disease.^{16,19,23-26} These low-risk types of HPV are almost never present in women with cervical cancer. In contrast, high-risk types of HPV, such as types 16, 18, 31, 33, and 35, are often observed in association with moderate dysplasia (CIN II) and severe dysplasia or carcinoma *in situ* (CIN III). These high-risk types are also observed in the majority of patients with cervical cancer.²³⁻²⁷ As discussed below, CIN II and III are intraepithelial lesions that have the potential for progressing to invasive cervical cancer. The HPV genome is usually present in an episomal (circular and nonintegrated) configuration in CIN, whereas in invasive cervical cancer, the genome is commonly integrated into the host DNA.²⁷

The viral proteins E6 and E7 produced by high-risk types of HPV are critical for malignant transformation because of their ability to bind and inactivate the host's p53 and Rb proteins, respectively.²⁷⁻³⁰ Since p53 and Rb are tumor-suppressor proteins that inhibit cell-cycle progression, their inactivation by viral proteins E6 and E7 leads to dysregulated entry of cells into S phase. E6 inactivates the function of wild-type p53 by enhancing its degradation, presumably resulting in insufficient intracellular levels of this tumor-suppressor protein.²⁷ In the minority of cervical-cancer cell lines that are not infected with HPV, p53 is inactivated by mutation. Thus, inactivation of p53, through either E6 binding or mutation, appears to be a central component of the process of malignant transformation in cervical cancer.^{31,32}

PAP-SMEAR SCREENING

Evidence of the effectiveness of Pap-smear screening is largely derived from retrospective analyses of the in-

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idence of cervical cancer and associated mortality. In the mid-1960s, Finland, Sweden, and Iceland implemented screening programs in which more than 80 percent of women participated, whereas Norway performed screening in only one county, which comprised 5 percent of the population.³³ All four countries noted a similar incidence of cervical cancer in 1960, which is not surprising given the homogeneity of their populations. During the ensuing 20 years, the incidence of cervical cancer did not change in Norway but decreased by approximately 50 percent in the other three countries, where mortality from cervical cancer also decreased. Likewise, with the implementation of Pap-smear screening programs in British Columbia, the incidence of cervical cancer decreased by 85 percent between 1955 and 1988.³⁴ Similarly, mortality from cervical cancer in the United States decreased by 70 percent between 1947 and 1984, a change coincident with the introduction of mass screening programs.^{35,36} Despite the lack of randomized trials, these data provide compelling evidence for the effectiveness of Pap-smear screening in the prevention of cervical cancer.³⁷⁻³⁹

The efficacy of Pap-smear screening is largely dependent on the quality of the specimen and the accuracy of the cytologic interpretation. Pap smears have been reported to be technically inadequate because of sampling errors in 12.3 percent of cases, and the reported findings may underestimate the intraepithelial lesion in 17.5 percent of cases.⁴⁰ Likewise, it has been estimated that approximately 15 to 25 percent of patients with intraepithelial lesions have normal Pap-smear results.^{41,42} Such false negative results can be minimized by ensuring that the proper technique is used to obtain the cytologic specimen. The transformation zone, which is the boundary between squamous epithelium of the exocervix and columnar epithelium of the endocervix, is the most common site for the development of intraepithelial lesions that may give rise to invasive disease. False negative results may be due to inadequate sampling of the transformation zone, which often regresses into the endocervical canal in postmenopausal women. In addition to the routine cervical scraping performed by using a spatula, an endocervical sample should be obtained with an endocervical brush, for instance. Also, the Pap smear must not be allowed to air-dry before fixation. Existing federal standards are designed to maintain the quality of Pap-smear interpretation by laboratories and may serve to decrease the number of false negative results.⁴¹ Despite occasional difficulties with sampling and interpretation, the long interval between the appearance of intraepithelial lesions and the development of invasive disease provides multiple opportunities to detect and interrupt the process of malignant transformation in the majority of patients.

The most cost-effective interval for Pap-smear screening is unknown. The American College of Obstetricians and Gynecologists and the American Cancer Society recommend that annual screening commence when women become sexually active or reach the age of 18 years.^{41,43} If three or more consecutive annual examina-

tions have been normal, Pap tests may be performed less frequently, at the physician's discretion, in a woman at low risk for cervical cancer. It is appropriate to continue to perform annual Pap tests in women considered to be at high risk for cervical cancer on the basis of the risk factors noted above.

INTERPRETATION OF PAP SMEARS

A definitive diagnosis of CIN or carcinoma can be made only by biopsy of suspicious lesions observed either grossly or during colposcopy, as discussed below. The Pap smear is a screening test designed to identify patients who may have premalignant or malignant lesions requiring further evaluation. Several cytologic classifications of Pap-smear findings have been proposed, with the Bethesda classification currently the most widely used (Fig. 1).^{41,44-46} Additional information may be obtained from several comprehensive reviews of Pap-smear classification.⁴⁷⁻⁴⁹

The Bethesda classification recognizes two categories of cytologic abnormalities suggesting the presence of intraepithelial lesions. The first category, termed "low-grade squamous intraepithelial lesion" (LGSIL), is associated with a heterogeneous group of histologic abnormalities on subsequent biopsy (Fig. 1). Patients with a Pap-smear report of LGSIL often have a biopsy that reveals CIN I, a lesion that usually undergoes spontaneous resolution. LGSIL may also be reported in the presence of HPV infection, without any evidence of CIN I on biopsy. In a minority of patients with a Pap-smear report of LGSIL, however, the biopsy shows CIN II or III, lesions that have the potential for progressing to invasive cancer.⁵⁰⁻⁵² Thus, the report of LGSIL on Pap smear does not always indicate the presence of a low-risk lesion, and such a finding requires further evaluation with colposcopy, as outlined below.

The second category of abnormal findings on the Pap smear that suggests the presence of an intraepithelial lesion is termed "high-grade squamous intraepithelial lesion" (HGSIL). A Pap-smear report of HGSIL suggests the presence of CIN II or III on biopsy (Fig. 1). In some cases, however, a report of HGSIL is associated with the finding of invasive cancer on biopsy. Thus, a Pap smear demonstrating HGSIL always calls for colposcopic evaluation.

In addition to LGSIL and HGSIL, the Bethesda classification includes a group of lesions characterized by "atypical squamous cells of uncertain significance" (ASCUS). The meaning of this category is somewhat controversial, although it is important to note that patients with a Pap-smear report of ASCUS may have CIN on biopsy.

EVALUATION AND CARE OF PATIENTS WITH ABNORMAL PAP SMEARS

Intraepithelial lesions are generally not visible to the naked eye. The colposcope is a low-power magnification device that permits the identification of mucosal abnormalities characteristic of CIN or invasive cancer. Such abnormalities are often best visualized by washing

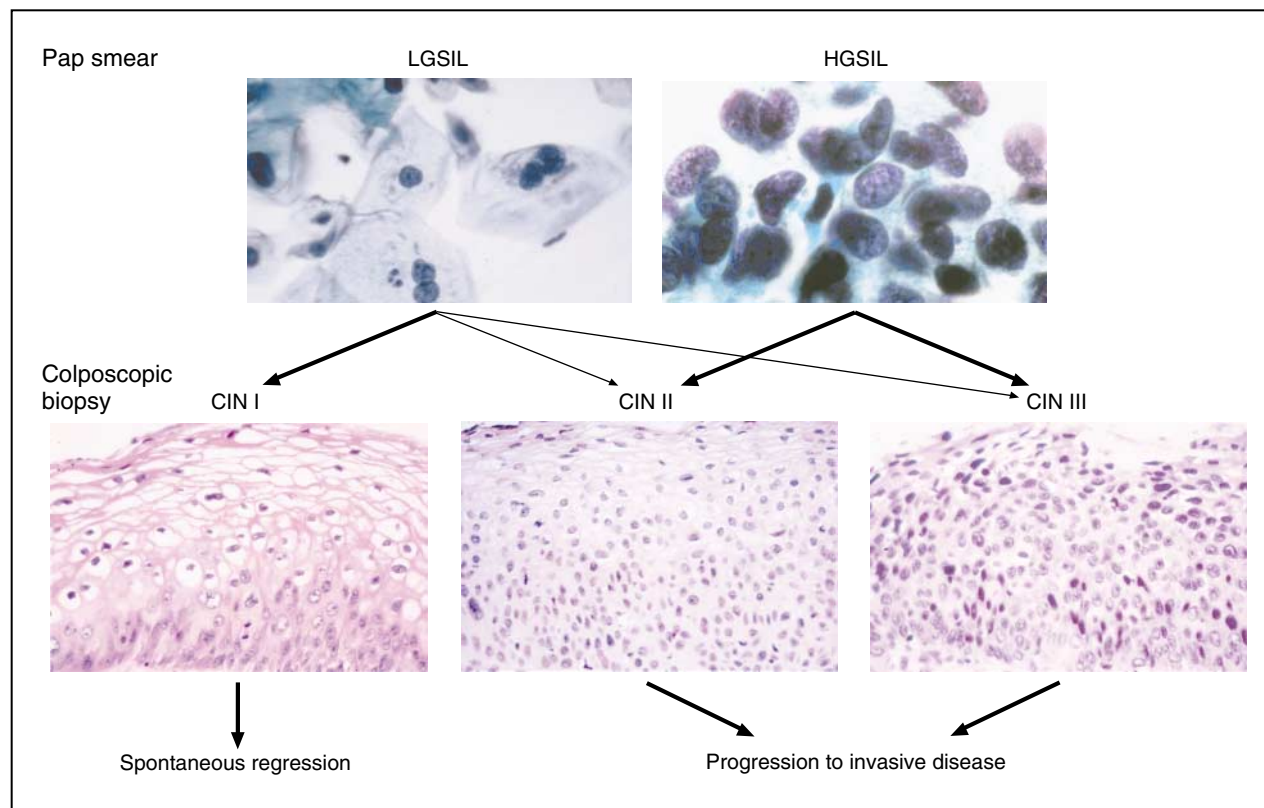


Figure 1. Relation between Cytologic Findings on the Pap Smear and Histologic Findings on Biopsy.

Low-grade and high-grade squamous intraepithelial lesions (LGSIL and HGSIL) represent categories of abnormal Pap-smear findings in the Bethesda classification. When these cytologic findings are reported, colposcopy is performed to permit visualization and biopsy of the lesion. The biopsy findings are described as cervical intraepithelial neoplasia (CIN) I, II, or III. A Pap-smear report of LGSIL usually reflects the presence of CIN I (mild dysplasia) on biopsy, although it may be associated with CIN II (moderate dysplasia) or CIN III (severe dysplasia or carcinoma in situ). LGSIL may also indicate the presence of human papillomavirus infection, without associated CIN. Most patients with a Pap-smear report of HGSIL have CIN II or III, but some have invasive disease. Thus, the Pap smear is only a screening test, and a biopsy is required for a definitive diagnosis. The cytologic specimens have been magnified 100 times (Papanicolaou's stain), and the biopsy specimens have been magnified 40 times (hematoxylin and eosin). The thin arrows indicate the less common histologic findings. Photomicrographs were provided courtesy of Dr. Graziella Abu-Jawdeh, Beth Israel Hospital, Boston.

the cervix with a dilute solution of acetic acid, which imparts an opaque, white color to areas high in nucleic acid (Fig. 2). The goals of colposcopy are to identify suspicious areas that require biopsy and to determine the extent of the lesion.

Treatment of intraepithelial lesions is determined on the basis of the histologic diagnosis and the extent of the lesion on colposcopic examination (Fig. 3). Patients with CIN I documented by biopsy require no further treatment, since the majority of such lesions resolve spontaneously.⁵⁰ In contrast, patients with CIN II or CIN III require treatment to prevent the subsequent development of invasive disease. There are two approaches to eradicating such lesions. The first approach comprises conservative outpatient techniques, including cryotherapy, laser vaporization, and the loop electric excision procedure (LEEP). The second approach, called cervical conization or cone biopsy, is a surgical procedure involving resection of a conical area of cervical tissue, which includes part of the endocervical canal. Most patients with CIN II or III can be safely treated with conservative outpatient techniques. Cryotherapy, laser vaporization, or LEEP is appropriate

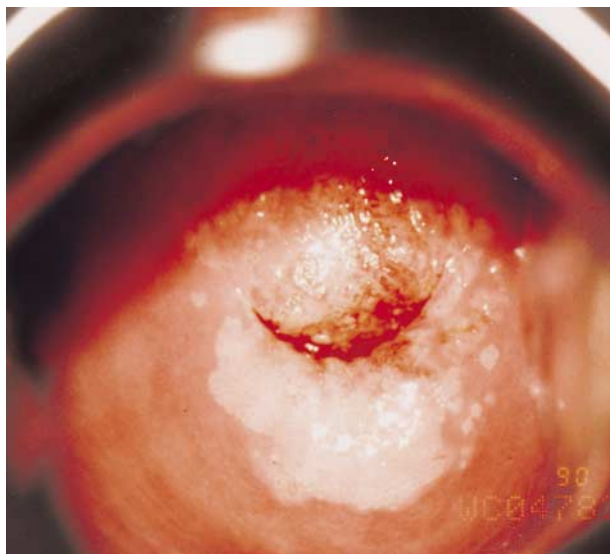
when the entire lesion and the entire transformation zone can be visualized by colposcopy, there is no evidence of endocervical involvement, the results of the Pap smear and biopsy are closely correlated, and there is no evidence of invasive disease. Patients who do not meet the criteria for conservative outpatient therapy undergo cone biopsy, performed to rule out the presence of invasive disease by obtaining a tissue specimen adequate for histologic evaluation. The care of the patient with an abnormal Pap smear is summarized in Figure 3.

MANAGEMENT OF INVASIVE DISEASE

Invasive cervical cancer is often asymptomatic, although patients may report vaginal discharge and post-coital vaginal bleeding. In some cases, patients present with advanced disease that extends beyond the cervix and involves pelvic lymph nodes, resulting in lower-extremity edema, deep venous thrombosis, or ureteral obstruction. The diagnosis of invasive disease is usually made by biopsy of a lesion visible on gross pelvic examination. It is important to note that any grossly visible, suspicious cervical lesion requires biopsy, regardless of



A



B

Figure 2. Appearance of CIN during Colposcopy.

With colposcopy, the cervix is visualized directly under low-power magnification, permitting identification and biopsy of suspicious lesions. Panel A shows the colposcopic appearance of the cervix in a patient with a Pap-smear report of HGSIL. The lesion surrounding the cervical os is barely visible. Panel B shows the same lesion after the application of a dilute solution of acetic acid, which highlights areas high in nucleic acid. Subsequent biopsy of this lesion revealed CIN III. Photographs were provided courtesy of Dr. Louis Burke, Beth Israel Hospital, Boston.

the Pap-smear findings. Invasive disease may also be diagnosed by biopsy of a lesion observed during colposcopy performed for evaluation of an abnormal Pap smear.

The staging system for cervical cancer is based on clinical criteria (Table 1).^{53,54} Stage I disease is limited to the cervix; stage II disease extends beyond the cervix to the upper two thirds of the vagina or the parametrial tissue but not to the pelvic side wall; stage III tumors have spread to the pelvic side wall, the pelvic nodes, or the lowest third of the vagina; and stage IV tumors have invaded the mucosa of the bladder or rectum or

have spread to distant sites. Although it is beyond the scope of this review to describe in detail the technical aspects of surgery or radiotherapy in the treatment of cervical cancer, several points are noted below and summarized in Figure 4.

Stage IA

Patients with stage IA tumors have microscopical evidence of early invasion. These microinvasive tumors are associated with a low risk of lymph-node metastases and, consequently, a favorable prognosis. Patients with microinvasive disease do not require as radical a treatment approach as those who have more deeply invasive tumors. The International Federation of Gynecology and Obstetrics has defined microinvasive tumors as lesions that do not exceed 5 mm in depth from the basement membrane or 7 mm in width.⁵⁴ Another definition often used in the United States for management decisions is that proposed by the Society of Gynecologic Oncologists in 1974: a microinvasive lesion is characterized by 3 mm or less of stromal invasion beneath the basement membrane, without evidence of lymphovascular involvement.⁵⁵ The diagnosis of microinvasive disease is usually first suggested by the results of a colposcopic biopsy. A cone biopsy must then be performed to ensure that the lesion meets the criteria for a microinvasive tumor (Fig. 3).

Patients with microinvasive tumors typically undergo a simple hysterectomy, which involves the removal of the uterine corpus and cervix, without resection of the parametria, ureterosacral ligaments, or any portion of the vagina. A pelvic lymph-node dissection is not performed because of the low likelihood of metastasis to the lymph nodes.⁵⁴⁻⁵⁷ Among patients treated with a simple hysterectomy for stage IA disease, survival at five years exceeds 95 percent. A more conservative approach, involving careful follow-up after a cone biopsy, may be considered in women with early microinvasive tumors who are of childbearing age and wish to preserve their fertility.⁵⁶ Finally, it is important to note that a subgroup of patients with microinvasive disease have evidence of invasion at the margin of the cone-biopsy specimen. Since such patients often have evidence of deep invasion in the hysterectomy specimen, they are best treated as though they had stage IB tumors.⁵⁸

Stages IB and IIA

The majority of patients who present with cervical cancer have stage IB or IIA disease. Such patients undergo clinical staging, which usually includes a pelvic examination, often performed while the patient is under anesthesia, as well as cystoscopy and proctoscopy. A chest radiograph is obtained, and an imaging study of the urinary tract is performed, since the presence of hydronephrosis may indicate local extension or pelvic lymph-node involvement.

The use of surgery or radiotherapy for the treatment of stage IB or early stage IIA tumors produces equivalent results (survival at five years, 80 to 90 percent).⁵⁹⁻⁶⁴ Surgery consists of a radical hysterectomy and pelvic lymph-node dissection. A radical hysterectomy differs

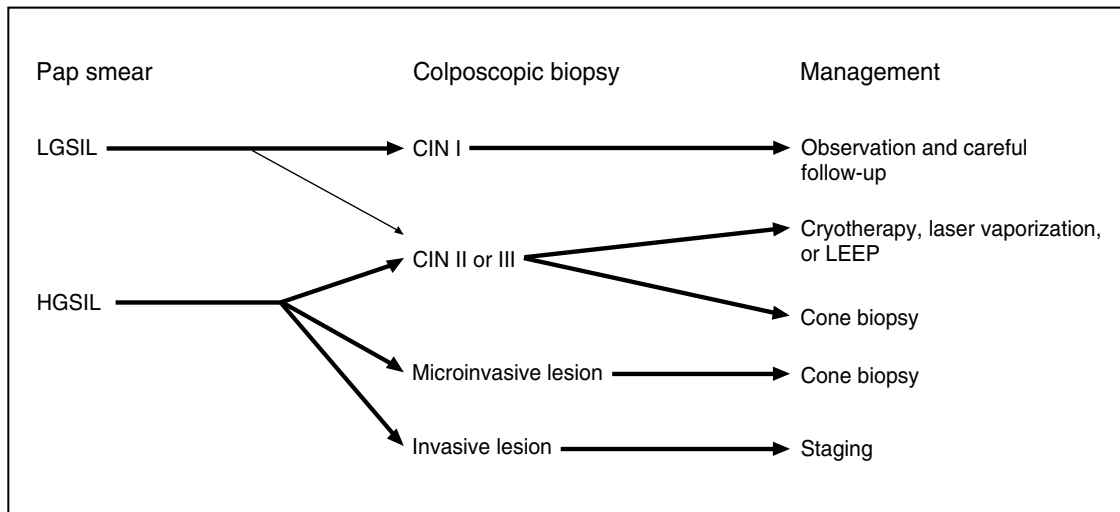


Figure 3. Algorithm for Managing Pap-Smear Findings Suggestive of an Intraepithelial Lesion.

CIN I usually undergoes spontaneous regression. If Pap smears remain positive for LGSIL, repeated colposcopy is indicated to rule out the presence of CIN II or III. For CIN II or III, cryotherapy, laser vaporization, or the loop electric excision procedure (LEEP) is appropriate only when the entire lesion and transformation zone can be seen by colposcopy, the endocervical canal is not involved, there is a close correlation between the Pap-smear and colposcopic-biopsy findings, and there is no evidence of invasive disease. If these criteria are not met, the lesion should be further evaluated by cone biopsy, which is performed in an attempt to remove the entire lesion and provide a specimen suitable for ruling out invasive disease. When a colposcopic biopsy suggests a microinvasive lesion, a cone biopsy is required to rule out a more deeply invasive lesion. Invasive disease that does not meet the criteria for microinvasion requires staging and management as outlined in Table 1 and Figure 4. The thin arrow indicates the less common histologic finding.

from a simple hysterectomy in that the parametria, uterosacral ligaments, and a 2-to-3-cm cuff of vagina are resected en bloc with the uterus and cervix. Oophorectomy is not necessary in premenopausal women, since metastases to the ovaries are rare. The ovaries are sometimes transposed out of the pelvis so that they will not be in the radiation field, should radiotherapy be required postoperatively. The principal complication of a radical hysterectomy is a urinary fistula, which occurs in less than 1 percent of cases.⁶⁵ Other possible complications include bladder dysfunction and lymphocyst formation.

Pelvic radiotherapy is usually administered after surgery if the tumor is present in the margin of the surgical specimen or has metastasized to pelvic or para-aortic lymph nodes.^{66,67} This treatment is effective in decreasing the risk of a local recurrence, although the effect of pelvic radiotherapy on overall survival in patients with lymph-node metastasis is unclear.⁶⁸ Among patients with stage IB or IIA disease who have pelvic lymph-node metastasis, the rate of survival at five years is approximately 45 percent,⁶⁹ as compared with survival of over 80 percent in patients with early-stage disease who do not have this high-risk feature. Survival among patients with metastasis to the para-aortic nodes ranges from 10 to 30 percent.⁷⁰⁻⁷²

Patients who wish to remain sexually active often prefer radical hysterectomy, since pelvic radiotherapy may result in vaginal stenosis. In patients with stage IB or IIA tumors who are not suitable candidates for a radical hysterectomy, external-beam radiotherapy is delivered to a field that includes the pelvic nodes.⁶⁷ Intracavitary treatment, in which a radioisotope such as cesium-137 is temporarily inserted into the uterine cavity and vaginal fornices, is then administered to provide

the high local doses necessary for adequate control of the tumor. In addition to vaginal scarring, radiotherapy may result in bladder and gastrointestinal dysfunction, as well as the cessation of ovarian function.

Radiotherapy is the preferred initial treatment for stage I disease that is characterized by an endophytic pattern of growth into the cervical canal, associated with expansion of the cervical diameter. These tumors, which are sometimes referred to as barrel-shaped, are difficult to resect with tumor-free margins. Nevertheless, central pelvic recurrences are frequent when barrel-shaped cervical tumors are managed with radiotherapy alone, in part because the bulky dimensions of the tumor make it difficult to deliver an adequate dose of radiation to the uppermost aspects of the tumor mass. Therefore, in an attempt to decrease the risk of central pelvic recurrence, a simple hysterectomy is often performed after radiotherapy for barrel-shaped tumors.⁷³⁻⁷⁵

Stages IIB, III, and IVA

Patients with extensive locoregional disease have a high rate of local relapse if treated surgically. For this reason, patients with stage IIB, III, or IVA tumors are treated with radiotherapy, which results in five-year survival rates of 65, 40, and less than 20 percent, respectively.^{67,76-78} Patients who present with stage IVB disease (distant metastases) may also benefit from local radiotherapy, although at this stage the tumor is not curable and the control of systemic disease often requires chemotherapy, as described below.

MANAGEMENT OF RECURRENT DISEASE

Approximately 30 percent of women with invasive cervical cancer die from recurrent or persistent disease

after the initial therapy. Cervical cancer often recurs in a local or regional distribution, in the form of pelvic or para-aortic adenopathy, but it may also metastasize to distant sites, such as the lungs and bone. Because local recurrence is often a component of relapse, patients may have pelvic pain and lower-extremity edema due to lymphatic obstruction; they may eventually die from ureteral obstruction. A small number of patients have a local pelvic relapse without evidence of distant disease. If technically feasible, either pelvic exenteration or pelvic radiotherapy may result in long-term survival in a minority of such patients.^{79,80} The morbidity associated with pelvic exenteration has been reduced with the development of continent urinary diversions, methods to reconstitute the gastrointestinal tract, and innovative techniques for vaginal reconstruction.⁸¹⁻⁸³

Most patients with recurrent cervical cancer have disease at both local and distant sites. The most active agent in the treatment of metastatic squamous-cell cancer of the cervix is cisplatin, which induces responses in approximately 20 percent of patients with recurrent disease.⁸⁴⁻⁸⁶ Other active agents include ifosfamide⁸⁷ and mitolactol,⁸⁸ although most combination regimens that include cisplatin are not clearly superior to cisplatin alone, on the basis of historical-control data.⁸⁶ The Gynecologic Oncology Group has recently completed a randomized trial of cisplatin alone, cisplatin with ifosfamide, and cisplatin with mitolactol.⁸⁹ Although the combination of cisplatin and ifosfamide produced higher response rates than did cisplatin alone, this effect did not result in an overall survival benefit, and the combination therapy was associated with greater toxicity. Cisplatin combined with mitolactol was not superior to cisplatin alone.

Disease involving extrapelvic sites, such as the lungs, is more likely to respond to chemotherapy than disease confined to the pelvis.⁹⁰ This observation may be partly related to the difficulty in accurately assessing the extent of pelvic disease by examination and computed tomographic scanning, as well as to the possibility of dimin-

Table 1. Staging of Cervical Cancer.*

Stage I: The tumor is confined to the uterus.	
IA	Microinvasive disease, with the lesion not grossly visible.†
IB	Larger tumor than in stage IA or grossly visible tumor confined to the cervix.‡
Stage II: The tumor extends beyond the uterus but does not involve the pelvic side wall or lowest third of the vagina.	
IIA	Involvement of the upper two thirds of the vagina, without lateral extension into the parametrium.
IIB	Lateral extension into parametrial tissue.
Stage III: The tumor involves the lowest third of the vagina or the pelvic side wall or causes hydronephrosis.	
IIIA	Involvement of the lowest third of the vagina.
IIIB	Involvement of the pelvic side wall or hydronephrosis.
Stage IV: The tumor demonstrates extensive local infiltration or has spread to a distant site.	
IVA	Involvement of bladder or rectal mucosa.
IVB	Distant metastasis.

*Based on the staging system established by the International Federation of Gynecology and Obstetrics.^{53,54} Staging may be based on information obtained from a pelvic examination performed while the patient is under anesthesia, intravenous pyelography, cystoscopy, and proctoscopy. The stage is determined clinically and does not change on the basis of findings at the time of surgery.

†Microinvasive disease is defined as a lesion not exceeding 5 mm in depth from the basement membrane and no wider than 7 mm. A recent distinction has been made between stage IA1 (≤3 mm deep and ≤7 mm wide) and stage IA2 (>3 mm but ≤5 mm deep and ≤7 mm wide).⁵⁴ The Society of Gynecologic Oncologists defines microinvasive disease as a lesion ≤3 mm in depth beneath the basement membrane, without evidence of involvement of the lymphovascular space.

‡A recent distinction has been made between stage IB1 lesions (≤4 cm in diameter) and stage IB2 lesions (>4 cm in diameter).⁵⁴

ished delivery of drugs to pelvic tumors because of vascular damage induced by prior radiotherapy. The goal of chemotherapy in patients with relapsed disease is palliative, the responses to treatment are often short-lived, and the use of cisplatin may require ureteral stenting if renal obstruction is present. These considerations should temper the use of chemotherapy in patients with relapsed cervical cancer who have comorbid disease and poor performance status, since the benefits of systemic treatment may not outweigh the risks in this situation.

CHEMOTHERAPY IN PATIENTS WITH NEWLY DIAGNOSED DISEASE

The role of chemotherapy as an adjunct to surgery or radiotherapy or both in the management of locally ad-

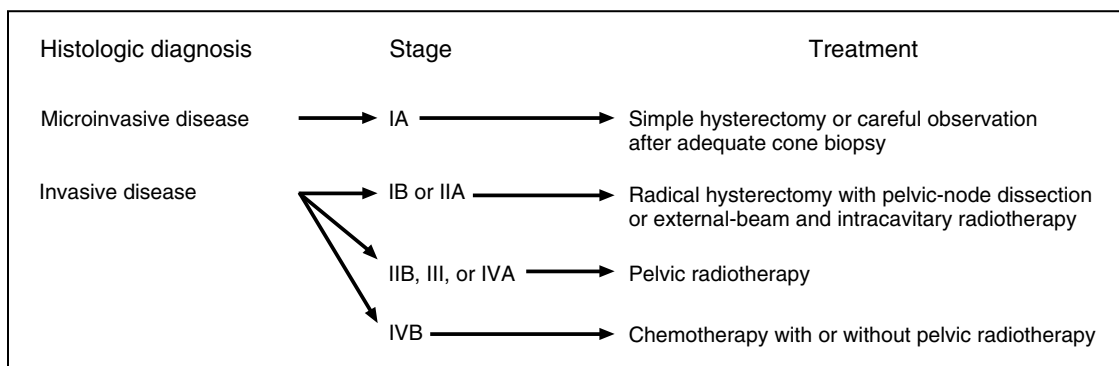


Figure 4. Algorithm for Managing Microinvasive or Invasive Disease.

The standard treatment for patients with microinvasive disease is a simple hysterectomy. A more conservative approach of careful observation after an adequate cone biopsy is sometimes considered in patients with early microinvasive disease who wish to preserve their fertility. Patients with stage IB or IIA lesions may be treated with either surgery or radiotherapy, since the two approaches have an equivalent survival benefit. Distant metastases in squamous-cell cancer of the cervix often involve the lung and bone. Cisplatin is currently the most effective agent, although the response rate is only approximately 20 percent among patients with relapses. Patients with metastatic cervical cancer should therefore be encouraged to participate in clinical trials of new classes or combinations of active agents.

vanced cervical cancer has a good theoretical rationale. The use of chemotherapy to reduce a locally advanced tumor may facilitate surgical resection or improve the effectiveness of radiotherapy, which is typically greatest in patients with low-volume disease. In addition, since patients with locally advanced disease have an increased risk of systemic relapse, chemotherapy may be capable of eradicating micrometastatic disease and thereby improving survival. Finally, some forms of chemotherapy may function as radiosensitizers, potentiating the effects of radiotherapy and thus improving local control.⁹¹

Response rates as high as 92 percent have been reported in studies of platinum-based regimens administered to previously untreated patients with locally advanced disease.^{86,92} Nevertheless, at least four randomized studies have failed to show a survival benefit of chemotherapy in the management of newly diagnosed cervical cancer.⁹³⁻⁹⁶ Although it is beyond the scope of this review to outline in detail the results of these trials, a few points are worth noting. Patients at high risk for local and distant recurrences who are typically eligible for such trials include those with stage IIB, III, or IVA disease, those with bulky stage IB tumors (>4 cm in diameter), and those with involvement of pelvic nodes. Despite the lack of a survival benefit in patients treated with chemotherapy, most studies have shown a high initial response rate and evidence of pathologic down-staging as reflected by a lower incidence of nodal metastases. A randomized study using vincristine, bleomycin, and cisplatin has shown a survival advantage in favor of chemotherapy before surgery and radiotherapy in a subgroup of patients with bulky stage IB primary tumors larger than 4 by 4 by 4 cm.⁹² A confirmatory study with larger numbers of patients and longer follow-up will be necessary to validate these findings. The weight of negative findings from randomized studies suggests that the use of platinum-containing regimens in patients with newly diagnosed, locally advanced cervical cancer should be reserved for clinical trials.

SUMMARY AND FUTURE DIRECTIONS

Cervical cancer is often a preventable disease. Pap-smear screening, followed by colposcopy in appropriate patients, is an effective method for identifying intraepithelial lesions, which can often be treated on an outpatient basis. It is clear that universal screening has the potential for decreasing the worldwide incidence of cervical cancer. Patient education and the provision of resources necessary to perform and interpret Pap smears are important steps toward reducing mortality from this type of cancer.⁹⁷

Although women with cervical cancer usually present with early-stage disease, which is often cured by surgery or radiotherapy, approximately 4800 women in the United States die from this tumor each year. Patients at high risk for relapse include those with an advanced clinical stage and those with involvement of the pelvic or para-aortic nodes. The use of chemotherapy with platinum-containing regimens in such patients has not yet been

proved to reduce the risk of systemic relapse or improve survival, suggesting the need for other active agents or therapeutic strategies. Drugs such as topoisomerase I inhibitors, taxanes, interferon alfa, and isotretinoin (13-*cis*-retinoic acid) are currently under investigation.^{98,99}

Finally, the important role of HPV in the pathogenesis of cervical cancer offers the potential for developing new therapeutic approaches. For instance, it may be possible to develop small-molecule drugs that interfere with the interaction between the HPV E6 protein and wild-type p53 protein, thereby restoring the normal inhibitory function of p53 in cell-cycle regulation. Also, because HPV proteins are capable of eliciting an immune response,¹⁰⁰ efforts are being made to develop vaccines, which may represent the ultimate preventive strategy for this potentially lethal tumor. Clearly, a better understanding of the ways in which HPV currently escapes immune surveillance will be necessary before effective methods of vaccination to prevent cervical cancer become a reality.

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