

## SECTION 2 Cancer of the Cervix, Vagina, and Vulva

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### **CARCINOMA OF THE CERVIX**

#### **EPIDEMIOLOGY**

The American Cancer Society estimated that 12,800 new cases of invasive cervical cancer would be diagnosed in the United States in 1999.<sup>1</sup> During the same year, 4800 patients were expected to die of cervical cancer; this represents approximately 1.8% of all cancer deaths in women and 18% of deaths from gynecologic cancers. However, for women aged 20 to 39 years, cervical cancer remains the second leading cause of cancer deaths after breast cancer.<sup>1</sup> In the United States, age-adjusted death rates from cervical cancer have declined steadily since statistics on the disease were first collected in the 1930s. Although this improvement is primarily because of the adoption of routine screening programs including pelvic examinations and cervical cytologic evaluation, the death rates from cervical cancer had begun to decrease before the implementation of Papanicolaou (Pap) screening, suggesting that other unknown factors may have played some role.<sup>2,3</sup>

Squamous cell carcinoma of the cervix and its intraepithelial precursor follow a pattern typical of sexually transmitted disease. The risk of cervical cancer is increased in prostitutes and in women who have first coitus at a young age, have multiple sexual partners, have sexually transmitted diseases, or bear children at a young age. Promiscuous sexual behavior in male partners is also a risk factor.<sup>4,5</sup> Other factors that may be associated with cervical cancer include cigarette smoking, immunodeficiency, vitamin A or C deficiency, and oral contraceptive use.<sup>6</sup> In the United States, the incidence of cervical cancer is greatest in American Indian, African American, Vietnamese, and Hispanic women.<sup>7,8</sup> and 9

International incidences of cervical cancer tend to reflect differences in cultural attitudes toward sexual promiscuity and the penetration of mass screening programs. Some of the lowest incidences are in the United States, China, North Africa, and the Middle East, where estimated crude rates of cervical cancer are less than 10 per 100,000.<sup>10</sup> However, cervical cancer continues to be the leading cause of cancer deaths for women in many developing countries. Incidences are particularly high in Latin America, Southern and Eastern Africa, India, and Polynesia.<sup>10,11</sup> In the United States, Hispanic women have approximately twice the incidence and Vietnamese women approximately five times the incidence of white women.<sup>12</sup> The incidence is also higher in African Americans than in whites, although this

difference has been steadily decreasing, particularly for women less than 50 years old.

A number of studies suggest that the incidence of cervical adenocarcinoma has been increasing, particularly among women in their 20s and 30s.<sup>13,14</sup> and 15 Several investigators have reported a correlation between cervical adenocarcinoma and prolonged oral contraceptive use.<sup>16,17</sup> However, the likelihood of a causative relationship is less certain because of the many potential confounding risk factors.<sup>18</sup>

Molecular and epidemiologic studies have demonstrated a strong relationship between human papillomavirus (HPV), cervical intraepithelial neoplasia (CIN), and invasive carcinomas of the cervix.<sup>19,20</sup> HPV DNA has been identified in more than 95% of cervical carcinomas<sup>21</sup>; HPV DNA transcripts and protein products have also been identified in invasive cervical carcinomas.<sup>22,23</sup> and 24 In high-grade CIN and invasive carcinoma, papillomavirus DNA is typically integrated into the human genome rather than remaining in an intact viral capsid.<sup>25</sup> It has been theorized that integration of HPV DNA in the human genome, possibly at the E2 site, causes persistent transcription of the E6 and E7 genes. Functional inactivation of p53 by E6 protein or of Rb by E7 protein disrupts normal cell-cycle control mechanisms.<sup>26,27</sup> and 28 As the sensitivity and specificity of tests for HPV DNA have improved, it has become increasingly apparent that most of the covariables that have historically been associated with an increased risk of cervical cancer (e.g., age at first coitus, number of partners, socioeconomic status, and so forth) are surrogates for HPV infection.<sup>29,30</sup> Investigators have suggested a number of cofactors that may contribute to disease progression. However, in more recent epidemiologic studies, cigarette smoking was the only consistent independent contributor to the risk of cervical cancer development after controlling for HPV infection.<sup>30</sup> Taken together, the molecular and epidemiologic data provide compelling evidence that HPV infection plays a central causative role in the development of cervical neoplasia.<sup>29,30</sup> and 31

More than 100 HPV subtypes have been identified, and many of these have now been isolated, sequenced, and cloned.<sup>32,33</sup> Approximately 25 subtypes are tropic to the genital tract mucosa. Types 6 and 11 usually cause benign genital warts (condyloma acuminata) but are occasionally associated with invasive cervical lesions. Types 16, 18, 31, 35, and 39 are commonly associated with high-grade CIN and invasive cervical cancer (Table 36.2-1).<sup>34</sup> HPV 18 has been associated with poorly differentiated carcinomas, an increased incidence of lymph node involvement, a poor response to treatment, and a high rate of disease recurrence, whereas HPV 16 has been associated with large cell keratinizing tumors and a lower recurrence rate.<sup>35,36</sup> and 37 Although the overall prevalence of HPV DNA is similar between countries, significant variation has been found in the prevalence of some less common HPV types; for example, HPV 45 is most common in western Africa, whereas HPV 39 and HPV 59 are rarely found outside Central and South America.<sup>21</sup> The strong correlation between high-risk HPV subtypes and carcinoma has led to the suggestion that HPV detection and typing be incorporated into mass screening programs<sup>38,39</sup> and has encouraged efforts to develop a prophylactic HPV vaccine.<sup>40</sup>

**TABLE 36.2-1.** Relationship between Human Papillomavirus Type and Cervical Pathology

In 1993 the Centers for Disease Control and Prevention added cervical cancer to the list of acquired immunodeficiency syndrome–defining neoplasms.<sup>41</sup> However, the impact of acquired immunodeficiency syndrome and human immunodeficiency virus (HIV) on the incidence and virulence of cervical cancer remains uncertain.<sup>42,43,44,45</sup> and <sup>46</sup> Although several studies suggest that the incidence of CIN is higher in HIV-positive women than in the general population,<sup>47,48</sup> overlap in risk factors for the two diseases may influence these results. Although Serraino et al.<sup>46</sup> reported a possible increase in the risk of invasive cervical cancer in European HIV-positive women, several studies in Africa<sup>42</sup> and a large epidemiologic study in the United States<sup>44</sup> have failed to

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reveal any significant linkage. However, changes in cell-mediated immunity may play a role in the development of cervical cancer,<sup>48,49</sup> and <sup>50</sup> and some investigators<sup>43,51,52</sup> have suggested that cervical cancer is a more aggressive disease in immunosuppressed patients. For these reasons, regular surveillance with Pap smears, pelvic examination, and colposcopy (when indicated) should be part of the routine care of HIV-positive women.

## NATURAL HISTORY AND PATTERN OF SPREAD

Most cervical carcinomas arise at the junction between the primarily columnar epithelium of the endocervix and the squamous epithelium of the ectocervix. This junction is a site of continuous metaplastic change; this change is most active *in utero*, at puberty, and during a first pregnancy and declines after menopause. The greatest risk of neoplastic transformation coincides with periods of greatest metaplastic activity. Virally induced atypical squamous metaplasia developing in this region can progress to higher grade squamous intraepithelial lesions.

The mean age of women with CIN is approximately 15 years younger than that of women with invasive cancer, suggesting a slow progression of CIN to invasive carcinoma.<sup>53,54</sup> In a 13-year observational study of women with CIN 3, Miller<sup>55</sup> found that disease progressed in only 14%, whereas it remained the same in 61% and disappeared in the remainder. Syrjanen et al.<sup>56</sup> reported spontaneous regression in 38% of high-grade HPV-associated squamous intraepithelial lesions. However, in a large prospective study, Richart and Barron<sup>57</sup> reported mean times to development of carcinoma *in situ* of 58, 38, and 12 months for patients with mild, moderate, or severe dysplasia, respectively, and predicted that 66% of all dysplasias would progress to carcinoma *in situ* within 10 years.

Once tumor has broken through the basement membrane, it may penetrate the cervical stroma directly or through vascular channels. Invasive tumors may develop as exophytic growths protruding from the cervix into the vagina or as endocervical lesions that can cause massive expansion of the cervix despite a relatively normal-appearing cervical portio. From the cervix, tumor may extend superiorly to the lower uterine segment, inferiorly to the vagina, or into the paracervical spaces by way of the broad or uterosacral ligaments. Tumor may become fixed to the pelvic wall by direct extension or by coalescence of central tumor with regional adenopathy. Tumor may also extend anteriorly to involve the bladder or posteriorly to the rectum, although rectal mucosal involvement is a rare finding at initial presentation.

The cervix has a rich supply of lymphatics organized in three anastomosing plexuses that

drain the mucosal, muscularis, and serosal layers.<sup>58</sup> The lymphatics of the cervix also anastomose extensively with those of the lower uterine segment, possibly explaining the high frequency of uterine extension from endocervical primary tumors. The most important lymphatic collecting trunks exit laterally from the uterine isthmus in three groups (Fig. 36.2-1).<sup>58,59</sup> The upper branches, which originate in the anterior and lateral cervix, follow the uterine artery, are sometimes interrupted by a node as they cross the ureter, and terminate in the uppermost hypogastric nodes. The middle branches drain to deeper hypogastric (obturator) nodes. The lowest branches follow a posterior course to the inferior and superior gluteal, common iliac, presacral, and subaortic nodes. Additional posterior lymphatic channels arising from the posterior cervical wall may drain to superior rectal nodes or may continue upward in the retrorectal space to the subaortic nodes overlying the sacral promontory. Anterior collecting trunks pass between the cervix and bladder along the superior vesical artery and terminate in the internal iliac nodes.

**FIGURE 36.2-1.** The lymphatic system of the female genital organs. [Reprinted from ref. 481, with permission; adapted from Meigs JV (ed). *Surgical treatment of cancer of the cervix*. New York: Grune & Stratton, 1954:90.]

Table 36.2-2 summarizes the reported incidences of pelvic and paraaortic node involvement for patients who underwent lymphadenectomy as part of primary surgical treatment or before radiotherapy for cervical carcinomas.<sup>60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82</sup> and <sup>83</sup> The incidences reported for patients who underwent radical hysterectomy vary widely, probably reflecting differences in the criteria used by surgeons to select patients for radical surgery rather than for primary radiation treatment. Many series excluded patients with extrapelvic disease. Variations in the completeness of lymphadenectomies and histologic processing may also lead to underestimates of the true incidence of regional spread from carcinomas of the cervix.<sup>60,84</sup>

**TABLE 36.2-2.** Rates of Lymph Node Metastasis in Patients with Carcinoma of the Cervix

Cervical cancer usually follows a relatively orderly pattern of metastatic progression initially to primary echelon nodes in the pelvis, then to paraaortic nodes and distant sites. Even patients with locoregionally advanced disease rarely have detectable hematogenous metastases at initial diagnosis of their cervical cancer. The most frequent sites of distant recurrence are lung, extrapelvic nodes, liver, and bone.<sup>85,86</sup> Although early studies suggested that the lumbar spine was a relatively frequent site of skeletal metastases, more recent studies using abdominal imaging demonstrate that most patients with isolated lumbar spine

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involvement actually have direct extension of disease from paraaortic nodes.<sup>87</sup>

## PATHOLOGY

### ***Cervical Intraepithelial Neoplasia***

Several systems have been developed for classifying cervical cytologic findings (Table 36.2-3). Although criteria for the diagnosis of CIN vary somewhat between pathologists, the important characteristics of this lesion are cellular immaturity, cellular disorganization, nuclear abnormalities, and increased mitotic activity. The degree of neoplasia is determined on the basis of the extent of the mitotic activity, immature cell proliferation, and nuclear atypia. If mitoses and immature cells are present only in the lower third of the epithelium, the lesion is usually designated CIN 1. Lesions involving the middle or upper third are diagnosed as CIN 2 or CIN 3, respectively.

**TABLE 36.2-3.** Comparison of Cytology Classification Systems

The term *cervical intraepithelial neoplasia*, as proposed by Richart,<sup>88</sup> refers only to a lesion that may progress to invasive carcinoma. Although CIN 1 to 2 is sometimes referred to as mild to moderate dysplasia, *CIN* is now preferred over *dysplasia*. Because the word *dysplasia* means “abnormal maturation,” proliferating metaplasia without mitotic activity has sometimes been erroneously called dysplasia.

The Bethesda system of classification, designed to further standardize reporting of cervical cytologic findings, was developed after a National Cancer Institute consensus conference in 1988 and was refined in 1991.<sup>89</sup> This system, which separates condylomata and CIN 1, classified as low-grade squamous intraepithelial lesions, from high-grade squamous intraepithelial lesions, is meant to replace the Papanicolaou system and is now widely used in the United States. The Bethesda system introduced the term *atypical squamous cells of undetermined significance*. This uncertain diagnosis is now the most common abnormal Pap test result.<sup>90</sup> In United States laboratories, 1.6% to 9.0% of Pap smears are reported as having atypical squamous cells of undetermined significance.<sup>91</sup> Although most reflect a benign process, approximately 5% to 10% are associated with underlying high-grade squamous intraepithelial lesions, and one-third or more of high-grade squamous intraepithelial lesions are heralded by a finding of atypical squamous cells of undetermined significance on a Pap smear.<sup>92</sup>

### ***Adenocarcinoma In Situ***

The diagnosis of adenocarcinoma *in situ* (AIS) is made when normal endocervical gland cells are replaced by tall, irregular columnar cells with stratified, hyperchromatic nuclei and increased mitotic activity, but the normal branching pattern of the endocervical

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glands is maintained and there is no obvious stromal invasion. Approximately 20% to 50% of women with cervical AIS also have squamous CIN, and AIS is often an incidental finding in patients operated on for squamous carcinoma.<sup>93,94</sup> Because AIS is frequently

multifocal, cone biopsy margins are unreliable.<sup>93,95</sup>

### ***Microinvasive Carcinoma***

Because the definition of microinvasive carcinoma is based on the maximum depth and linear extent of involvement, this diagnosis can only be made after examination of a specimen that includes the entire neoplastic lesion and cervical transformation zone. This requires a cervical cone biopsy.

The earliest invasion appears as a protrusion of cells from the stromoepithelial junction; these cells are better differentiated than the adjacent noninvasive cells and have abundant pink-staining cytoplasm, hyperchromatic nuclei, and small- to medium-sized nucleoli.<sup>96</sup> As the tumor progresses, invasion occurs at multiple sites, and its depth and linear extent become measurable. The depth of invasion should be measured with a micrometer from the base of the epithelium to the deepest point of invasion. Lesions that have invaded less than 3 mm [International Federation of Gynecology and Obstetrics (FIGO) stage IA1] rarely metastasize; 5% to 10% of tumors that invade 3 to 5 mm (FIGO stage IA2) have positive pelvic lymph nodes.<sup>97,98</sup> and 99

Although investigators occasionally label small adenocarcinomas as *microinvasive*, the term probably should not be used for these tumors. Because invasive adenocarcinomas may originate either from the mucosal surface or from the periphery of underlying glands, no reliable method has been found for measuring the depth of invasion of these tumors. For this reason adenocarcinomas are generally classified as either AIS or invasive carcinoma (FIGO stage IB).

### ***Invasive Squamous Cell Carcinoma***

Between 80% and 90% of cervical carcinomas are squamous. A number of systems have been used to grade and classify squamous

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carcinomas, but none have consistently been demonstrated to predict prognosis. One of the most commonly used systems categorizes squamous neoplasms as large cell keratinizing, large cell nonkeratinizing, or small cell carcinoma.<sup>100</sup> Small cell squamous carcinomas have small- to medium-sized nuclei, open chromatin, small or large nucleoli, and abundant cytoplasm. Most authorities believe that patients with small cell squamous carcinoma have a poorer prognosis than those with large cell neoplasms with or without keratin. However, small cell squamous carcinoma should not be confused with anaplastic small cell carcinoma. The latter resembles oat cell carcinoma of the lung because it contains small tumor cells that have scanty cytoplasm, small round to oval nuclei, small or absent nucleoli, finely granular chromatin, and high mitotic activity.<sup>101</sup> Approximately 30% to 50% of anaplastic small cell carcinomas display neuroendocrine features. Small cell anaplastic carcinomas behave more aggressively than poorly differentiated small cell squamous carcinomas; most investigators report survival rates of less than 50% even for patients with early stage I disease.<sup>102,103</sup> and 104

### ***Adenocarcinoma***

Invasive adenocarcinoma may be pure or mixed with squamous cell carcinoma (adenosquamous carcinoma). A wide variety of cell types, growth patterns, and degrees of differentiation have been observed. Approximately 80% of cervical adenocarcinomas are made up predominantly of cells whose differentiated features resemble endocervical glandular epithelium with intracytoplasmic mucin production. The remaining tumors are populated by endometrioid cells, clear cells, intestinal cells, or a mixture of more than one cell type. By histologic examination alone, some of these tumors are indistinguishable from those arising elsewhere in the endometrium or ovary.

Minimal-deviation adenocarcinoma (adenoma malignum) is a rare, extremely well differentiated adenocarcinoma that is sometimes associated with Peutz-Jeghers syndrome.<sup>105,106</sup> Because the branching glandular pattern strongly resembles normal endocervical glands, minimal-deviation adenocarcinoma may not be recognized as malignant in small biopsy specimens. Earlier studies reported a dismal outcome for women with this tumor, but more recently, patients have been reported to have a favorable prognosis if the disease is detected early.<sup>107,108</sup>

Young and Scully<sup>109</sup> have described a villoglandular papillary subtype of adenocarcinoma that primarily affects young women, appears to metastasize infrequently, and has a favorable prognosis. Glucksmann and Cherry<sup>110</sup> were the first to describe glassy cell carcinoma, a form of poorly differentiated adenosquamous carcinoma with cells that have abundant eosinophilic, granular, ground-glass cytoplasm; large round to oval nuclei; and prominent nucleoli. Other rare variants of adenosquamous carcinoma include adenoid basal carcinoma and adenoid cystic carcinoma.<sup>111</sup> Adenoid basal carcinoma is a well-differentiated tumor that histologically resembles basal cell carcinoma of the skin and tends to have a favorable prognosis. Adenoid cystic carcinomas consist of basaloid cells in a cribriform or cylindromatous pattern and tend to have aggressive behavior with frequent metastases, although the natural history of these tumors may be long. Whether the prognoses of these rare subtypes are different from those of other adenocarcinomas of similar grade is uncertain.

A variety of neoplasms may infiltrate the cervix from adjacent sites presenting differential diagnostic problems. In particular, it may be difficult or impossible to determine the origin of adenocarcinomas involving the endocervix and uterine isthmus. Although endometrioid histology suggests endometrial origin and mucinous tumors in young patients are most often of endocervical origin, both histologic types can arise in either site.<sup>112</sup> Metastatic tumors from the colon, breast, or other sites may involve the cervix secondarily. Malignant mixed Müllerian tumors, adenosarcomas, and leiomyosarcomas arise occasionally in the cervix but more often involve it secondarily. Primary lymphomas and melanomas of the cervix are extremely rare.

## CLINICAL MANIFESTATIONS

Preinvasive disease is usually detected during routine cervical cytologic screening. Early invasive disease may not be associated

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with any symptoms and is also detected during screening examinations. The earliest symptom of invasive cervical cancer is usually abnormal vaginal bleeding, often following

coitus or vaginal douching. This may be associated with a clear or foul-smelling vaginal discharge. Pelvic pain may result from locoregionally invasive disease or from coexistent pelvic inflammatory disease. Flank pain may be a symptom of hydronephrosis, often complicated by pyelonephritis. The triad of sciatic pain, leg edema, and hydronephrosis is almost always associated with extensive pelvic wall involvement by tumor. Patients with advanced tumors may have hematuria or incontinence from a vesicovaginal fistula caused by direct extension of tumor to the bladder. External compression of the rectum by a massive primary tumor may cause constipation, but the rectal mucosa is rarely involved at initial diagnosis.

## **DIAGNOSIS, CLINICAL EVALUATION, AND STAGING**

### ***Diagnosis***

The long preinvasive stage of cervical cancer, the relatively high prevalence of the disease in unscreened populations, and the sensitivity of cytologic screening make cervical carcinoma an ideal target for cancer screening. In the United States, screening with cervical cytologic examination and pelvic examination has led to more than a 70% decrease in the mortality from cervical cancer since 1940.<sup>1,113</sup> Only nations with comprehensive screening programs have experienced substantial decreases in cervical cancer death rates during this period.

Authorities disagree about the optimal frequency of cervical cancer screening. In a 1988 consensus statement, the American Cancer Society and other medical groups recommended annual Pap smears beginning at age 18 years or with the onset of sexual activity and added that, after three or more consecutive normal annual examinations, the cytologic evaluation could be performed less frequently at the discretion of the physician.<sup>114,115</sup> For patients who have had repeated negative test results, the marginal gain from screening more often than every 3 years decreases sharply.<sup>116,117</sup> and <sup>118</sup> The United States Preventative Services Task Force has recommended that screening be discontinued after age 65 years if results have been consistently normal, and the Canadian Task Force suggests that the screening interval be extended to 5 years after age 35 if previous studies have been normal.<sup>115</sup> Although these groups have suggested tailoring the frequency of Pap smears to patient risk, practical definitions of low and high risk remain controversial. As a result, most clinicians continue to recommend that their patients be screened more frequently than recommended by the national guidelines.<sup>115</sup> The rate of false-negative findings on the Pap test is approximately 10% to 15% in women with invasive cancer.<sup>53,54,114</sup> The sensitivity of the test may be improved by ensuring adequate sampling of the squamocolumnar junction and the endocervical canal; smears without endocervical or metaplastic cells are inadequate and must be repeated. Because AIS originates near or above the transformation zone, it may be missed with conventional cervical smears. Detection of high endocervical lesions may be improved when specimens are obtained with a cytobrush. Also, because hemorrhage, necrosis, and intense inflammation may obscure the results, the Pap smear is a poor way to diagnose gross lesions; these should always be biopsied.

Patients with abnormal findings on cytologic examination who do not have a gross cervical



lesion must be evaluated by colposcopy and directed biopsies. Following application of a 3% acetic acid solution, the cervix is examined under 10- to 15-fold magnification with a bright, filtered light that enhances the acetowhitening and vascular patterns characteristic of dysplasia or carcinoma. The skilled colposcopist can accurately distinguish between low- and high-grade dysplasia,<sup>119,120</sup> and <sup>121</sup> but microinvasive disease cannot consistently be distinguished from intraepithelial lesions on colposcopy.<sup>122,123</sup>

If no abnormalities are found on colposcopic examination or if the entire squamocolumnar junction cannot be visualized in a patient with an atypical Pap smear result, endocervical curettage should be performed. Some authorities advocate the routine addition of endocervical curettage to colposcopic examination to minimize the risk of missing occult cancer within the endocervical canal.<sup>122,123</sup> and <sup>124</sup> However, it is probably reasonable to omit this step in previously untreated women if the entire squamocolumnar junction is visible with a complete ring of unaltered columnar epithelium in the lower canal.

Cervical cone biopsy is used to diagnose occult endocervical lesions and is an essential step in the diagnosis and management of microinvasive carcinoma of the cervix. The geometry of the cone is individualized and tailored to the geometry of the cervix, the location of the squamocolumnar junction, and the site and size of the lesion. Cervical cone biopsy yields an accurate diagnosis and decreases the incidence of inappropriate therapy when (1) the squamocolumnar junction is poorly visualized on colposcopy and a high-grade lesion is suspected, (2) a high-grade dysplastic epithelium extends into the endocervical canal, (3) the cytologic findings suggest a high-grade dysplasia or carcinoma *in situ*, (4) a microinvasive carcinoma is found on directed biopsy, (5) the endocervical curettage specimens show high-grade CIN, or (6) the cytologic findings are suspicious for AIS.<sup>55,114,125</sup>

### ***Clinical Evaluation of Patients with Invasive Carcinoma***

All patients with invasive cervical cancer should be evaluated with a detailed history and physical examination, with particular attention paid to inspection and palpation of the pelvic organs with bimanual and rectovaginal examinations. Standard laboratory studies should include a complete blood cell count and renal function and liver function tests. All patients should have chest radiography to rule out lung metastases and an intravenous pyelogram [or computed tomography (CT)] to determine the kidney's location and to rule out ureteral obstruction by tumor. Cystoscopy and either a proctoscopy or a barium enema study should be done in patients with bulky tumors.

Many clinicians obtain CT or magnetic resonance imaging (MRI) scans to evaluate regional nodes, but the accuracy of these studies is compromised by their failure to detect small metastases and because patients with bulky necrotic tumors often have enlarged reactive lymph nodes.<sup>126,127</sup> In a large Gynecologic Oncology Group (GOG) study that compared the results of radiographic studies with subsequent histologic findings, Heller et al.<sup>126</sup> found that 79% of the cases with paraaortic lymph node involvement were detected by lymphangiography, whereas only 34% were detected by CT. Unfortunately, lymphangiography is no longer available in many centers. More recent studies suggest that positron emission tomography may be a sensitive noninvasive method of evaluating the regional nodes of patients with cervical cancers.<sup>128</sup> MRI can provide useful

information about the distribution and depth of invasion of tumors in the cervix<sup>129,130</sup> and <sup>131</sup> but tends to yield less accurate assessments of the parametrium.<sup>132,133</sup>

### **Clinical Staging**

FIGO has defined the most widely accepted staging system for carcinomas of the cervix.<sup>134,135</sup> The latest (1994) update of this system is summarized in Table 36.2-4. Since the earliest versions of the cervical cancer staging system<sup>136</sup> there have been numerous changes, particularly in the definition of stage I disease.<sup>137</sup> Preinvasive disease was not placed in a separate category until 1950, and the stage IA category for “cases with early stromal invasion” was first described in 1962. Cases of early stromal invasion and occult invasion were redistributed between stages IA1, IA2, and IB<sub>occult</sub> several times until 1985, when FIGO eliminated stage IB<sub>occult</sub> and provided the first specific definitions of microinvasive disease (stages IA1 and IA2). In 1994 these definitions were changed again, and, for the first time, stage IB tumors were subdivided according to tumor diameter (see Table 36.2-4). Although these changes have gradually improved the discriminatory value of the staging system, the many fluctuations in the definitions of stages IA and IB have complicated our ability to compare the outcomes of patients whose tumors were staged and treated during different periods.<sup>137</sup> In addition, many gynecologic oncologists in the United States use the Society of Gynecologic Oncologists' definition of a microinvasive carcinoma (i.e., tumor that “invades the stroma in one or more places to a depth of 3 mm or less below the base of the epithelium and in which lymphatic or vascular involvement is not demonstrated”), a definition that still differs from the current FIGO classification.<sup>138</sup>

**TABLE 36.2-4.** International Federation of Gynecology and Obstetrics Staging of Carcinoma of the Cervix (1994)

FIGO stage is based on careful clinical examination and the results of specific radiologic studies and procedures. These should be performed and the stage should be assigned before any definitive therapy is administered. The clinical stage should never be changed on the basis of subsequent findings. When it is doubtful to which stage a particular case should be allotted, the case should be assigned to the earlier stage. According to FIGO,<sup>134</sup> “a growth fixed to the pelvic wall by a short and indurated, but not nodular, parametrium should be allotted to stage IIb.” A case should be classified as stage III “only if the parametrium is nodular to the pelvic wall or if the growth itself extends to the pelvic wall.” In its rules for clinical staging, FIGO states that palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and radiographic examination of the lungs and skeleton may be used for clinical staging. Suspected bladder or rectal involvement should be confirmed by biopsy. Findings of bullous edema or malignant cells in cytologic washings from the urinary bladder are not sufficient to diagnose bladder involvement. FIGO specifically states that findings on examinations such as lymphangiography, laparoscopy, CT scan, and MRI are of value for planning therapy but, because these are not yet generally available and the interpretation of results is variable, should not be the basis for changing the clinical stage. Examination under

anesthesia is desirable but not required. The rules and notes outlined in the FIGO staging system are integral parts of the clinical staging system and should be strictly observed to minimize inconsistencies in staging between institutions.

Although most clinicians use the FIGO classification system, a number of European groups use a staging system that divides stage IIB tumors according to the extent of parametrial involvement and divides stage III tumors according to whether there is unilateral or bilateral pelvic wall fixation. Until the mid 1980s most reports from The University of Texas M. D. Anderson Cancer Center used a similar staging system that also categorized patients with

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bulky endocervical tumors in a special category.<sup>137</sup> Although surgically treated patients are sometimes classified according to a tumor, node, metastases (TNM) pathologic staging system, this practice has not been widely accepted because it cannot be applied to patients who are treated with primary radiotherapy.<sup>139</sup>

### ***Surgical Evaluation of Regional Spread***

In the 1970s, studies of diagnostic preradiation lymph node dissection used a transperitoneal approach that led to unacceptable morbidity and mortality from radiation-related bowel complications, particularly after treatment with high radiation doses and extended fields.<sup>81,140</sup> More recently, extraperitoneal dissection, which induces fewer bowel adhesions, has been recommended. With this approach, postradiation bowel complications occur in fewer than 5% of patients.<sup>141</sup> A number of groups are currently investigating the use of laparoscopic lymph node dissection to evaluate patients with cervical cancer.<sup>142,143</sup> This approach reduces the length of postoperative hospitalization. However, the rate of late complications from radiotherapy following laparoscopic lymphadenectomy has not yet been determined.

Although the indications for surgical staging are controversial, advocates argue that the procedure identifies patients with microscopic paraaortic or common iliac node involvement who can benefit from extended-field irradiation. Some investigators have also suggested, on the basis of first principles and encouraging results with regard to control of pelvic disease, that debulking of large pelvic nodes before radiotherapy may improve outcome.<sup>144,145</sup> Because patients with radiographically positive pelvic nodes are at greatest risk for occult metastasis to paraaortic nodes, these patients may have the greatest chance of benefiting from surgical staging.

Some authors have advocated pretreatment blind biopsy of the scalene node in patients with positive paraaortic nodes and in patients with a central recurrence who are being considered for pelvic exenteration. The reported incidence of supraclavicular metastasis varies widely (5% to 20% or more) for patients with positive paraaortic lymph nodes.<sup>146,147</sup>

### ***Prognostic Factors***

Although rates of survival and control of pelvic disease in cervical cancer patients are correlated with FIGO stage, prognosis is also influenced by a number of tumor

characteristics that are not included in the staging system. Clinical tumor diameter is strongly correlated with prognosis for patients treated with radiation (Fig. 36.2-2)<sup>148,149</sup> or surgery.<sup>63,65,150,151</sup> For this reason, FIGO modified the stage I category so that these tumors are subdivided according to clinical tumor diameter (i.e., less than or equal to 4 or greater than 4 cm).<sup>135</sup> For patients with more advanced disease, other estimates of tumor bulk, such as the presence of medial versus lateral parametrial involvement in FIGO stage IIB tumors or of unilateral versus bilateral parametrial or pelvic wall involvement, have also been correlated with outcome.<sup>152,153</sup> and <sup>154</sup> The predictive value of the staging system itself may, in part, reflect an association between the stage categories and the primary tumor volume. Operative findings often do not agree with clinical estimates of parametrial or pelvic wall involvement,<sup>69,155,156</sup> and some authors have found that the predictive power of stage diminishes or is lost when comparisons are corrected for differences in clinical tumor diameter.<sup>75,157</sup>

**FIGURE 36.2-2.** Relationship between tumor diameter and the disease-specific survival rates of 1526 patients with stage IB squamous cell carcinomas of the cervix treated with radiotherapy at M. D. Anderson Cancer Center. Numbers in parentheses represent the number of patients at risk at 10 or 20 years. (Reprinted from ref. 148, with permission.)

Lymph node metastasis is also an important predictor of prognosis. For patients treated with radical hysterectomy for stage IB disease, survival rates are usually reported as 85% to 95% for patients with negative nodes and 45% to 55% for those with lymph node metastases.<sup>61,63,158</sup> Inoue and Morita<sup>159</sup> reported that survival was correlated with the size of the largest node, and several authors have reported correlations between the number of involved pelvic lymph nodes and survival.<sup>62,150,158,160</sup> Survival rates for patients with positive paraaortic nodes treated with extended-field radiotherapy vary between 10% and 50% depending on the extent of pelvic disease and paraaortic lymph node involvement (Table 36.2-5).<sup>77,78,80,81,140,161,162,163,164,165,166,167</sup> and <sup>168</sup>

**TABLE 36.2-5.** Results of Extended-Field Radiation Therapy to the Paraaortic Nodes for Biopsy-Proven Paraaortic Node Metastases from Carcinoma of the Cervix

For patients treated with radical hysterectomy, other histologic parameters that have been associated with a poor prognosis are lymph-vascular space invasion (LVSI) (Table 36.2-6),<sup>62,150,151,158,169,170,171,172</sup> and <sup>173</sup> deep stromal invasion (greater than or equal to 10 mm or greater than 70% invasion),<sup>62,63,67,71,150,151,158</sup> and parametrial extension.<sup>62,71,155,174</sup> Roman and colleagues<sup>175</sup> reported a correlation between the quantity of LVSI (percent of histopathologic sections containing LVSI) and the incidence of lymph node metastases. A strong inflammatory response in the cervical stroma tends to predict a good outcome.<sup>176</sup> Uterine body involvement is associated with an increased rate of distant metastases in patients treated with radiation or surgery.<sup>177,178,179</sup> and <sup>180</sup>

**TABLE 36.2-6.** Relationship between Lymph-Vascular Space Invasion, Pelvic Node Involvement, and Recurrence Rate in Patients Treated with Radical Hysterectomy

Several investigators have reported similar survival rates for patients with squamous carcinomas and those with adenocarcinomas.<sup>84,181,182,183,184</sup> and <sup>185</sup> However, other investigators have drawn the opposite conclusion, noting unusually high pelvic relapse rates in patients treated surgically for adenocarcinomas and poorer survival rates among patients treated with surgery or irradiation for cervical adenocarcinomas.<sup>186,187,188,189,190</sup> and <sup>191</sup> In a multivariate analysis of 1767 patients treated with radiation for FIGO stage IB disease, Eifel and colleagues<sup>188</sup> reported a highly significant independent correlation between histologic features and survival. Using Cox regression analysis, the relative risk of death from cancer for 106 patients with adenocarcinomas 4 cm or more in diameter was determined to be 1.9 times that for patients with squamous

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tumors ( $P < .01$ ) (Fig. 36.2-3). Pelvic disease control rates were similar for patients with squamous carcinomas and those with adenocarcinomas, but there was a significantly higher incidence of distant metastases in patients with adenocarcinomas. Although the prognostic significance of histologic grade has been disputed for squamous carcinomas, there is a clear correlation between the degree of differentiation and the clinical behavior of adenocarcinomas.<sup>189,192,193,194</sup> and <sup>195</sup>

**FIGURE 36.2-3.** Relationship between histologic type and the disease-specific survival rates of 903 patients treated at M. D. Anderson Cancer Center for stage IB carcinomas of the cervix measuring 4 cm or greater in diameter. Numbers in parentheses represent the number of patients at risk at 10 or 20 years. AC, adenocarcinoma; SCC, squamous cell carcinoma. (Reprinted from ref. 188, with permission.)

Several studies have demonstrated a relationship between hemoglobin level and prognosis in patients with locally advanced cervical cancer.<sup>196,197</sup> and <sup>198</sup> The strongest evidence that anemia plays a causative role in pelvic recurrence comes from a small 1978 randomized study conducted at the Princess Margaret Hospital.<sup>196</sup> All patients were maintained at a hemoglobin level of at least 10 gm%, but those in the treatment arm were maintained, through the use of transfusions, at hemoglobin levels of at least 12.5 gm%. The locoregional recurrence rate was significantly higher for the 25 anemic patients in the control arm than it was for the patients who received transfusions. Unfortunately, the results of this small study have never been confirmed, and subsequent studies aimed at overcoming the theoretical radiobiologic consequences of intratumoral hypoxia (hypoxic cell sensitizers, hyperbaric oxygen breathing, neutron therapy) have not been successful.<sup>199,200,201,202,203,204</sup> and <sup>205</sup> Several investigators have correlated low intratumoral oxygen tension levels with a high rate of lymph node metastases and poor survival.<sup>206,207</sup> and <sup>208</sup>

The serum concentration of squamous cell carcinoma antigen appears to correlate with the stage and size of squamous carcinomas and the presence of lymph node metastases.<sup>209,210,211</sup> and <sup>212</sup> However, investigators disagree about the independent predictive value of this test. Other clinical and biologic features that have been investigated for their predictive power, with variable results, include patient age,<sup>158,213,214,215</sup> and <sup>216</sup> peritoneal cytology,<sup>217,218</sup> platelet count,<sup>219,220</sup> tumor vascularity,<sup>221,222</sup> DNA ploidy or S phase,<sup>223,224</sup> and HPV subtype.<sup>35,225,226</sup> In two studies of patients with histologically negative lymph nodes, investigators have reported higher rates of disease recurrence when a polymerase chain reaction assay of the lymph nodes was strongly positive for HPV DNA.<sup>227,228</sup>

## TREATMENT

A number of factors may influence the choice of local treatment, including tumor size, stage, histologic features, evidence of lymph node involvement, risk factors for complications of surgery or radiation, and patient preference. However, as a rule, intraepithelial lesions are treated with superficial ablative techniques; microinvasive cancers invading less than 3 mm (stage IA1) are managed with conservative surgery (excisional conization or extrafascial hysterectomy); early invasive cancers

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(stages IA2 and IB1 and some small stage IIA tumors) are managed with radical surgery or radiotherapy; and locally advanced cancers (stages IB2 through IVA) are managed with radiotherapy. Selected patients with centrally recurrent disease after maximum radiotherapy may be treated with radical exenterative surgery; pelvic recurrence after hysterectomy is treated with irradiation. The results of randomized trials<sup>229,230,231,232</sup> and <sup>233</sup> have led to the addition of concurrent cisplatin-containing chemotherapy to radiotherapy for patients whose cancers have a high risk of local-regional recurrence.

### ***Preinvasive Disease (Stage 0)***

Patients with noninvasive squamous lesions can be treated with superficial ablative therapy (cryosurgery or laser therapy) or with loop excision if (1) the entire transformation zone has been visualized colposcopically, (2) directed biopsies are consistent with Pap smear results, (3) endocervical curettage findings are negative, and (4) there is no suspicion of occult invasion on cytologic or colposcopic examination. If patients do not meet these criteria, a conization should be performed.

With cryotherapy, abnormal tissue is frozen with a supercooled metal probe until an ice ball forms that extends 5 mm beyond the lesion. Because cryonecrosis tends to be patchy and may be inadequate after a single freeze, the tissue should be frozen a second time after it has visibly thawed.<sup>234,235</sup> Another common and equally effective technique ablates tissue with a carbon dioxide laser beam. After laser ablation there is less distortion and more rapid healing of the cervix, but the procedure requires more training and more expensive equipment than does cryosurgery.

Many practitioners now consider loop diathermy excision to be the preferred treatment for noninvasive squamous lesions. With this technique, a charged electrode is used to excise the entire transformation zone and distal canal. Although control rates are similar to those

achieved with cryotherapy or laser ablation,<sup>236</sup> loop diathermy is easily learned, is less expensive than laser excision, and preserves the excised lesion and transformation zone for histologic evaluation.<sup>237,238,239</sup> and 240 However, some authorities think that low-grade lesions may be overtreated with this method.<sup>241</sup> Because loop excision may inadequately treat disease within the cervical canal and complicate further treatment, this technique should not be considered an alternative to formal excisional conization when microinvasive or invasive cancer is suspected or for patients with AIS.

Cryotherapy, laser excision, and loop excision are all outpatient office procedures that preserve fertility. Although recurrence rates are low (10% to 15%) and progression to invasion rare (less than 2% in most series), life long surveillance of these patients must be maintained. The risk of recurrence may be somewhat increased in women with HPV type 16 or 18.<sup>236</sup> Treatment with vaginal or type I abdominal hysterectomy currently is reserved for women who have other gynecologic conditions that justify the procedure; invasive cancer still must be excluded before surgery to rule out the need for a more extensive operative procedure.

### ***Microinvasive Carcinoma (Stage IA)***

The standard treatment for patients with stage IA1 disease is total (type I) or vaginal hysterectomy. Because the risk of pelvic lymph node metastases from these minimally invasive tumors is less than 1%, pelvic lymph node dissection is not usually recommended.<sup>71,123,242</sup>

Selected patients with tumors that meet the Society of Gynecologic Oncologists' definition of microinvasion (FIGO stage IA1 disease without LVSI) and who wish to maintain fertility may be adequately treated with a therapeutic cervical conization if the margins of the cone are negative. In 1991, Burghardt et al.<sup>243</sup> reported one recurrence (which was fatal) in 93 women followed for more than 5 years after therapeutic conization for minimal (less than 1 mm) microinvasion. Morris et al.<sup>244</sup> reported no invasive recurrences in 14 patients followed for a mean of 26 months after conization for tumors invading 0.5 to 2.8 mm. However, patients who have this conservative treatment must be followed closely with periodic cytologic evaluation, colposcopy, and endocervical curettage.

Diagnostic or therapeutic conization for microinvasive disease is usually performed with a cold knife or carbon dioxide laser on a patient under general or spinal anesthesia. Because an accurate assessment of the maximum depth of invasion is critical, the entire specimen must be sectioned and carefully handled to maintain its original orientation for microscopic assessment. Complications occur in 2% to 12% of patients, are related to the depth of the cone, and include hemorrhage, sepsis, infertility, stenosis, and cervical incompetence.<sup>245</sup> The width and depth of the cone should be tailored to produce the least amount of injury while providing clear surgical margins.

For patients whose tumors invade 3 to 5 mm into the stroma (FIGO stage IA2), the risk of nodal metastases is approximately 5%.<sup>65,99</sup> Therefore, a bilateral pelvic lymphadenectomy should be performed in conjunction with a modified radical (type II) hysterectomy. Modified radical hysterectomy is a less extensive procedure than a classic radical hysterectomy (Fig. 36.2-4). The cervix, upper vagina, and paracervical tissues are removed after careful

dissection of the ureters to the point of their entry to the bladder. The medial half of the cardinal ligaments and

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the uterosacral ligaments are also removed. With this treatment, significant urinary tract complications are rare and cure rates exceed 95%.<sup>246,247 and 248</sup>

**FIGURE 36.2-4.** The pelvic ligaments and spaces. Dotted lines indicate the tissues removed with a type II or type III hysterectomy. (Reprinted from ref. 541, with permission.)

Although surgical treatment is standard for *in situ* and microinvasive cancer, patients with severe medical problems or other contraindications to surgical treatment can be successfully treated with radiotherapy. Grigsby and Perez<sup>249</sup> reported a 10-year progression-free survival rate of 100% in 21 patients with carcinoma *in situ* and in 34 patients with microinvasive carcinoma treated with radiation alone. Hamberger et al.<sup>250</sup> reported that all patients with stage IA disease and 89 (96%) of 93 patients with small stage IB disease (less than one cervical quadrant involved) were disease free 5 years after treatment with intracavitary irradiation alone.

### Stages IB and IIA

Early stage IB cervical carcinomas can be treated effectively with combined external-beam irradiation and brachytherapy or with radical hysterectomy and bilateral pelvic lymphadenectomy. The goal of both treatments is to destroy malignant cells in the cervix, paracervical tissues, and regional lymph nodes. Studies indicate that selected subgroups of patients who require radiotherapy also benefit from concurrent chemotherapy.<sup>229,230 and 231</sup>

Overall survival rates for patients with stage IB cervical cancer treated with surgery or radiation usually range between 80% and 90%, suggesting that the two treatments are equally effective (Table 36.2-7).<sup>63,66,67,72,148,149,251,252,253,254,255,256,257,258,259,260,261 and 262</sup> However, biases introduced by patient selection, variations in the definition of stage IA disease, and variable indications for postoperative radiotherapy or adjuvant hysterectomy confound comparisons about the efficacy of radiotherapy versus surgery. Because young women with small, clinically node-negative tumors tend to be favored candidates for surgery and because tumor diameter and nodal status are inconsistently described in published series, it is difficult to compare the results reported for patients treated with the two modalities.

**TABLE 36.2-7.** Five-Year Survival Rates for Patients with International Federation of Gynecology and Obstetrics Stage IB Carcinoma of the Cervix

In 1997, Landoni and colleagues reported results from the only prospective trial comparing radical surgery with radiotherapy alone.<sup>263</sup> In their study, patients with stage IB or IIA



disease were randomly assigned to receive treatment with type III radical hysterectomy or a combination of external-beam and low dose-rate intracavitary radiotherapy. In the surgical arm, findings of parametrial involvement, positive margins, deep stromal invasion, or positive nodes led to the use of postoperative pelvic irradiation in 62 (54%) of 114 patients with tumors 4 cm or smaller in diameter and in 46 (84%) of 55 patients with tumors measuring less than 4 cm. Patients in the radiotherapy arm received a relatively low total dose of radiation to the cervix, with a median dose to point A of 76 Gy. With a median follow-up of 87 months, the 5-year actuarial disease-free survival rates for patients treated in the surgery and radiotherapy groups were 80% and 82%, respectively, for patients with tumors that were 4 cm or smaller and 63% and 57%, respectively, for patients with larger tumors. The authors reported a significantly higher rate of complications in the patients treated with initial surgery, and they attributed this finding to the frequent use of combined modality treatment in this group.

For patients with stage IB1 squamous carcinomas, the choice of treatment is based primarily on patient preference, anesthetic and surgical risks, physician preference, and an understanding of the nature and incidence of complications with radiotherapy and hysterectomy (described in detail here). For patients with similar tumors, the overall rate of major complications is similar with surgery and radiotherapy, although urinary tract complications tend to be more frequent after surgical treatment and bowel complications are more common after radiotherapy. Surgical treatment tends to be preferred for young women with small tumors because it permits preservation of ovarian function and may cause less vaginal shortening.

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Radiotherapy is often selected for older, postmenopausal women to avoid the morbidity of a major surgical procedure.

Some surgeons have also advocated the use of radical hysterectomy as initial treatment for patients with stage IB2 tumors.<sup>264,265 and 266</sup> However, patients who have tumors measuring more than 4 cm in diameter usually have deep stromal invasion and are at high risk for lymph node involvement and parametrial extension. Because patients with these risk factors have an increased rate of pelvic disease recurrence, surgical treatment is usually followed by postoperative irradiation, which means that the patient is exposed to the risks of both treatments. Consequently, many gynecologic and radiation oncologists believe that patients with bulky (stage IB2) carcinomas are better treated with radical radiotherapy.

Two prospective randomized trials<sup>229,230</sup> indicate that patients who are treated with radiation for bulky central disease benefit from concurrent administration of cisplatin-containing chemotherapy. A third study suggests that patients who require postoperative radiation because of findings of lymph node metastasis or involved surgical margins also benefit from concurrent chemoradiation.<sup>231</sup> These studies are discussed in more detail in the following sections.

## **RADICAL HYSTERECTOMY.**

The standard surgical treatment for stage IB and stage IIA cervical carcinomas is radical (type III) hysterectomy and bilateral pelvic lymph node dissection. This procedure involves

*en bloc* removal of the uterus, cervix, and paracervical, parametrial, and paravaginal tissues to the pelvic side walls bilaterally, with removal of as much of the uterosacral ligaments as possible (see Fig. 36.2-4). The uterine vessels are ligated at their origin, and the proximal third of the vagina and paracolpium are resected. For women younger than 40 to 45 years, the ovaries usually are not removed. If intraoperative findings suggest a need for postoperative pelvic irradiation, the ovaries may be transposed out of the pelvis.

Intraoperative and immediate postoperative complications of radical hysterectomy include blood loss (average 0.8 L), ureterovaginal fistula (1% to 2%), vesicovaginal fistula (less than 1%), pulmonary embolus (1% to 2%), small bowel obstruction (1% to 2%), and postoperative fever secondary to deep vein thrombosis, pulmonary infection, pelvic cellulitis, urinary tract infection, or wound infection (25% to 50%).<sup>267</sup> Subacute complications include lymphocyst formation and lower extremity edema, the risk of which is related to the extent of the node dissection. Lymphocysts may obstruct a ureter, but hydronephrosis usually improves with drainage of the lymphocyst.<sup>268</sup> The risk of complications may be increased in patients who receive preoperative or postoperative irradiation.

Although most patients have transient decreased bladder sensation after radical hysterectomy, with appropriate management severe long-term bladder complications are infrequent. However, chronic bladder hypotonia or atony occurs in approximately 3% to 5% of patients, despite careful postoperative bladder drainage.<sup>269,270</sup> Bladder atony probably results from damage to the bladder's innervation and may be related to the extent of the parametrial and paravaginal dissection.<sup>271,272</sup> Radical hysterectomy may be complicated by stress incontinence, but reported incidences vary widely and may be influenced by the addition of postoperative radiotherapy.<sup>273,274</sup> Patients may also experience constipation and, rarely, chronic obstipation after radical hysterectomy.

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## **RADIOTHERAPY AFTER RADICAL HYSTERECTOMY.**

The role of postoperative irradiation in patients with cervical carcinoma is still being defined. Most investigators have reported that postoperative irradiation decreases the risk of pelvic recurrence in patients whose tumors have high-risk features (lymph node metastasis, deep stromal invasion, insecure operative margins, or parametrial involvement).<sup>275,276,277,278,279</sup> and 280 However, because the patients who received postoperative radiotherapy in these studies were selected for the high-risk features of their tumors, it is difficult to determine the impact of adjuvant irradiation on survival.

The GOG<sup>281</sup> reported results of a prospective trial testing the benefit of adjuvant pelvic irradiation in patients who have an intermediate risk of recurrence after radical hysterectomy for stage IB carcinoma. Patients were eligible if they had at least two of the following risk factors: greater than one-third stromal invasion, lymphatic space involvement, or clinical diameter of at least 4 cm. Patients with metastases to the pelvic lymph nodes were excluded. After radical hysterectomy, 277 patients were randomly assigned to receive 46.0 to 50.6 Gy of adjuvant radiotherapy to the pelvis or no further treatment. Overall, there was a 47% reduction in the risk of recurrence with adjuvant radiotherapy ( $P = .008$ ). In this preliminary analysis, follow-up was too immature for a significance level to be

assigned to the overall survival comparison, but there were 18 deaths (13%) in the radiotherapy arm versus 30 (21%) in the radical hysterectomy only arm (relative mortality, 0.64).<sup>281</sup>

Although pelvic irradiation also reduces the risk of recurrence for patients with pelvic lymph node metastases or parametrial involvement, the risk of pelvic and distant recurrence remains high for these women.<sup>278,282</sup> Some authors have hypothesized that the dose of radiation that can be given safely after surgery may be inadequate to control microscopic disease in a surgically disturbed, hypovascular site.<sup>283</sup> If this were true, it would be an argument for primary radiotherapeutic management of tumors with known high-risk features. Preliminary results of a prospective study conducted by the Southwest Oncology Group suggest that administration of cisplatin-containing chemotherapy concurrent with adjuvant pelvic irradiation may improve the rate of control of pelvic disease and the rate of survival for patients with lymph node metastases, parametrial involvement, or involved surgical margins.<sup>231</sup>

The overall risk of major complications (particularly small bowel obstruction) is probably increased in patients who receive postoperative pelvic irradiation, but inconsistencies in the methods of analysis and the relatively small number of patients in most series make studies of this subject difficult to interpret.<sup>263,265,280,284,285,286,287</sup> and <sup>288</sup> Bandy et al.<sup>289</sup> reported that patients who were irradiated after hysterectomy had more long-term problems with bladder contraction and instability than those treated with surgery alone.

## **RADICAL RADIOTHERAPY.**

Radiotherapy also achieves excellent survival and pelvic disease control rates in patients with stage IB cervical cancers. Eifel et al.<sup>148</sup> reported a 5-year disease-specific survival rate of 90% for 701 patients treated with radiation alone for stage IB1 squamous tumors less than 4 cm in diameter. The central and pelvic tumor control rates were 99% and 98%, respectively. Disease-specific survival rates were 86% and 67% for patients with tumors measuring 4.0 to 4.9 cm or 5 cm or more in diameter, respectively. Pelvic tumor control was achieved in 82% of patients with tumors of 5 cm or more in diameter. Perez et al.<sup>149</sup> and Lowrey et al.<sup>252</sup> reported similar excellent disease control rates for patients with stage IB tumors treated with radiotherapy. Survival rates for patients with FIGO stage IIA disease treated with irradiation range between 70% and 85% and are also strongly correlated with tumor size.<sup>149,152,252</sup> For patients with bulky tumors, studies suggest that results may be improved further with concurrent administration of chemotherapy.<sup>229,230</sup>

As with radical surgery, the goal of radiation treatment is to sterilize disease in the cervix, paracervical tissues, and regional lymph nodes in the pelvis. Patients are usually treated with a combination of external-beam irradiation to the pelvis and brachytherapy. Clinicians balance external and intracavitary treatment in different ways for these patients, weighting one or the other component more heavily. However, brachytherapy is a critical element in the curative radiation treatment of all carcinomas of the cervix. Even relatively small tumors that involve multiple quadrants of the cervix are usually treated with total doses of 80 to 85 Gy to point A. The dose may be reduced by 5% to 10% for small superficial tumors. Although patients with small tumors may be treated with somewhat smaller fields than patients with more advanced locoregional disease, care must still be taken to cover

adequately the obturator, external iliac, low common iliac, and presacral nodes. Radiation technique is discussed in more detail in the next section.

### **IRRADIATION FOLLOWED BY HYSTERECTOMY.**

In a 1969 report from M. D. Anderson Cancer Center, Durrance and colleagues<sup>290</sup> reported a lower pelvic recurrence rate for patients with bulky endocervical tumors (greater than or equal to 6 cm) treated with external-beam and intracavitary irradiation followed by extrafascial hysterectomy than for those treated with radiation alone. Many groups subsequently adopted combined treatment as a standard approach to bulky stage IB or IIA disease. However, in a 1992 update of the M. D. Anderson experience, Thoms and colleagues<sup>157</sup> suggested that the differences observed in earlier reports may have resulted from a tendency to select patients with massive tumors (greater than or equal to 8 cm) or clinically positive nodes for treatment with radiation alone. When these patients were excluded, pelvic disease control rates were similar with the two approaches.

In 1991, Mendenhall et al.<sup>291</sup> reported no difference in pelvic disease control or survival rates for patients treated before or after the University of Florida adopted a policy (in the mid-1970s) of using combined treatment for patients with bulky (greater than or equal to 6 cm) tumors. In a study of 1526 patients with stage IB squamous carcinomas, Eifel and colleagues<sup>148</sup> reported central tumor recurrence rates of less than 10% for tumors as large as 7.0 to 7.9 cm treated with radiation alone, suggesting that the margin for possible improvement with adjuvant hysterectomy is small. Perez and Kao<sup>292</sup> also found that central recurrences were rare if adequate doses of irradiation (greater than 80 Gy to point A) were delivered. Addition of concurrent chemotherapy should further reduce the margin for improvement with adjuvant hysterectomy.<sup>230</sup>

There is, therefore, no clear evidence that adjuvant hysterectomy improves the outcome of patients with a bulky stage IB or IIA tumor, although many clinicians continue to recommend combined treatment.<sup>293</sup> When combined treatment is planned, the dose of intracavitary irradiation is usually reduced by 15% to

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25%. A type I, extrafascial hysterectomy is usually performed, in which the cervix, adjacent tissues, and a small cuff of the upper vagina in a plane outside the pubocervical fascia are removed. This procedure involves minimal disturbance of the bladder and ureters.

Intrafascial hysterectomy is not used for cervical cancer because it does not remove all cervical tissue,<sup>294</sup> and radical hysterectomy is avoided after high-dose irradiation because of an increased risk of urinary tract complications.<sup>295</sup>

In 1991, the GOG completed a prospective randomized trial of irradiation with or without extrafascial hysterectomy in patients with stage IB tumors of 4 cm or more in diameter. Preliminary analysis demonstrated no significant improvement in the survival rate of patients who had an adjuvant hysterectomy.<sup>296</sup>

### **CHEMOTHERAPY FOLLOWED BY RADICAL SURGERY.**

During the 1990s, a number of investigators reported the results of treating patients with bulky stage IB or stage II cervical carcinomas with a combination of neoadjuvant

chemotherapy followed by radical surgery.<sup>297,298</sup> and 299 Neoadjuvant chemotherapy has usually included cisplatin and bleomycin plus one or two other drugs (Table 36.2-8). The results of uncontrolled studies cannot be easily compared with the results with more traditional treatments because the series are small and often have short follow-up and the criteria for patient selection are not always clear. Some or all of the patients in each of these series received postoperative pelvic irradiation, but detailed descriptions of this additional treatment are not always given. Only one prospective randomized trial has compared radical hysterectomy followed by postoperative radiotherapy with chemotherapy followed by surgery and irradiation.<sup>299</sup> In this study, Sardi et al. observed similar outcomes with the two treatments for patients who had tumors smaller than 60 cm<sup>3</sup> (measured ultrasonographically), but they reported a significantly better projected 4-year disease-free survival with neoadjuvant chemotherapy for patients who had larger tumors. However, most patients had been followed for less than 3 years at the time of the report. Ultimately, the cost and morbidity of this triple-modality treatment may only be justified if it proves to be more effective than treatment with radiation or chemoradiation alone. However, studies comparing these approaches have not yet been reported.

**TABLE 36.2-8.** Response Rates to Neoadjuvant Chemotherapy in Patients with Previously Untreated Locally Advanced Cervical Cancer

### ***Stages IIB, III, and IVA***

Radiotherapy is the primary local treatment for most patients with locoregionally advanced cervical carcinoma. The success of treatment depends on a careful balance between external-beam radiotherapy and brachytherapy, optimizing the dose to tumor and normal tissues and the overall duration of treatment. Five-year survival rates of 65% to 75%, 35% to 50%, and 15% to 20% are reported for patients treated with radiotherapy alone for stage IIB, IIIB, and IV tumors, respectively.<sup>134,149,152,154,214,252</sup> In a French Cooperative Group study of

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1875 patients treated with radiotherapy according to Fletcher guidelines, Barillot et al.<sup>152</sup> reported 5-year survival rates of 70%, 45%, and 10% for patients with stage IIB, IIIB, and IVA tumors, respectively (Fig. 36.2-5). With appropriate radiotherapy, even patients with massive locoregional disease have a significant chance for cure.

**FIGURE 36.2-5.** Relationship between International Federation of Gynecology and Obstetrics stage and the actuarial survival rates of 1383 patients with invasive carcinoma of the cervix treated with radiotherapy. (Reprinted from ref. 253, with permission.)

External-beam irradiation is used to deliver a homogeneous dose to the primary cervical tumor and to potential sites of regional spread. An initial course of external irradiation may also improve the efficacy of subsequent intracavitary treatment by shrinking bulky endocervical tumor (bringing it within the range of the high-dose portion of the

brachytherapy dose distribution) and by shrinking exophytic tumor that might prevent satisfactory placement of vaginal applicators. For this reason, patients with locally advanced disease usually begin with a course of external-beam treatment. Subsequent brachytherapy exploits the inverse square law to deliver a high dose to the cervix and paracervical tissues while minimizing the dose to adjacent normal tissues.

Although many clinicians delay intracavitary treatment until pelvic irradiation has caused some initial tumor regression, breaks between external-beam and intracavitary therapy should be discouraged, and every effort should be made to complete the entire treatment in less than 7 to 8 weeks. The favorable results documented in reports from large single-institution studies have been based on policies that dictate relatively short overall treatment durations (less than 8 weeks),<sup>300</sup> and several studies in patients with locally advanced cervical cancer have suggested that longer treatment courses are associated with decreased pelvic disease control and survival rates.<sup>301,302,303,304</sup> and <sup>305</sup>

### EXTERNAL-BEAM TECHNIQUE.

High-energy photons (15 to 18 MV) are usually preferred for pelvic treatment because they spare superficial tissues that are unlikely to be involved with tumor. At these energies, the pelvis can be treated either with four fields (anterior, posterior, and lateral fields) or with anterior and posterior fields alone (Fig. 36.2-6). When high-energy beams are not available, four fields are usually used because less-penetrating 4- to 6-MV photons often deliver an unacceptably high dose to superficial tissues when only two fields are treated. However, lateral fields must be designed with great care because clinicians' estimates of the location of potential sites of disease on a lateral radiographic view may be inaccurate. In particular, *standard* anterior and posterior borders that have been described in the past may shield regions at risk for microscopic regional disease in the presacral and external iliac nodes and in the presacral and cardinal ligaments; care must also be taken not to underestimate the posterior extent of central cervical disease in patients with bulky tumors.<sup>306,307</sup> and <sup>308</sup>

**FIGURE 36.2-6.** Typical fields used to treat the pelvis with a four-field technique. When lateral fields are used to treat cervical cancers, particular care must be taken to adequately encompass the primary tumor and potential sites of regional spread in the radiation fields.

The caudad extent of disease can be determined by placing radiopaque seeds in the cervix or at the lowest extent of vaginal disease. Information gained from radiologic studies can also improve estimates of disease extent. Lymphangiograms are helpful in tailoring blocks, particularly at the anterior border of lateral fields. MRI and CT scans can improve clinicians' understanding of uterine position and thus help clinicians design anterior and posterior field borders. In fact, some investigators have argued that these studies should be obtained routinely for patients with bulky disease to avoid errors in lateral field design.<sup>309</sup> However,

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when all these factors are considered, differences in the volume treated with a four-field or

a high-energy two-field technique may be small. For this reason, some clinicians prefer to use the simpler technique for patients with bulky tumors.

Tumor response should be evaluated with periodic pelvic examinations to determine the best time to deliver brachytherapy. Some practitioners prefer to maximize the brachytherapy component of treatment and begin as soon as the tumor has responded enough to permit a good placement (with very bulky tumors this may still require greater than or equal to 40 Gy). Subsequent pelvic irradiation is delivered with a central block. A somewhat higher total paracentral dose can be delivered with this approach, but greater reliance is placed on the complex match between the brachytherapy dose distribution and the border of the central shield. This may result in overdoses to medial structures such as the ureters<sup>310</sup> or underdosage of posterior uterosacral disease.<sup>311</sup> For these reasons, other clinicians prefer to give an initial dose of 40 to 45 Gy to the whole pelvis, believing that the ability to deliver a homogeneous distribution to the entire region at risk for microscopic disease and the additional tumor shrinkage achieved before brachytherapy outweighs other considerations. However, external-beam doses of more than 40 to 50 Gy to the central pelvis tend to compromise the dose deliverable to paracentral tissues and increase the risk of late complications.<sup>154</sup>

## ROLE OF PARAAORTIC IRRADIATION.

The role of extended field irradiation in the treatment of cervix cancer is still being defined. Numerous small series of patients with documented paraaortic node involvement demonstrate that some enjoy long-term survival (see Table 36.2-5).<sup>77,80,140,161,162,163</sup> and <sup>164,166,167</sup> Patients with microscopic involvement have a better survival than do those with gross lymphadenopathy, but even 10% to 15% of patients with gross lymphadenopathy appear to be curable with aggressive management. Survival is also strongly correlated with the bulk of central disease. A 1991 study by Cunningham et al.<sup>167</sup> reported a 48% 5-year survival rate in patients who had paraaortic node involvement discovered at exploration for radical hysterectomy that was then aborted. This experience with patients who had small, radiocontrollable primary disease demonstrates that patients with paraaortic node metastases can often be cured if their primary disease can be sterilized. This indicates that patients may have extensive regional spread without distant metastases and provides an argument for surgical staging in high-risk patients.

Two randomized prospective trials have addressed the role of prophylactic paraaortic irradiation in patients without known paraaortic node involvement. In a study conducted by the Radiation Therapy Oncology Group, 367 patients with primary stage IIB or stage IB or IIA tumors more than 4 cm in diameter were randomly assigned to receive either standard pelvic radiotherapy or extended-field radiotherapy before brachytherapy.<sup>312</sup> No consistent method was used to evaluate the paraaortic nodes. For the 337 evaluable patients, absolute survival was significantly better for those treated with extended fields than for those treated with standard pelvic radiotherapy (67% vs. 55% at 5 years;  $P = .02$ ) (Fig. 36.2-7). There was no significant difference in disease-free survival ( $P = .56$ ).

**FIGURE 36.2-7.** Overall survival rates for patients with stage IB, IIA, or IIB carcinoma of the cervix

treated with irradiation to the pelvis alone or to the pelvic and paraaortic nodes on Radiation Therapy Oncology Group study 79-20. (Reprinted from ref. 312, with permission.)

A second trial, from the European Organization for Research and Treatment of Cancer, involved a similar randomization between pelvic irradiation and extended fields but had very different eligibility criteria.<sup>313</sup> This study included patients with bulky stage IIB (involving distal vagina or lateral parametrium) and III disease and patients with stage I disease or less bulky stage IIB disease who had positive pelvic nodes on lymphangiography or at surgery. The 4-year disease-free survival rates for patients treated with pelvic or extended fields were not significantly different (49.8% and 53.3%, respectively). However, the rate of paraaortic node recurrence was significantly higher in the pelvic field group, and for patients in whom local control was achieved, the rate of distant metastases was 2.8 times greater if treatment was with pelvic irradiation only ( $P < .01$ ).

Both studies revealed an increased rate of enteric complications in patients treated with extended fields. In the Radiation Therapy Oncology Group study,<sup>312</sup> most small bowel obstructions occurred in patients who had undergone pretreatment transperitoneal staging. The European Organization for Research and

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Treatment of Cancer<sup>313</sup> did not mention a relationship between surgical staging and enteric complications.

Taken together, these data clearly indicate that some paraaortic metastases are not detected by radiographic studies and that patients with occult disease can be cured if the paraaortic nodes are included in radiation fields. However, the addition of concurrent chemotherapy to the regimen of many patients with locally advanced disease increases the importance of careful selection of patients for large field irradiation because of the greater acute toxicity when chemotherapy is combined with extended-field radiotherapy.<sup>314,315</sup> and 316

## **BRACHYTHERAPY TECHNIQUE.**

Fletcher described three conditions that should be met for successful cervical brachytherapy: (1) the geometry of the radioactive sources must prevent underdosed regions on and around the cervix, (2) an adequate dose must be delivered to the paracervical areas, and (3) mucosal tolerance must be respected.<sup>317</sup> Although some clinicians have proposed a number of variations on the low-rate intracavitary brachytherapy techniques practiced at M. D. Anderson, Fletcher's conditions continue to dictate the character, intensity, and timing of brachytherapy for cervical cancer.

Brachytherapy is usually delivered using afterloading applicators that are placed in the uterine cavity and vagina. A number of different intracavitary systems have been used; in the United States, variations of the Fletcher-Suit-Delclos low dose-rate system are still used most commonly.<sup>293,317,318,319</sup> and 320 The intrauterine tandem and vaginal applicators are carefully positioned, usually with the patient under anesthesia, to provide



an optimal relationship between the system and adjacent tumor and normal tissues. Vaginal packing is used to hold the tandem and colpostats in place and to maximize the distance between the sources and the bladder and rectum. Radiographs should be obtained at the time of insertion to verify accurate placement, and the system should be repositioned if positioning can be improved. Encapsulated radioactive sources are inserted in the applicators after the patient has returned to her hospital bed, reducing exposure to personnel during applicator placement. Remote afterloading devices that further reduce personnel exposure are often used in departments that treat many patients with gynecologic disease. Although  $^{226}\text{Ra}$  was used to treat most patients before the 1980s, it has gradually been replaced by  $^{137}\text{Cs}$ , which produces a similar dose distribution and avoids the radiation protection problems caused by the radon gas by-product of radium decay.

### **Brachytherapy Dose**

Ideal placement of the uterine tandem and vaginal ovoids produces a pear-shaped distribution, delivering a high dose to the cervix and paracervical tissues and a reduced dose to the rectum and bladder (Fig. 36.2-8).

**FIGURE 36.2-8.** Posteroanterior and lateral views of a Fletcher-Suit-Delclos applicator system in a patient with invasive carcinoma of the cervix. Units on the isodose contours are cGy/h. A, point A; B, bladder reference point; R, rectal reference point.

Treatment dose has been specified in a number of ways, making it difficult to compare experiences. Paracentral doses are most frequently expressed at a single point, usually designated *point A*. This reference point has been calculated in a number of different ways, but it is usually placed 2 cm lateral and 2 cm superior to the external cervical os, in the central plane of the intracavitary system (see Fig. 36.2-8). Point A lies approximately at the crossing of the ureter and the uterine artery, but it bears no consistent relationship to the tumor or target volume. Point A was originally developed as part of the Manchester treatment system (a modification of the earlier Paris system). It was meant to be used in the context of a detailed set of rules governing the placement and loading of the intracavitary system. Today this context is often lost.

Other measures have been used to describe the intensity of intracavitary treatment. *Mg-hrs* or *mgRaEq-hrs* are proportional to the dose of radiation at relatively distant points from the system and therefore give a sense of the dose to the whole pelvis. In 1985 the International Commission on Radiation Units and Measurements recommended use of total reference air Kerma, expressed in mGy at 1 m, as an alternative to mg-hrs that allows for the use of various radionuclides.<sup>321</sup> The International Commission on Radiation Units and Measurements also defined reference points for estimating the dose to the bladder and

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rectum. These points have been widely, although not universally, accepted. Although normal tissue reference points provide useful information about the dose to a portion of normal tissue, several studies have demonstrated that they consistently underestimate the

maximum dose to those tissues.<sup>322,323</sup> and 324

Whatever system of dose specification is used, emphasis should always be placed on optimizing the relationship between the intracavitary applicators and the cervical tumor and other pelvic tissues. Source strengths and positions should be carefully chosen to provide optimal tumor coverage without exceeding normal tissue tolerance. However, optimized source placement can rarely correct for a poorly positioned applicator.

A detailed description of the characteristics of an ideal intracavitary system and of the considerations that influence source strength and position are beyond the scope of this chapter but can be found elsewhere.<sup>320,321,325</sup> However, an effort should always be made to deliver at least 85 Gy (with low dose-rate brachytherapy) to point A for patients with bulky central disease. If the intracavitary placement has been optimized, this can usually be accomplished without exceeding a dose of 75 Gy to the bladder reference point or 70 Gy to the rectal reference point, doses that are usually associated with an acceptably low risk of major complications.<sup>326,327</sup> The dose to the surface of the lateral wall of the apical vagina should not usually exceed 130 to 140 Gy.<sup>325</sup> Suboptimal placements occasionally force compromises in the dose to tumor or normal tissues. To choose a treatment that optimizes the therapeutic ratio in these circumstances requires experience and a detailed understanding of factors that influence tumor control and normal tissue complications.

A total dose (external-beam and intracavitary) of 50 to 55 Gy appears to be sufficient to sterilize microscopic disease in the pelvic nodes in most patients. It is customary to boost the dose to a total of 60 to 65 Gy in lymph nodes known to contain gross disease and in heavily involved parametria.

### ***Brachytherapy Dose Rate***

Traditionally, cervical brachytherapy has been performed with sources that yield a dose rate at point A of approximately 40 to 50 cGy/h. These low dose rates permit repair of sublethal cellular injury, preferentially spare normal tissues, and optimize the therapeutic ratio. In an effort to reduce the 3 to 4 days of hospitalization needed to deliver an appropriate dose of low dose-rate irradiation, some investigators have explored the use of *intermediate* dose-rate brachytherapy (80 to 100 cGy/h). However, in a randomized trial, Haie-Meder et al.<sup>328</sup> reported a significant increase in complications when the dose rate was doubled from 40 to 80 cGy/h, indicating that the total dose must be reduced and the therapeutic ratio of treatment may be compromised with higher dose rates. On the basis of laboratory studies, Amdur and Bedford have suggested that differences in the magnitude of the dose-rate effect between tumor and normal tissues may in part reflect differences in the half-times for repair of sublethal radiation damage.<sup>329</sup>

During the past two decades, computer technology has made it possible to deliver brachytherapy at very high dose rates (greater than 100 cGy/min) using a high-activity <sup>60</sup>Co or <sup>192</sup>Ir source and remote afterloading. High dose-rate intracavitary therapy is now being used for radical treatment of cervical cancer by a number of groups, including several in Japan, Canada, and Europe, and more recently by some groups in the United States.<sup>330,331,332,333,334,335,336,337</sup> and 338 Clinicians have found this approach

attractive because it does not require that patients be hospitalized and may be more convenient for the patient and the physician. However, unless it is heavily fractionated, high dose-rate brachytherapy loses the radiobiologic advantage of low dose-rate treatment, potentially narrowing the therapeutic window for complication-free cure.<sup>339,340</sup> Advocates of high dose-rate treatment disagree about the number of fractions and total dose that should be delivered. Published experiences suggest that survival rates are roughly similar to those achieved with traditional low dose-rate treatment, but these experiences are difficult to compare because of the same potential problems of selection bias that confound other nonrandomized comparisons.<sup>336,339</sup> Many of the retrospective reviews provide incomplete descriptions of tumor and treatment details.<sup>336</sup> Two purported randomized trials<sup>335,337</sup> also have been criticized for methodologic flaws. The use of high dose-rate brachytherapy for cervical cancer continues to be a source of controversy.

### **INTERSTITIAL BRACHYTHERAPY.**

Several groups have advocated the use of interstitial brachytherapy to treat patients whose anatomy or tumor distribution make it difficult to obtain an ideal intracavitary placement. Interstitial implants are usually placed transperineally, guided by a Lucite template that encourages parallel placement of hollow needles that penetrate the cervix and paracervical spaces; needles are usually loaded with <sup>192</sup>Ir. Advocates of the procedure describe the relatively homogeneous dose distribution achieved with this method, the ease of inserting implants in patients whose uteri are difficult to probe, and the ability to place sources directly into the parametrium. Early reports were enthusiastic, describing these theoretical advantages and high initial local control rates, but these early reports rarely included sufficient numbers of patients or had long enough follow-up to provide long-term survival rates.<sup>341,342,343,344</sup> and 345

In two of the larger early series, Syed and colleagues reported an encouraging projected 5-year survival rate of 53% for 26 patients with stage IIIB disease,<sup>345</sup> and Martinez and colleagues reported an 83% local control rate in 37 patients with stage IIB and IIIB disease.<sup>344</sup> However, survival results from two more recent reports have been disappointing. In a 1995 review of the combined experiences of Stanford and the Joint Center for Radiation Therapy, the 3-year disease-free survival rates for patients with stage IIB and IIIB disease were only 36% and 18%, respectively. Local control rates were 22% and 44%, respectively, and for patients with local control, the rate of complications requiring surgical intervention was high.<sup>346</sup> A 1997 report of the Irvine experience also described disappointing survival rates of 21% and 29%, respectively, for stage IIB and IIIB, again with a high rate of major complications.

Several groups have been exploring the use of transrectal ultrasound, MRI, or laparoscopic guidance,<sup>347,348</sup> and 349 interstitial hyperthermia,<sup>350</sup> and high dose-rate interstitial therapy<sup>351</sup> to improve local control and complication rates. However, outside of an investigational setting, interstitial treatment of primary cervical cancers should probably be limited to patients who cannot accommodate intrauterine brachytherapy and patients with distal vaginal disease that requires a boost with interstitial brachytherapy.

### **COMPLICATIONS OF RADICAL RADIOTHERAPY.**

During radiotherapy of the pelvis, most patients have mild fatigue and mild to moderate diarrhea that usually is controllable with antidiarrheal

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