Cervical Cancer: Prevention, Diagnosis, and Therapeutics

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ABSTRACT  Cervical cancer is a leading cause of cancer deaths in women worldwide. Because of its association with human papilloma virus infection, as well as the ability to screen for premalignant stages of the disease, it is now largely a preventable disease. This article describes the molecular basis for cervical cancer, and presents a clinical overview of current treatment approaches and technological advances, emphasizing the unique aspects of this viral disease as it relates to the immune system and vaccination or other immunotherapeutic strategies. (CA Cancer J Clin 2001;51:92-114.)

INTRODUCTION

Cervical cancer was the most common cause of cancer deaths in US women in the 1930s. With the introduction of the Papanicolaou (Pap) smear, however, early detection and treatment of preinvasive disease became possible. Incidence and mortality rates for cervical cancer in the US have declined dramatically during the remainder of the 20th century, with 12,900 new cases and 4,400 deaths estimated for 2001.

Worldwide, however, both incidence and mortality from cervical cancer are second only to breast cancer, and in parts of the developing world, cervical cancer is the major cause of death in women of reproductive age. This geographical disparity is related to the absence of effective screening programs, as epidemiologic and biological studies have not shown significant differences in tumor biology in countries with high rates of cervical cancer.

Few other solid tumors are as well understood from the epidemiologic and molecular biologic perspective as cervical carcinoma. Cervical cancer is largely a preventable disease with a known causative agent: Human papilloma virus (HPV). Although approximately 5% of cervical carcinomas may be unrelated to HPV, this ubiquitous virus is the key to understanding the natural history of this disease process and its relationship to the immune system. This known viral trigger (at the molecular level) and the well-described stages of disease progression make cervical carcinoma an ideal model for investigating potential immune therapies or adjuvant treatments.

From a clinical perspective, cervical cancer is readily managed in its early stages by surgery, with radiation or chemoradiation therapy reserved for high-risk early or advanced stages. Chemotherapy alone is generally ineffective against this relatively slow-growing disease. Vaccines and immunotherapy may be the most
promising additions to our current therapeutic inventory. Substantially more progress in our understanding of the basic disease process, however, must occur before these new modalities become standard treatment options.

RISK FACTORS AND EPIDEMIOLOGY

Classic Risk Factors

Young age at first intercourse, high number of sexual partners, high parity, cigarette smoking, race, and low socioeconomic status have consistently emerged as significant risk factors for cervical cancer.6,7,8 These, however, are linked to sexual behavior and the acquisition of HPV, and, except for smoking, none have consistently been shown to be significant independent risk factors.

There has been considerable controversy regarding the association between oral contraceptives and cervical cancer.9,10,11 While E6 and E7 HPV oncogene expression can be potentiated by estrogen in laboratory experiments,12-15 few epidemiologic studies of oral contraceptive use and cervical cancer have been able to control for the fact that women using oral contraceptives tend not to use barrier contraceptives and may have more sexual contacts.

A common practice pattern among some clinicians has been to stop oral contraceptives when an abnormal Pap result is reported. This practice can result in unplanned pregnancy just as the patient presents for diagnostic evaluation.
and management. The instruction to discontinue oral contraceptives also ignores the current understanding of the epidemiology and natural history of the disease.

Cigarette smoking (even passive smoke) has been linked to an increased risk of cervical cancer.\textsuperscript{16-19} Interestingly, any observed effect appears to be linked to squamous carcinomas and not adenocarcinomas or adenosquamous carcinomas.\textsuperscript{16} The presence of cigarette carcinogens in cervical mucus has been described as a possible biological explanation for the epidemiologic association.\textsuperscript{20-22}

\textbf{US Epidemiology}

Although the incidence of cervical cancer has fallen dramatically in the US, the trend has reversed since the mid-1990s. African-American women have also experienced a decline in incidence, but still suffer a 72% excess in incidence and 13% lower five-year survival rate compared with Caucasians.\textsuperscript{23} Another striking difference between racial groups is the continued rise in age-specific incidence for cervical cancer in African-Americans. While Caucasian women demonstrate an incidence that plateaus around 15 per 100,000 starting at age 45, the incidence in African-American women steadily rises to about 50 per 100,000 by age 85.\textsuperscript{23}

There are marked geographical variations in US mortality rates for cervical cancer. The Midwest, South, and particularly Appalachia, have the highest mortality rates, which may be attributed, in part, to rural and socioeconomic factors related to access to health care (Fig. 1).\textsuperscript{23}

\textbf{Rising Incidence of Adenocarcinoma}

The incidence of adenocarcinoma has more than doubled between the early 1970s and the mid-1980s among women younger than 35 years of age and currently accounts for more than 10% of all cervical cancers.\textsuperscript{24-26} It appears that this is not simply attributable to a relative decrease in squamous carcinomas prevented by good screening practices, but that there is a trend towards an absolute increase in adenocarcinomas and adenocarcinomas in situ (AIS) in younger women—which may account for the recent reversal in declining cervical cancer rates in the US. The cause of this trend is not known, and, as mentioned previously, studies suggesting the use of oral contraceptives as a contributing factor failed to control for the obvious confounding variables of barrier contraceptive use and number of sexual partners.\textsuperscript{20}

\textbf{ROLE OF HPV}

HPV is a double-strand DNA tumor virus that belongs to the papovavirus family (papilloma, polyoma, and simian vacuolating viruses).\textsuperscript{27} Papilloma viruses are ubiquitous in higher vertebrates, infecting, for example, parrots, rabbits, dogs, horses, cows, elk, deer, and even whales and manatees. The more than 80 human types are specific for epithelial cells including skin, respiratory mucosa, or the genital tract. Genital tract HPV types are classified by their relative malignant potential as low-, intermediate-, and high-risk types (Fig. 2).

Although the HPV is a central causative agent in cervical carcinogenesis, many other molecular alterations have been characterized that may not directly involve HPV. Alterations in the epidermal growth factor receptor and HER-2/neu (overexpression), H-ras and K-ras (mutation), and c-myc (amplification/overexpression) in squamous cervical cancers have been described with varying frequency.\textsuperscript{28-30} Whether these alterations are secondary to HPV-induced cell transformation or are part of the primary transforming events is uncertain. Nonetheless, the common, unifying oncogenic feature of the vast majority of cervical cancers is the presence of HPV.
Molecular Basis of Oncogenesis

The molecular basis for oncogenesis in cervical carcinoma can be explained to a great degree by the regulation and function of the two viral oncogenes E6 and E7. These two genes have been shown to possess transforming ability when transfected into cell lines.\textsuperscript{31,32} Furthermore, their constitutive expression is necessary for the maintenance of the malignant phenotype. Targeting the expression of E6/E7 has been shown to reduce the growth properties of cervical cancer cell lines and primary tumor explants,\textsuperscript{33} and represents a promising new approach for anticancer therapy.

The E6 and E7 genes are under the regulation of the E2 gene product. A characteristic, but not necessary, event in malignant transformation is the integration of the circular viral genome into the patient's genome. The E2 gene is often the site for integration, resulting in disruption of the E2 gene and subsequent derepression of E6 and E7.\textsuperscript{34}

The E6 gene product binds to the resident p53 tumor suppressor gene and induces p53 degradation. E7 targets another tumor suppressor, the retinoblastoma gene product (pRb).\textsuperscript{27,35,36} By binding to it and altering its phosphorylation state, it functionally inactivates this protein, which, like p53, functions in cell cycle control. Specifically, pRb normally binds the transcription factor E2F, which functions in cell cycle progression from G1 to the S phase following interaction with cyclins and cyclin-dependent kinases. The presence of E7 results in an inactive E7-pRb complex and disrupted binding of E2F to pRb, allowing E2F to bind DNA and induce cell growth and proliferation.\textsuperscript{37-39}

The ability of HPV E6/E7 to target the function of the p53 and pRb suppressors is not a unique phenomenon. Gene products of other DNA tumor viruses such as SV40 (large T antigen) and Adenovirus (E1A and E1B) have similar binding and inactivation activity against p53 and pRb.\textsuperscript{35,40} This fundamental pathway for inducing oncogenic transformation is depicted in Figures 3A and 3B.

HPV types

There are more than 80 types of HPV, of which about 25 infect the genital tract. HPV types are stratified into low-, intermediate-, and high-risk categories based on the strength of their association with high-grade and invasive lesions. The higher risk HPV types exhibit greater inactivation of p53 and pRb, and a single amino acid difference (aspartic acid in high-risk, glycine in low-risk viruses) accounts for the different binding affinities to pRb.\textsuperscript{41} The absence of HPV in about 5% of cervical carcinomas has been described as a negative prognostic factor.\textsuperscript{42}

Compared to the diverse pattern of mortality rates from cervical cancer seen around the world and within the US, there is relatively little variation in HPV types.
Interactions of HPV with histocompatibility antigens may help explain why the same HPV type leads to invasive cancer in one patient but not in another.

HPV16 comprises a greater proportion of squamous cervical carcinomas than does HPV18, while the converse is true for adenocarcinomas. HPV16 comprises a greater proportion of squamous cervical carcinomas than does HPV18, while the converse is true for adenocarcinomas. However, interesting associations between HLA and HPV are being described. One HLA class II locus (DR 1501) has been linked to a higher risk of HPV16 cervical cancer,43 while the DRB1 locus has been associated with HPV18 infections.46 Loss of an HLA class I locus B44 in precancerous lesions of the cervix has been associated with disease progression in HPV16 positive cases, and an HPV16 variant that may result in altered antigen presentation by HLA B7 has been described.47 Interactions of HPV with histocompatibility antigens may thus help explain why the same HPV type leads to invasive cancer in one patient but not in another. As more is understood regarding the interaction of the immune system and HPV, these associations will be delineated further and may lead to new screening or intervention strategies.

HIV AND CERVICAL CANCER

Human immunodeficiency virus (HIV) seropositivity in women with cervical cancer before the age of 35 is considered an acquired immune deficiency (AIDS)-defining illness by the Centers for Disease Control.48 It has been well established that cervical dysplasia in HIV-infected women is associated with more multifocal lesions and higher incidence, more rapid progression, and higher recurrence rates when compared with HIV-negative women.49,50 Furthermore, it is well known that HIV-positive women with invasive cervical cancer tend to have advanced stage disease, resistance to therapy, and shortened survival.51,52 Paradoxically, however, there is a missing link between the high prevalence/rapid progression of preinvasive cervical lesions and the actual development of invasive cervical cancer in HIV-infected women. There has been no consistently documented rise in the incidence of invasive cervical carcinomas in HIV-infected women. It is possible that many
of these women die of other causes before developing invasive cancers.

NEW SCREENING AND DETECTION MODALITIES

Screening for cervical neoplasia with the Pap smear is the most cost-effective cancer reduction program yet devised. In all populations in which it has been studied adequately, there is a direct relationship between the proportion of the population screened and declining incidence of cervical cancer and deaths from cervical cancer. While the Pap smear has been a tremendous cancer prevention success story, it is nonetheless a screening—not diagnostic—tool with a 15% to 25% false-negative rate for detecting cervical dysplasia.

The Bethesda System

The Bethesda System was originally proposed in 1988 and is now the most widely accepted nomenclature for Pap smears. Three major changes were introduced with this system:

1. HPV changes (koilocytosis) and mild dysplasias (CIN 1: cervical intraepithelial neoplasia 1) were combined into an “LGSIL” (low-grade intraepithelial neoplasia) category;
2. Moderate dysplasia, severe dysplasia, and
carcinoma in situ were combined into the “HGSIL” (high-grade squamous intraepithelial neoplasia) category;

3. A new term—“ASCUS” (atypical squamous cells of undetermined significance)—was introduced.

While the first two changes have had little clinical impact, the term ASCUS has led to an ongoing controversy about its exact meaning and implications. A 1993 College of American Pathologists survey of 900 laboratories found a median ASCUS rate of 2.8%, with 10% of labs reporting rates in excess of 9%. This has shifted a large burden of further diagnostic evaluation of Pap smears with some atypicality but no obvious dysplasia to the clinician, who must either repeat the Pap smear, or perform colposcopic evaluation.

In 12 studies published between 1994 and 1997, the median SIL rate based on biopsies performed after a cytologic diagnosis of ASCUS was 37%, with a range of 30% to 61%. The corresponding rate for HGSIL was 12%, with a range of 3% to 25%. Up to 50% of patients with invasive cancer or high-grade lesions are found to have ASCUS-only smears in the three years preceding their diagnoses, when reviewed retrospectively.

Frustrated physicians who are exposed to the overuse of ASCUS have derided this terminology as another acronym for “Don’t ask us,” or as a “wastebasket” term. In the literature, there has been frank discussion about the ASCUS “swamp” and the “Litigation Cell.” An alternative view is that ASCUS cells have always been present, but in the past were inconsistently reported as negative, reactive, or dysplasia, or with a hodgepodge of pre-Bethesda System terms as inflammatory atypia, minor atypia, squamous atypia, kiolocytotic atypia, etc. Consequently, these lesions were often inconsistently ignored or overtreated.

Although there is very significant inter-observer variability, even among experts, in the diagnosis of ASCUS, creation of morphologic criteria and standardized nomenclature for this category represents an important step toward improving consistency of cervical cytopathology and recognizing the limitations of the conventional Pap test. A key solution to this diagnostic and management problem is for clinicians to have good understanding of the diagnostic trends in their cytopathology laboratories, as well as the risk profile of their patient population.

Role of HPV Typing

Given the disparity between the prevalence of “low-risk” HPV subtypes in cervical carcinomas compared with low-grade lesions, it would seem logical that HPV typing could identify those atypical or dysplastic Pap smears that warrant aggressive treatment and those that can be followed conservatively. As shown by Borst et al., however, the relatively high prevalence of high-risk HPV subtypes in atypical and low-grade lesions (at least 50%) reduces the positive predictive value and makes sole reliance on HPV typing impractical. Syrjanen et al. observed that progression rates from HPV-detection to dysplasias ranged from 15% to 30% for HPV types 18 and 16, compared with 5% to 25% for types 6 and 11. Regression rates were about 30% for all viral types.

Although HPV typing cannot be recommended as a standard clinical practice, it may be clinically appealing for some clinicians when deciding between treatment or observation of mild dysplasia, psychologically reassuring both patient and physician that the “right decision was made.” In the presence of equivocal or atypical smears, a negative HPV test confers a negative predictive value greater than 98%. Thus, testing for the presence of HPV may, in some lower-risk populations, serve as a useful triage for ASCUS Pap smears by eliminating the need to further evaluate HPV-negative cases, as illustrated in Figure 4A.
Computerized Screening

Because human fatigue and error may be major contributors to false-negative readings of Pap smears, computer-assisted image analysis and artificial intelligence have been introduced as a means of improving the sensitivity of the Pap smear.

Two automated screening systems have been FDA-approved for use: AutoPap System (Neopath, Inc. Redmond, VA) and PapNet (PapNet, NetMed Inc., Columbus, OH). AutoPap, which reviews negative smears and selects a population at increased risk for abnormalities, was initially approved for quality control re-screening and most recently for primary screening. PapNet, on the other hand, is designed as an adjunct to manual screening by selecting the most abnormal 128 images on a slide for review.

The cost-effectiveness of these technologies is being studied and intensely debated. The...
costs of finding an additional case of LGSIL or higher with these technologies has been estimated to be in the range of $2,000-$4,000.66

**Liquid-Based Sampling Techniques**

Only about 20% of exfoliated cells obtained by a wooden spatula end up on a Pap smear slide. Interpretation is often confounded by the presence of inflammatory cells and debris. A recent “low tech” innovation that may significantly improve the detection of abnormal cells is the Thin-Prep, which allows liquid elution of exfoliated cells from a plastic sampling instrument, followed by filtering of cells to prepare a clean, representative distribution of cells for screening.

A similar technique is used by the AutoCyte PREP system (AutoCyte, Inc., Elon College, NC). In a split sample design, where the residual cells after standard smearing on glass slides were collected and processed by liquid techniques, the detection of dysplasia and invasive cancer was improved 31%, a statistically significant result.67 There was also a 39% reduction in “unsatisfactory” slides and 44% fewer “satisfactory but limited by” reports.

While the enhanced detection of Pap smear abnormalities may not yet be justified by the
additional costs of the cell preparation, this kind of innovation deserves further attention by the medical community, health insurers, and regulators. The PapNet, AutoPap, and Thin-Prep innovations are examples of refinements to the time-honored Pap smear technique. HPV typing, on the other hand, offers a discrete adjunct to the Pap smear screening system, and can readily be incorporated with the new liquid-based sampling techniques.69

Figure 4A presents an example of how these technologies (HPV typing and computerized re-screening) could be incorporated into an efficient and logical triage system. This kind of pre-colposcopy triage could potentially reduce the number of false-negative Pap smears, as well as the number of false-positive cases referred for colposcopy.

The cost-effectiveness of this type of algorithm for screening the general population has not been well established. It is possible that extending basic screening (using “low tech” technologies) to high-risk/underserved populations might prevent more cancers than screening or re-screening existing populations with “high tech” methods.

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**CONVENTIONAL TRIAGE OF ABNORMAL PAP SMEARS**

The conventional management of abnormal Pap smears has changed little in the past 10 years, and the fundamental treatment algorithm (Fig. 4B) has not significantly changed from the pre-Bethesda System era (pre-1988). An ASCUS reading on a Pap smear does not mandate specific actions by the clinician—the decision to proceed directly with colposcopy or to repeat the Pap smear is left to the practitioner.

Cost-benefit analyses have not established a superior choice, and most clinicians base their decisions on the risk profile of the individual patient. An indigent, HIV-positive patient with a history of dysplasia presenting to a teaching program colposcopy clinic with an ASCUS smear may not be an ideal candidate for a repeat Pap in three or four months; in contrast, it may be reasonable to instruct a compliant woman in a mutually monogamous relationship presenting with her first abnormal (ASCUS) smear to follow up with her physician in three or four months for a repeat Pap. In the former case, the chance of missing a significant lesion or losing the patient to follow-up is significant, while in the latter case, the risks of conservative management are substantially less.

The management of atypical glandular cells of undetermined significance (AGCUS) involves a higher index of suspicion and greater attention to possible endocervical or endometrial origins. Endocervical curettage is important in ruling out AIS or invasive adenocarcinoma, and cone biopsy may become necessary if no other explanation for AGCUS can be found. The “adenocarcinoma exception” will be discussed later as well.

The decision to treat mild dysplasia or CIN1 (LGSIL) again rests on the clinician’s index of suspicion. The two case scenarios described above can be applied to argue for treatment versus no treatment of LGSIL. HPV typing may aid in this decision-making process, although its general clinical utility remains debatable.

Moderate-severe dysplasia, or CIN2-3 (HGSILs) are still managed by excision or ablation (e.g., cryotherapy, Loop Electro-surgical Excision Procedures/LEEP, or laser...
vaporization). Carcinoma in situ may be managed by ablative methods if an expert colposcopist has ruled out a more extensive/invasive lesion, although LEEP excision is now commonly used for both diagnostic and therapeutic purposes. Cervical conization is usually reserved for suspected endocervical disease or microinvasion. While LEEP or laser instruments can accomplish a cone-shaped excision as well, cold-knife conization remains an important classic technique for obtaining an excellent diagnostic and therapeutic specimen.

Cure rates for standard ablative procedures range from 90% to 94%, and follow-up Pap smears every three to four months monitor for recurrences of dysplasia.

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**PRETREATMENT EVALUATION FOR INVASIVE CARCINOMA**

The initial workup and clinical staging of patients with invasive cervical cancer includes history and physical examination, chest radiography, intravenous pyelogram (IVP) or computed tomography (CT) scan, cystoscopy/proctosigmoidoscopy, and HIV testing (especially for the younger, at-risk patient). In small-volume disease, IVP or CT scan are done selectively, and some centers do not routinely use IVP/CT or cystoscopy/proctosigmoidoscopy for early stage I disease because of relatively low yield.

The CT scan has become increasingly popular in the workup and management of cervical cancer. Several authors have suggested its use in clinical staging; however, there are important limitations with its use. CT scans are unreliable in detecting subclinical parametrial disease and nodal metastasis less than 2 cm in diameter. In patients who are not candidates for surgical staging, however, a CT scan can be helpful in assessing nodal disease. Enlarged lymph nodes should be studied histo/cytologically by either surgical excision or fine-needle aspiration because of the 5% to 10% false-positive rate of CT.

More recently, magnetic resonance imaging has emerged as a radiologic modality capable of detecting early parametrial and nodal disease. Likewise, positron emission tomography scanning has been reported as a novel and useful way to predict para-aortic disease in locally advanced cervical carcinomas, with a sensitivity and positive predictive value of 75%, and a specificity and negative predictive value of 92%. Further experience is needed to establish the utility and cost-effectiveness of these technologies.

Because of infrequent colon involvement, the use of barium enema should be restricted to symptomatic patients. Routine bone scan is unproductive unless the patient complains of bone pain.

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**CLINICAL VERSUS SURGICAL STAGING**

Cervical cancer remains a clinically staged malignancy according to the International Federation of Gynecology & Obstetrics Staging System (FIGO; Table 1). Surgical-pathologic staging would not be feasible for advanced-stage disease or in early-stage patients treated primarily with radiation, especially in nations that do not routinely offer surgical extirpation due to limited health care resources.

The definition of microinvasive (Stage IA) cervical cancer proposed in 1973 by the Society of Gynecologic Oncologists (SGO) has now been partially incorporated into the new FIGO staging system. Stage IA1 now represents stromal invasion up to 3 mm deep and no wider than 7 mm. Stage IA2 is still defined by an upper limit of stromal invasion of 5.0 mm or less and horizontal spread of 7.0 mm or less. Lymph-vascular space invasion is not taken into consideration in the FIGO staging system.
Stage IB carcinomas are now divided into IB1 (less than 4 cm diameter) and IB2 (greater than 4 cm). The remainder of the staging classification is unchanged from the previous system.

Studies comparing clinical with surgical-pathologic staging (which includes status of lymph nodes) consistently have shown underestimation of disease extent by clinical staging. The FIGO staging system is based on the belief that cervical cancer is primarily a local disease in the pelvis, and that a surgical staging system cannot be widely employed worldwide, especially in developing countries.
or in parts of developed countries where surgical staging expertise is not readily available.

Surgical staging of cervical cancer, which includes pelvic and para-aortic lymphadenectomy, can provide potentially useful information for the radiation oncologist, who may be consulted postoperatively for administration of radiotherapy. Extraperitoneal approaches limit intraperitoneal adhesion formation and morbidity from radiation. Furthermore, surgical and pathologic data from staging laparotomies are important for precise analysis of survival and prognostic risk factors.

Some clinicians feel, however, that surgical staging should be confined to investigational settings because proven benefits to patients in terms of survival and pelvic control have been modest, at best. It is uncertain whether future staging systems will incorporate surgical and histopathologic variables to further refine the utility of surgical staging in clinical decision-making.

### MANAGEMENT OF INVASIVE DISEASE

#### Microinvasive, Stage IA1 Disease

According to the SGO, microinvasion is defined as squamous cell carcinoma invading the cervical stoma to a depth of 3 mm or less and in which there is no evidence of lymphatic or vascular space invasion and no confluence of invasive “tongues.” In the absence of lymph-vascular invasion, carcinomas invading to less than 3 mm (Stage IA1) have no more than a 1% chance of lymph node spread, thus allowing for conservative surgical resection of the primary tumor by simple extrafascial hysterectomy. Patients desiring to preserve fertility may be treated by cervical conization alone, provided that all conization margins are free of disease. The decision to proceed with conization versus extrafascial hysterectomy is based on the reproductive desires of the patient. In either case, nearly 100% cure rates are obtainable.

Currently, the presence of lymph-vascular invasion with less than 3 mm invasion does not alter the FIGO clinical staging, and its significance is debated. Most practitioners, however, favor radical surgery or radiation when faced with invasion of the lymph-vascular spaces.

#### The Adenocarcinoma Exception

The management of adenocarcinomas is fundamentally different for the preinvasive and early stages (I-IIA) of disease. AGCUS on Pap smear, unlike the ASCUS cells discussed previously, are often treated with a much higher index of suspicion, prompting consideration of cone biopsy and/or endocervical/endometrial sampling in addition to repeat Pap smear or colposcopy only. Similarly, AIS (versus squamous carcinoma in situ) should be treated more aggressively because of the possibility of skip lesions. Invasive adenocarcinoma has been found in 13% to 20% of hysterectomy specimens following cone biopsy for AIS, with 30% to 50% residual AIS in the hysterectomy specimens. Thus cone biopsy alone may be inadequate therapy for AIS, and hysterectomy should be considered in women who have completed childbearing. For women who do not undergo hysterectomy, even if cone margins were negative for AIS, close follow-up is warranted.

### Management of Stage IA2-IIA

#### Stage IA2

About 7% of all patients with cervical cancer invading the stroma to a depth of 3 to 5 mm (Stage IA2) have lymph node metastasis. Patients whose tumors invade the stroma more than 3 mm or have any lymph-vascular space involvement should be treated with radical
hysterectomy and lymphadenectomy or with radiation therapy.  

Stage IB

Patients with Stage IB1 (less than 4 cm) cervical cancer can be treated effectively by either radical hysterectomy with lymphadenectomy (pelvic ± para-aortic) or with radiation therapy. Although surgery and radiation therapy produce similar survival rates, radical hysterectomy is considered by many to be the treatment of choice for young, healthy patients with IB1 lesions. Excellent survival rates can be achieved in these patients along with preservation of ovarian function. Radiotherapy consisting of external and intracavitary radiation is indicated in those patients who have medical contraindications to radical surgery.

Stage IB2, or barrel-shaped cervical cancers, can be treated by radiation therapy alone or by radical hysterectomy and lymphadenectomy (pelvic ± para-aortic). However, many of these tumors extend anatomically beyond the curative isodose curve of radiation, and contain central hypoxic areas that are resistant to ionizing radiation. As a result, central recurrence rates for patients with Stage IB2 tumors treated with radiation therapy alone have been significant. Therefore, preoperative radiation therapy followed by extrafascial hysterectomy has been recommended by several groups. Since pelvic lymph node metastases are present in 20% to 25% of patients with Stage IB2 cervical cancers, para-aortic lymph node dissection should be considered at the time of extrafascial hysterectomy, especially if the para-aortic nodes were not included in the preoperative radiation fields.

In the first large prospective randomized trial since 1975 examining primary surgery versus primary radiotherapy for Stage IB-IIA disease, Landoni et al. concluded that overall survival (83%) and five-year disease-free survival (74%) for the two groups were the same. Those receiving radiation after radical hysterectomy, however, had the highest complication rates. There was significantly higher severe morbidity in the surgery (28%) compared with the radiotherapy (12%) group, but women with adenocarcinomas tended to do better with surgical approaches compared with those with squamous carcinomas.

Approximately 54% of surgical patients with tumors 4 cm or less and 84% with tumors larger than 4 cm ultimately required adjuvant radiotherapy. Given the significantly higher morbidity of combined modality therapy, some have questioned whether stricter surgical selection criteria would eliminate much of the morbidity without compromising survival. With the improvements in disease control offered by combined chemoradiation therapy, to be discussed below, the debate over surgery versus radiation is being completely redefined to consider the relative merits of surgery, radiation, and chemotherapy in various combinations.

Chemotherapy alone is generally ineffective for cervical cancer, but Curtin et al. reported on a randomized multicenter trial of adjuvant chemotherapy (cisplatin and bleomycin) versus chemotherapy plus pelvic irradiation for high-risk patients who underwent radical hysterectomy for Stage IB-IIA disease. The addition of radiotherapy did not influence recurrence rates or patterns of recurrence (local, regional, or distant), suggesting that adjuvant chemotherapy played an important role. There was, however, no comparison with a radiation-only or no treatment group, leaving many questions unanswered.

A role for adjuvant radiotherapy in high-risk surgical patients is supported by the results of a randomized trial by the Gynecologic Oncology Group (GOG) Study 92. In evaluating 277 women with Stage IB disease who had at least two risk factors—large tumor size, deep
stromal invasion, or lymph-vascular space involvement—adjuvant radiotherapy after radical hysterectomy reduced the recurrence rate by 47%.

With 87% surviving in the radiotherapy group compared with 79% in the “no further therapy” group, it can be inferred that about one in 12 irradiated patients obtained a survival benefit. On the other hand, there was a trade-off: About one in 15 patients who received radiation therapy experienced severe or life-threatening radiation-related toxicities.

The unreported effects of adjuvant radiotherapy in this setting include vaginal stenosis or sexual dysfunction and must be considered when counseling patients. Thus, despite the positive finding in GOG 92, options regarding adjuvant radiotherapy for surgical patients with selected risk factors remain debatable. Furthermore, the emerging role of chemoradiation will force a re-evaluation of this debate, as adjuvant radiotherapy is, de facto, being converted to adjuvant chemoradiation in light of the latter’s success in clinical trials of locally advanced cervical cancer.

### Stage IIA

The optimal treatment for most patients with Stage IIA cervical cancer is radiation therapy consisting of a combination of external and intracavitary therapy. However, patients can also be treated effectively by radical hysterectomy with pelvic and para-aortic lymphadenectomy and upper vaginectomy, provided that adequate surgical margins can be obtained.
Chemoradiation for Locally Advanced (Stage IIB-IVA) and High-Risk Early-Stage Disease

In February 1999, the National Cancer Institute mailed all US physicians a national clinical advisory announcing the results of five clinical trials that demonstrated superiority of combined platinum-based chemoradiation compared with radiation alone for locally advanced (Stage IIB-IVA),95-97 high-risk early-stage (IA2-IIA),98 or bulky Stage IB299 cervical carcinomas (Table 2). This NCI announcement represents a major paradigm shift in cervical cancer radiotherapy, and pre-publication versions of some manuscripts were posted on the Internet due to their “possible implications for the public health.”

All of these clinical trials incorporated cisplatin as a component of chemoradiation, but despite strong consensus that chemoradiation is superior to radiation alone, there is no consensus about what constitutes the best chemotherapy regimen. In GOG 120, a phase III trial of women with FIGO Stages IIB-IVA cervical cancer, Rose et al.97 reported equivalent 65% 35-month survivals for the concurrent weekly cisplatin and 5-fluorouracil/cisplatin/hydroxyurea arms, compared with the 47% survival rate in the radiation-only arm. Although the concurrent weekly cisplatin therapy was a superior—as well as the best-tolerated—chemoradiation regimen in that study, the hydroxyurea contributed to the increased toxicity of the three-drug regimen and confounded attempts to determine the efficacy of 5-FU in combination with cisplatin.

As a result of the NCI clinical advisory, the GOG replacement protocol 165 subsequently dropped the radiation-only arm of its concurrent weekly cisplatin versus concurrent protracted 5-FU infusion versus radiotherapy alone phase III trial. Unfortunately, this study, too, does not address the question of 5-FU/cisplatin efficacy.

Doses for cisplatin in RTOG 9001 were 75 mg/m² on days 1 and 22 of external beam irradiation, followed by a 96-hour continuous infusion of 5-FU. In contrast, the GOG 120 study used cisplatin at 50 mg/m² on days 1 and 29 followed by the same 5-FU infusion, except that hydroxyurea was included with the 5-FU arm.97 Thus, it is not possible to compare regimens among the different studies, and the optimal cisplatin-containing chemoradiation regimen is still being debated and investigated.

Stage IVA Surgical Options

Stage IVA disease is rare, particularly with extension to the rectal mucosa. Treatment aimed at pelvic control usually consists of radical chemoradiation. In a rare patient with central pelvic disease only extending into the bladder mucosa, exenterative surgery may be chosen instead of primary irradiation. For patients who have persistent central disease after definitive chemoradiation or who have significant tumor or radiation-induced vesicovaginal or rectovaginal fistulae, exenteration may serve a curative or palliative role.

MANAGEMENT OF RECURRENT DISEASE

Overall, fewer than 5% of patients who develop recurrent carcinoma of the cervix are alive five years later.100,101 Patients who develop a pelvic recurrence after a radical hysterectomy, however, have up to a 40% five-year survival when treated with radiation therapy. Even patients with isolated late lung metastasis have a 25% five-year survival rate with surgical resection.69

Patients with central pelvic recurrences after primary treatment with radiation therapy may be salvaged with surgery. Those with small recurrences limited to the cervix or upper vagina can occasionally be treated with radical hysterectomy and partial
vaginectomy, with excellent results. Patients with larger central recurrences or who received previous very high doses of radiation therapy frequently have marked fibrosis between the bladder and/or rectum and the uterus that requires a pelvic exenteration for surgical salvage.

One-third of patients with negative pelvic lymph nodes and free surgical margins survive five years after pelvic exenterations. Recently, more attention has been directed to reconstructive procedures performed at the time of pelvic exenteration to improve quality of life. These include performing continent urinary conduits, primary colon reanastomosis, and vaginal reconstruction. When radiation or surgery is unable to cure recurrent disease, chemotherapy remains an option with limited efficacy. Cervical cancer, in general, is a slow-growing neoplasm with poor response to chemotherapy. Platinum remains the conventional choice for treating recurrences, although phase II trials are currently examining the efficacies of a broad range of compounds including, for example, unconventional agents (tamoxifen) and naturally derived agents (topotecan, paclitaxel, and bryostatin).

Combination therapy with agents such as paclitaxel and cisplatin, has been studied in phase II trials of recurrent or advanced squamous cell cancer of the cervix, with 12% complete responses and 34% partial response rates, although 61% of patients experienced grade 4 neutropenias and two patients (4.5%) died from neutropenic sepsis. Given the palliative nature of chemotherapy in the setting of recurrent disease, however, quality of life and toxicity profiles must be factored into the choice of agents.

**MONITORING FOR RECURRENT DISEASE**

As the majority of treated patients who develop recurrences do so in the first two years following primary therapy, physical examination including nodal assessment (especially supraclavicular), rectovaginal examination, and Pap smears should be performed at three-to-four-month intervals during this time. Thereafter, semiannual examinations are appropriate and beyond five years, annual examinations.

Symptoms of pain, vaginal bleeding, and gastrointestinal or genitourinary dysfunction must be promptly investigated. Interval abdominal-pelvic CT scans should be considered in those considered at high risk of recurrence, especially in the first two years. CT scans or IVPs post-treatment may also diagnose ureteral obstruction (pathologic or treatment-related) at potentially early stages. Interval chest X-ray or bone scans, however, are unlikely to benefit the patient because in most cases, they would be detecting incurable disease in the asymptomatic patient.

**CHEMOPREVENTION, VACCINATION, AND IMMUNOTHERAPY**

**Chemoprevention**

The relatively long premalignant phase of cervical carcinogenesis (five to 10 years) allows great opportunities for intervention with conservative measures and represents a large window for chemoprevention or vaccination to impact upon disease progression. The relatively long premalignant phase of cervical carcinogenesis (five to 10 years) allows great opportunities for intervention with conservative measures and represents a large window for chemoprevention or vaccination to impact upon disease progression. Cervical dysplasia is traditionally treated by ablative procedures, but biologic response modifiers have been investigated as...
conservative patient-applied therapeutic options. Although external warts of non-mucosal epithelia can now be treated by patient-applied podophyllotoxins (Condylox) or the novel immune stimulator imiquimod (Aldara), these agents are not currently suitable for application into the mucosal vaginal vault. Instead, investigators have focused on the retinoids as chemotherapeutic agents for cervical dysplasia based on their cell differentiating properties.106

Topical all-trans-retinoic acid has been shown to induce regression of mild and moderate dysplasias, but not advanced dysplasias, in a randomized phase III clinical trial.107 Other suitable agents for chemoprevention may include difluoromethylornithine and beta-carotene.

The cervix is an ideal, accessible organ not only for chemoprevention studies, but also for the study of squamous carcinogenesis. Cervical lesions are accessible and can be safely followed with Pap smears and colposcopy, perhaps supplemented by appropriate biomarkers.

Cervical biomarkers currently under study include proliferation markers (PCNA), regulation markers (growth factor receptors, ras, myc, p53, retinoic acid receptors, spermidine/spermine ratios), differentiation markers (involucrin, cornifin, keratins), and markers of genetic instability (chromosome polysomy).108

Vaccination

Given the viral nature of the vast majority of cervical cancers, it would seem that a vaccine would be the ideal cancer preventive. In mouse studies, HPV vaccines have been shown to produce cytotoxic T-cell responses that not only eradicate HPV-bearing tumors, but also protect against subsequent challenge by tumor.109

Vaccines targeting the outer surface of the virus might offer protection against infection, but would be ineffective against established HPV-bearing lesions. The L1 capsid protein has been targeted for neutralizing-antibody formation using a DNA or polynucleotide vaccine in the Cottontailed Rabbit Papilloma Virus model.110

An oral vaccine using “virus-like particles” (VLPs) induced IgG and IgA antibodies in mice, demonstrating the potential antigenic stability of VLPs in the gastrointestinal tract and the possibility of developing this approach for large-scale vaccination of human populations.111 Human clinical vaccine trials with HPV VLPs have begun; complete regression of genital warts was observed in 25 of 33 patients who were vaccinated with an HPV6b VLP that stimulated a potent immune response to the L1 capsid protein.112

Other HPV vaccine efforts are focused on targeting the oncogenic E6/E7 proteins as therapeutic vaccines. The NCI and the Leiden University Medical Center have embarked on an E6- or E7-based vaccine strategy designed to stimulate T-cell immunity.113 These peptide vaccines are designed to stimulate cytotoxic T-lymphocytes against specific E7 epitopes that have been shown to be conserved and constitutively expressed in cervical cancers. The NCI trial was based on a lipitated E7 peptide, while the Leiden group used peptides with immune adjuvants. Both groups are focusing on HPV16 in HLA-A2 positive patients. Thus, this HPV type and HLA restriction limits the immediate applicability to all cervical cancer patients.

Vaccinia virus constructs carrying mutated E6 or E7 may vaccinate without HLA restriction. At the University of Wales, eight patients with advanced cervical cancer received a vaccinia virus with a mutant HPV18 E6/E7 fusion gene with no toxic side effects. Three of eight developed an HPV-specific antibody response, and one of three evaluable patients developed HPV-specific cytotoxic T lymphocytes.114
An alternative strategy that circumvents HLA restriction by peptides involves heat shock protein (HSP) vaccines. HSP can chaperone multiple peptides into the patient’s antigen-presenting cells for potent immune presentation in the context of the proper HLA type, which makes them potentially useful as “messenger” vaccines. Another advantage for HSP vaccines is that multiple epitopes of HPV can be bound to the HSP. Since immune evasion by tumors often involves “antigen escape” by mutation, a vaccine based on multiple epitopes should be more effective for large-scale use and for preventing individual antigen escape.

**Immunotherapy**

The T-cell vaccine approach serves both protective and therapeutic functions. These vaccines are designed to stimulate HPV-specific cytotoxic T lymphocytes (CTLs) within the patient. An alternative approach called “adoptive immunotherapy” reconstitutes the vaccination process in the laboratory to stimulate and grow CTLs in large quantities. The induction and proliferation of CTLs in the laboratory can be controlled by addition of cytokines, and the ability to remove these T cells from the host, who may be harboring immune-suppressive factors produced by cervical cancer, represents another advantage over the vaccine approach. The CTLs produced can be re-infused into the patient in massive amounts to overwhelm the tumor with tumor-specific killer cells. It is estimated that this approach can result in a more than 10-fold greater induction of T-cells than can be obtained by vaccinating the patient. The exogenous infusion of T cells would allow this natural limit to be exceeded in hopes of obtaining more effective tumor control.

A number of investigators have been able to produce HPV-specific human CTLs in the laboratory, but technical limitations must be overcome to enable the survival, cloning, and expansion of these CTLs on a scale that is required for adoptive immunotherapy. T-cells inherently undergo apoptosis after a certain amount of stimulation, and genetic engineering of CTLs may be required to circumvent the immune system’s natural regulatory mechanisms. In this sense, CTL therapy seeks to create an “autoimmune” disease that targets only HPV-infected cells in the body.

If T-cell deficiency in AIDS accounts for rapid progression of cervical cancer, T-cell enhancement by vaccination or adoptive immunotherapy may lead to better disease control in otherwise healthy patients with cervical cancer. Although in vitro vaccination shares the same fundamental immunologic basis as in vivo vaccination, modern laboratory immunology techniques and conditions may overcome barriers to vaccination that occur within the affected host.

**CONCLUSION**

Cervical cancer is a disease of significant worldwide morbidity and mortality. From an epidemiologic and cancer prevention
perspective, great strides have been made in the developed world towards dramatically reducing the incidence and mortality from this disease.

Surgical, radiotherapeutic, and more recently, chemoradiotherapeutic approaches comprise the successful treatment modalities for invasive cervical carcinoma. Further efforts at early detection and prevention, however, are likely to produce even more significant gains. Computers, artificial intelligence, and molecular biology are beginning to merge at the clinical level to refine and enhance the cervical cytoclogic assessment developed by George Papanicolaou in the middle of the 20th century.

The well-characterized viral mechanisms for cervical carcinogenesis have established the basis for future development of HPV-specific therapies. The new century may bring prevention in an entirely different form: Vaccination. Benign genital warts are already being effectively treated with immune modulators (interferons, imiquimod), and further developments in tumor immunobiology may yield immunotherapies that can affect the malignant end of the HPV life cycle.
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