NIH Consensus Statement

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Cervical Cancer

NATIONAL INSTITUTES OF HEALTH
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This statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

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Abstract

Objective

To provide physicians and the general public with a responsible assessment of current screening, prevention, and treatment approaches to cervical cancer.

Participants

A non-Federal, nonadvocate, 13-member panel representing the fields of obstetrics and gynecology, gynecologic oncology, radiation oncology, and epidemiology. In addition, 28 experts in obstetrics and gynecology, gynecologic oncology, radiation oncology, gynecologic surgery, and psychology presented data to the panel and a conference audience of 500.

Evidence

The literature was searched through Medline and an extensive bibliography of references was provided to the panel and the conference audience. Experts prepared abstracts with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience.

Consensus Process

The panel, answering predefined questions, developed its conclusions based on the scientific evidence presented in open forum and the scientific literature. The panel composed a draft statement that was read in its entirety and circulated to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after the conference.

Conclusions

Carcinoma of the cervix is causally related to infection with the human papillomavirus (HPV). Reducing the rate of HPV infection by changes in sexual behaviors in young people and/or through the development of an effective HPV vaccine would reduce the incidence of this disease. Pap smear

screening remains the best available method of reducing the incidence and mortality of invasive cervical cancer. Persons with stage IA1 disease have a high cure rate with either simple hysterectomy or, where fertility preservation is an issue, by cone biopsy with clear margins. For patients with other stage I and stage IIA disease, radical surgery and radiation are equally effective treatments. These patients should be carefully selected to receive one treatment or the other but not both, as their combined use substantially increases the cost and morbidity of treatment. Women with more advanced, nonmetastatic disease should be treated with radiation. Recurrent cervical cancer confined to the pelvis should be treated with the modality not previously received. Radiation is recommended to palliate symptoms in patients with metastatic disease.

Introduction

Carcinoma of the cervix is one of the most common malignancies in women, accounting for 15,700 new cases (6 percent of all cancers) and 4,900 deaths in the United States each year. Worldwide, cervical cancer is second only to breast cancer as the most common malignancy in both incidence and mortality. More than 471,000 new cases are diagnosed each year, predominantly among the economically disadvantaged, in both developing and industrialized nations. During the last 50 years in the United States, the utilization of screening programs based on the Papanicolaou (Pap) smear and pelvic examination has led to a steep decline in incidence and deaths from cervical cancer.

Both invasive cervical cancers and precursor lesions have been firmly associated with the presence of human papillomavirus (HPV) DNA. It has also been well established that the majority of squamous cell cancers of the cervix progress through a series of well-defined preinvasive lesions and that during this usually lengthy process, the disease can be easily detected by Pap smear screening. During this preinvasive stage, cervical squamous intraepithelial lesions (SIL) can be controlled with nearly uniform success and with the retention of fertility.

Many treatment and quality-of-life issues remain unresolved for women with cervical cancer. For women with early-stage disease, key issues include determining guidelines for the extent of treatment, the pathologic and clinical indicators for the intensity of therapy, and the selection of a treatment modality among several competing options. For women with advanced-stage disease, critical issues include optimal radiotherapy techniques, whether chemotherapy or combined modality regimens improve outcome, the morbidity and benefit of salvage therapy for recurrent disease, and palliative treatment. Additional topics include advances in screening technology, the implementation of The Bethesda System for Pap smears, the role of HPV testing and subtyping, treatment selection for patients with preinvasive disease, advances in laparoscopic surgical staging and therapy techniques, and the application of newer imaging techniques such as magnetic resonance. Prospects for both prophylactic and therapeutic

vaccines against HPV offer hope for fundamental alterations in the prevention and management of this disease.

To address these and related issues, the National Cancer Institute and the NIH Office of Medical Applications of Research convened a Consensus Development Conference on Cervical Cancer. The conference was cosponsored by the National Institute of Nursing Research, the National Institute of Allergy and Infectious Diseases, the Office of Research on Minority Health and the Office of Research on Women's Health of the NIH, and the Centers for Disease Control and Prevention.

After 1 1/2 days of presentations and audience discussion, an independent, non-Federal consensus panel weighed the scientific evidence and developed a draft statement that addressed the following key questions:

- How can we strengthen efforts to prevent cervical cancer?
- What is the appropriate management of low-stage cervical cancer (FIGO stages I–IIA)?
- What is the appropriate management of advanced-stage and recurrent cervical cancer?
- What are new directions for research in cervical cancer?

How Can We Strengthen Efforts to Prevent Cervical Cancer?

A strong causal relationship between HPV and cervical cancer and its precursors has been established. The evidence for this statement is as follows:

- HPV DNA is present in virtually all cases (93 percent) of cervical cancer and its precursor lesions.
- Multiple epidemiological studies indicate that HPV infection is the major risk factor for squamous intra-epithelial lesions (SIL) and invasive cervical carcinoma.
- Studies have demonstrated that the HPV genes E6 and E7 are integrated into the host genome and that the transforming proteins encoded by these genes are tumorigenic.

More than 70 types of HPV have been identified. However, only 23 of these infect the uterine cervix; of these, only one-half are associated with SIL or invasive cervical cancer. These are further classified into low-risk types, HPV 6 and 11, and high-risk types, most commonly 16, 18, 31, and 45, which account for more than 80 percent of all invasive cervical cancers. An unknown percentage of women infected with HPV will develop either low-grade SIL (LSIL) or high-grade SIL (HSIL). One-third of all grades of SIL will regress, whereas 41 percent persist and 25 percent progress. Of lesions that progress, 10 percent progress to carcinoma in situ and 1 percent to invasive cancer. Three-quarters of all grades of SIL will not progress.

This virus is transmitted through sexual intercourse, with a peak prevalence of infection in women in the 22–25-year age group. The prevalence of infection decreases with increasing age suggesting that most infections in women and men resolve over time through host immune responses.

Epidemiologic studies are now focusing on cofactors and host factors that may explain the natural history of HPV infections and their associated lesions. Factors under investigation include smoking; use of hormonal contraceptives; number of live births; young age at first sexual intercourse;

use of vitamins such as carotenoids, vitamin C, and folic acid; co-infection with other sexually transmitted diseases (e.g., herpes simplex, HIV, chlamydia); growth factors; cytokines; and humoral and cellular immunity.

Screening

Squamous cell cervical cancer is an ideal disease for screening because of the typically long preclinical phase, which permits early detection. Use of the Pap smear is effective in reducing morbidity and mortality from cervical cancer. Despite the recognized benefits of Pap smear screening, substantial subgroups of American women have not been screened or are not screened at regular intervals. One-half of the women with newly diagnosed invasive cervical carcinoma have never had a Pap smear, and another 10 percent have not had a smear in the past 5 years.

The unscreened populations include older women, the uninsured, ethnic minorities, especially Hispanics and elderly blacks, and poor women, particularly those in rural areas. One-fourth of the cases of cervical cancer and 41 percent of the deaths occur in women age 65 and older. Data from the 1992 National Health Interview Survey indicate that one-half of all women age 60 and older have not had a Pap smear in the past 3 years. Although older women are screened less frequently, they have the same number of recent physician visits as younger women, which indicates the need to educate older women and their health care providers about the importance of Pap smear screening. For patients who are not involved in routine screening programs, any health care encounter should be an opportunity to obtain a Pap smear and offer other screening modalities. On the other hand, recent evidence demonstrates that the gap in the incidence of cervical cancer between black and white women under age 50 is disappearing, suggesting that the rate of screening has increased among young black women.

To improve outreach to unscreened populations, reasons for nonparticipation in screening must be determined and addressed with appropriate interventions. Community-based approaches to reaching diverse ethnic populations

are recommended and should include using community leaders and members to assess attitudes and concerns prior to instituting screening programs, and as part of the process of education and awareness. Culturally sensitive and linguistically compatible staffing for outreach and screening is a key component.

Logistical problems associated with screening in both metropolitan and rural settings should be addressed during outreach planning (e.g., transportation, child care, duration of appointments, multiple site referrals, accessible screening sites). Options such as mobile screening services and incentives should be considered.

A concerted effort to standardize Pap smear terminology resulted in The Bethesda System (TBS) (Table 1). TBS evaluates the specimen for adequacy, uses diagnostic terminology, and makes recommendations pertaining to the smear when necessary. Determining the adequacy of the specimen is a major contribution, because retrospective reviews of smears from women with cervical cancer have shown that many were unsatisfactory. Smears may be unsatisfactory for a variety of reasons, the most common of which are obscuring blood or inflammation. Evaluation of others may be less than optimal because of factors such as absence of sampling from the transformation zone.

Among the diagnostic terminologies are LSIL and HSIL. Another category of abnormal squamous cells is atypical squamous cells of undetermined significance (ASCUS). Management modalities for HSIL are established and include colposcopy-directed biopsy and endocervical curettage followed by conization with scalpel, cautery, laser, or loop electrocautery excision procedure. Management modalities for ASCUS and LSIL are not as uniform. A large clinical trial is currently under way to determine whether HPV testing can effectively triage these patients, to develop clinical management guidelines and provide prognostic information, and to identify areas for cost reduction in screening and treatment. The glandular cell abnormalities are divided into two categories, atypical glandular cells of undetermined significance (AGUS) and adenocarcinoma.

Table 1

The 1991 Bethesda System

Adequacy of the Specimen

- Satisfactory for evaluation
- Satisfactory for evaluation but limited by (specify reason)
- Unsatisfactory for evaluation (specify reason)

General Categorization (Optional)

- Within normal limits
- Benign cellular changes; see descriptive diagnosis
- Epithelial cell abnormality; see descriptive diagnosis

Descriptive Diagnoses

- Benign cellular changes
  - Infection
    - *Trichomonas vaginalis*
    - Fungal organisms morphologically consistent with Candida sp
    - Predominance of coccobacilli consistent with shift in vaginal flora
    - Bacteria morphologically consistent with Actinomyces sp
    - Cellular changes associated with herpes simplex virus
    - Other
  - Reactive changes
  - Reactive cellular changes associated with:
    - Inflammation (includes typical repair)
    - Atrophy with inflammation ("atrophic vaginitis")
    - Radiation
    - Intrauterine contraceptive device (IUD)
    - Other
- Epithelial cell abnormalities
  - Squamous cell
    - Atypical squamous cells of undetermined significance (ASCUS): qualify*
  - Low-grade squamous intraepithelial lesion (LSIL) encompassing HPV** mild dysplasia/CIN 1
  - High-grade squamous intraepithelial lesion (HSIL) encompassing moderate and severe dysplasia, CIS/CIN 2, and CIN 3
    - Squamous cell carcinoma
  - Glandular cell
    - Endometrial cells, cytologically benign, in a postmenopausal woman
    - Atypical glandular cells of undetermined significance: qualify*
    - Endocervical adenocarcinoma
    - Endometrial adenocarcinoma
    - Extrauterine adenocarcinoma
    - Adenocarcinoma, not otherwise specified
- Other malignant neoplasms: specify
- Hormonal evaluation (applies to vaginal smears only)
  - Hormonal pattern compatible with age and history
  - Hormonal pattern incompatible with age and history; specify
  - Hormonal evaluation not possible due to...(specify)

*Atypical squamous or glandular cells of undetermined significance should be further qualified as to whether a reactive or a premalignant/malignant process is favored.

**Cellular changes of HPV (previously termed "koilocytotic atypia" or "condylomatous atypia") are included in the category of low-grade squamous intraepithelial lesion.

Methods of specimen acquisition, preparation, and evaluation of the Pap smear have changed little since its introduction in the 1940's. Although it is highly effective in screening for preinvasive lesions of the cervix, a single test has a false-negative rate estimated to be 20 percent. One-half of the false negatives are due to inadequate specimen sampling, and the other half are attributed to a failure to identify the abnormal cells or to interpret them accurately. Pap smears should be obtained in conjunction with a pelvic examination. If a gross lesion is visualized, it should be biopsied, as a Pap smear alone is inadequate in this situation.

To improve the adequacy of the cervical smear specimen, a variety of sampling devices is available (e.g., spatula, endocervical brush, broom, and cotton swab). Liquid-based specimen collection methods are currently being evaluated to improve sampling and cell preservation and presentation.

In fall 1995, the Food and Drug Administration (FDA) approved two automated instruments for rescreening smears evaluated as negative on the initial screen. Data from clinical trials suggest that these could reduce the rate of false–negative smears. Neither the efficacy in routine practice nor the cost-benefit of these devices has been determined. In addition, these and other devices are being evaluated for use as primary screening instruments.

In 1988 a group of experts recommended that annual Pap smears and pelvic examinations begin at onset of sexual activity or age 18. After three consecutive normal examinations, the interval between screenings may increase at the discretion of the physician and patient. In 1995, the American College of Obstetricians and Gynecologists (ACOG) recommended that patients with one or more risk factors for cervical cancer (e.g., HIV or HPV infection, a history of LSIL, high-risk behavior) be screened annually. Women over the age of 65 should continue to be screened.

Prevention

Primary prevention of HPV infection will require (1) directing education efforts toward adolescents and health care providers regarding the strong causal link between acquisition of

HPV as a sexually transmitted disease and development of cervical cancer and its precursors, (2) encouraging delayed onset of sexual intercourse, (3) developing an effective prophylactic vaccine, and (4) developing effective vaginal microbicides. The data on the use of barrier methods of contraception to prevent the spread of HPV are controversial but do not support this as an effective method of prevention.

Secondary prevention efforts must focus on (1) developing effective antiviral agents to treat HPV and/or prevent transformation by E6/E7, (2) developing therapeutic vaccines to prevent HPV progression, (3) improving the sensitivity and specificity of screening for the precursors of cervical cancer, and (4) expanding education and screening programs to target underreached populations.

What Is the Appropriate Management of Low-Stage Cervical Cancer (FIGO Stages I–IIA)?

Table 2 lists the staging criteria based on the International Federation of Gynecologists and Obstetricians (FIGO) staging system for cervical cancer.

The diagnosis of stage IA1 cervical squamous cell carcinoma should be based on cone biopsy, not punch cervical biopsy, preferably by using a technique that does not result in cauterized margins. Systematic pathologic evaluation of the cone specimen is necessary. Where early invasion is identified, serial sections may be necessary to determine the extent of maximal depth of invasion, lateral involvement, and the presence of lymph vascular invasion. In patients with stage IA1 cervical squamous cell carcinoma, simple hysterectomy or cone biopsy (with negative margins) is virtually 100 percent curative of patients. The choice of therapy should be influenced by the patient's desire to preserve fertility. Although lymph vascular involvement is generally considered to be an adverse prognostic factor in cervical cancer, the prognostic significance of lymph vascular involvement in stage IA1 cervical squamous cell carcinoma is uncertain. Because of this uncertainty, some clinicians have suggested that the presence of lymph vascular involvement in stage IA1 disease might be more appropriately treated with either radical hysterectomy or radiation therapy.

At our present state of knowledge, a category of cervical adenocarcinoma that could be treated conservatively in order to preserve fertility cannot be identified. This needs further investigation.

Patients with IA2 lesions can be treated with primary radical or modified radical hysterectomy or primary radiation therapy with equivalent results. The choice of therapy should be influenced by such factors as ovarian preservation, comorbid conditions, and potential late side effects. The availability of physicians with appropriate experience and training in gynecologic oncology procedures and physicians expert in radiation therapy should also influence the decision. Estimates of nodal involvement in patients with IA2 range from 4 to 10

percent. Whether these patients should have lymph nodes addressed with lymphadenectomy or radiation should be determined on a case-by-case basis. Radiation therapy for stage IA2 disease consists of intracavitary brachytherapy.

Patients with stages IB and IIA cervical cancer are appropriately treated with either radical hysterectomy with pelvic lymphadenectomy or radiation therapy, with equivalent results. The choice of therapy should be influenced by the same factors as described in patients with stage IA2 disease.

TABLE 2

The FIGO Staging System for Cervix Cancer (1994)

Stage	Characteristic
0	Carcinoma *in situ,* intraepithelial carcinoma. *Cases of Stage 0 should not be included in any therapeutic statistics for invasive carcinoma.*
I	The carcinoma is strictly confined to the cervix *(extension to the corpus should be disregarded).*
IA	Invasive cancer identified only microscopically. All gross lesions, even with superficial invasion, are stage IB cancers. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm. *(The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space involvement, either venous or lymphatic, should not alter the staging.)*
IA1	Measured invasion of stroma no greater than 3 mm in depth and no wider than 7 mm.
IA2	Measured invasion of stroma greater than 3 mm and no greater than 5 mm in depth and no wider than 7 mm.
IB	Clinical lesions confined to the cervix or preclinical lesions greater than IA.
IB1	Clinical lesions no greater than 4 cm in size.
IB2	Clinical lesions greater than 4 cm in size.
II	The carcinoma extends beyond the cervix, but has not extended on to the pelvic wall; the carcinoma involves the vagina, but not as far as the lower third.
IIa	No obvious parametrial involvement.
IIb	Obvious parametrial involvement.
III	The carcinoma has extended on to the pelvic wall; on rectal examination there is no cancer-free space between the tumor and the pelvic wall; the tumor involves the lower third of the vagina; all cases with a hydronephrosis or nonfunctioning kidney should be included, unless they are known to be due to other cause.
IIIa	No extension on to the pelvic wall, but involvement of the lower third of the vagina.
IIIb	Extension on to the pelvic wall or hydronephrosis or nonfunctioning kidney.
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum.
IVa	Spread of the growth to adjacent organs.
IVb	Spread to distant organs.

To minimize morbidity, primary therapy should avoid the routine use of both radical surgery and radiation therapy. The combined use of radical surgery and radical radiation therapy results in high morbidity and cost. Radiation therapy for stages IB and IIA disease should consist of external beam therapy and brachytherapy. For patients with stages IB and IIA disease, factors such as nodal involvement, increasing lesion size, deeper stromal invasion, unfavorable histopathological type, and lymph vascular involvement adversely affect prognosis.

In patients with positive pelvic lymph nodes documented at radical hysterectomy, postoperative radiation reduces pelvic recurrence but has not been proven to affect survival. Pelvic radiation may also be useful in reducing subsequent pelvic relapse in those patients with either close or involved surgical margins. The value of reducing pelvic recurrence is important to ameliorate or prevent pelvic pain and bleeding, even in those patients who may experience subsequent distant recurrence. Patients who undergo simple hysterectomy for presumed benign disease and are found to have invasive cervical cancer (greater than stage IAI) are considered candidates for postoperative radiation therapy or radical parametrectomy and lymphadenectomy.

The optimal role for imaging studies to define the extent of disease at presentation as well as to plan radiation therapy needs further investigation. Modalities requiring further study include magnetic resonance imaging (MRI), ultrasound, computed tomography (CT), and positron emission tomography (PET). Lymphangiography with fine needle aspiration cytology has been demonstrated to be an effective means of assessing nodal status. Although lymphangiography is not widely available, it appears to be more effective in assessing pelvic and para-aortic nodal status than both MRI and CT scanning. However, MRI and CT are useful in some patients to assess extent of disease and to select and plan optimal therapy.

If grossly involved pelvic lymph nodes are detected at the time of radical hysterectomy, data suggest that excision of the grossly involved lymph nodes results in improved local control. However, these findings should be confirmed in additional studies. Conflicting data exist on whether to remove the uterus or to leave it in place to assist brachytherapy.

A subset of patients may exist who benefit from prophylactic or therapeutic para-aortic node radiation. The greatest benefit is likely to be noted in patients with bulky stage IB, IIA, or IIB carcinoma of the cervix with a high probability of control of disease in the pelvis and who have either no evidence of gross para-aortic disease or resected micrometastatic disease. One randomized study assessing the value of prophylactic para-aortic lymph node radiation showed survival benefit.

In patients who receive primary radiation therapy for bulky stage IB cervical cancer, published results do not justify routine performance of postradiation hysterectomy. In patients who can receive optimal brachytherapy, combining hysterectomy with primary radiation therapy for bulky stage IB tumors increases cost and morbidity without clear improvement in local tumor control.

Stage for stage, the outcome of the treatment of pregnant patients with cervical cancer is similar to that of nonpregnant patients. Although limited data are available, information suggests that patients with stage IA and small stage IB disease may have limited delays in therapy to allow fetal viability without seriously compromising patient survival. The safety of therapy delay for patients with bulky stage I lesions or more advanced stages has not yet been established.

Neoadjuvant chemotherapy before planned radiation therapy in bulky stage IB and II disease has been investigated in several studies, but has not been demonstrated to provide a benefit. Several prospective randomized trials evaluating neoadjuvant chemotherapy before planned radiation therapy were recently completed, and the results of these trials will be of interest. The potential usefulness of neoadjuvant chemotherapy before planned surgery is also under investigation.

The measurement of serum tumor markers in patients with invasive cervical cancer has not been found to be of clear benefit but is worthy of further study. Estrogen replacement therapy may be safely prescribed to patients with invasive cervical cancer regardless of their histology and stage.

What Is the Appropriate Management of Advanced-Stage and Recurrent Cervical Cancer?

For advanced-stage disease, FIGO IIB or greater, the standard of care is primary radiation therapy using external beam radiation and brachytherapy. With improved radiation techniques, especially the increased use of brachytherapy, improvement in tumor control and long-term survival has been noted in studies examining the patterns of practice in the United States since 1973. Increased risk of therapeutic failure is most closely associated with patients who have a large volume of primary tumor, bilateral parametrial disease, nodal metastases, poor performance status, and low hemoglobin values. Retrospective studies have demonstrated increased risk of pelvic recurrence when lower total doses of radiation and prolonged treatment schedules are employed. In patients with advanced disease, the prognostic effect of different histologic types is not clearly an independent prognostic variable.

Optimal management utilizes megavoltage radiation energies and brachytherapy. Multiple field arrangements need to provide adequate coverage for the tumor volume especially when lateral fields are used. The use of low dose rate brachytherapy (LDR) has been shown to significantly reduce the rate of local recurrence in patients with advanced-stage disease. LDR is the most commonly used and most extensively defined technique in the United States. The use of high dose rate brachytherapy (HDR) has been increasing, although more studies are needed to define optimal fractionation schemes as well as long-term complications of this method. Pending further study, the use of HDR fractionation schemes that demonstrate rates of local control equivalent to LDR techniques and use smaller dose per fraction are recommended to decrease the probability of long-term complications with HDR. Interstitial therapy has been used for unusual or difficult tumor geometry. Primary surgical therapy for advanced cervical cancer is limited to the management of some patients with stage IVA cancers who present with vesicovaginal and/or rectovaginal fistulas.

The utility of cytotoxic chemotherapy in patients with more advanced or recurrent disease has been investigated in clinical trials with a variety of study designs. These include neoadjuvant chemotherapy, administered prior to surgical resection or radiation; concomitant chemotherapy and radiation, in which both modalities are administered together; adjuvant chemotherapy, in which surgery or radiation is followed by chemotherapy; and chemotherapy as sole treatment for patients with widely disseminated tumor not suitable for palliative radiation.

Cisplatin is the drug with the best documented single-agent activity in cervical cancer, with response rates of 18–31 percent in multiple trials conducted in more than 900 patients. Addition of other drugs to cisplatin has not been associated with survival advantages, although the objective response rate is sometimes increased. One large randomized trial found both diminished survival and increased pelvic failure rates with neoadjuvant chemotherapy prior to radiation therapy. While results of ongoing randomized trials of neoadjuvant chemotherapy are awaited, there is little to be gained from additional Phase II studies.

Early controlled trials of concomitant hydroxyurea with radiotherapy were suggestive of survival benefit, but were flawed methodologically. Radiation techniques have matured, necessitating reconsideration of a radiation therapy alone arm in such studies. Presently, there is no evidence that hydroxyurea or any other concomitant chemotherapy agent should be incorporated into standard practice.

Several controlled trials of adjuvant chemotherapy administered after completion of radiation are under way or in the planning stage, but at present no data support this practice.

Recurrent Disease After Primary Surgical Therapy

Patients with locally recurrent disease after hysterectomy should receive pelvic radiation therapy because radiation can provide long-term pelvic control and prolonged survival in approximately 40 percent of patients. The role of concomitant chemotherapy for recurrent disease awaits definition. The results of ongoing trials for locally advanced disease may help to define this issue.

Surgery for Recurrence After Radiation Therapy

Therapy for recurrence of cervical cancer after maximal radiation therapy is dependent on site of recurrence and extent of disease. The clearest role for surgical therapy is for centrally recurrent disease, and the surgery chosen is usually a form of pelvic exenteration. More limited surgical techniques such as radical hysterectomy have been explored for recurrent small lesions located on the cervix. Although there has been a suggestion of benefit in patients with lesions of less than 2 centimeters, this approach was associated with a high incidence of urinary tract complications. For the majority of patients, tailored pelvic exenteration remains the standard surgical approach. Candidates must be chosen carefully on the basis of their psychological and medical status.

The procedure-related mortality from pelvic exenteration when performed by experienced surgeons is less than 10 percent and continues to decline. Additionally, advances in continent urinary reservoirs, vaginal reconstruction, and low rectal anastomoses allow resumption of a more normal lifestyle following the procedure. The overall 5-year survival after exenteration varies between 30 and 60 percent.

For pelvic sidewall recurrences or other limited but not central pelvic recurrences, investigational therapy has employed combinations of surgery and intraoperative electron beam or brachytherapy. Aggressive therapies for recurrent disease after radiation are emotionally, physically, and economically costly for women. All these factors should be considered in making treatment decisions.

Palliative Therapy

Palliative treatment is appropriate for patients with symptomatic disease. The goals of the intervention should be defined with the patient prior to initiation of therapy. Palliation of pelvic symptoms can be achieved in most patients by radiation therapy. Short courses of radiation are well suited to this population. However, large single fractions of radiation have been associated with higher late complication rates in some studies. Symptomatic extrapelvic sites such

as bone are also effectively palliated with short courses of radiation. Systemic chemotherapy may also have a role in palliation of symptoms, although the benefit is usually of short duration. Oncologists should assure patients that psychological support and adequate treatment of all symptoms, including pain, are part of the treatment plan.

What Are New Directions for Research in Cervical Cancer?

Although much is known about the incidence, etiology, and treatment of cervical cancer, many issues remain unresolved.

It is well recognized that invasive carcinoma of the cervix is, in theory, a preventable disease. Modification of high-risk behavior in young people could change the pattern of HPV infection, and research in this area is warranted. Additional research is needed to determine the optimal methods of evaluating and treating HIV-positive women with preinvasive and invasive lesions of the cervix. Improving screening in populations that are typically underscreened, such as the elderly, ethnic minorities, and the poor, will require research directed towards overcoming the barriers specific to each group. Support should be given to research on provider behaviors that influence patient and clinician compliance with Pap smear screening. Additional research into methods of improving the accuracy and interpretation of cytologic sampling techniques, including liquid-based systems and computer automation, should be encouraged.

Currently, there are large numbers of women with Pap smears showing SIL each year. The minority of these women will progress to invasive cancer, and it would be advantageous to develop predictive markers to identify those women. This would allow low-risk women to avoid costly and potentially morbid diagnostic and therapeutic procedures. Additional research to identify molecular, pathologic, and immunologic markers that would assist in this triage is needed. Clinical trials, including the ASCUS/LSIL trial, deserve support.

In women with invasive cancer of the cervix, a number of key issues merit further investigation. Research into the role of modern radiologic imaging (CT, MRI, ultrasound, PET) for determination of tumor volume and extent of disease is warranted. This imaging information could also be incorporated into radiotherapeutic treatment planning. For those patients with microinvasive adenocarcinoma, an acceptable definition and guidelines for selecting patients for fertility-preserving treatment are needed. Additional information to identify those patients with microinvasive squamous cancer

who can safely be treated with conservative, fertility-sparing surgery is also indicated.

Methods to improve the traditional modalities of surgery and radiation therapy in the treatment of cervical cancer represent an important area of research. The advent of newer laparoscopic procedures offers the potential for a relatively nonmorbid histopathologic staging technique of pelvic and para-aortic lymph nodes. The status of these lymph nodes determined either laparoscopically or by other methods is one of the most important prognostic indicators, and pretreatment knowledge of lymph node status could allow for a more rational allocation of patients into therapeutic groups. Prospective trials evaluating the usefulness of histopathologic lymph-node staging are indicated.

Studies are needed to assess quality-of-life issues in patients undergoing therapy for both preinvasive and invasive lesions of the cervix. In patients with LSIL, studies regarding the impact of followup only versus active intervention are needed. The impact of frequent followup visits and the uncertainty of receiving no treatment for a preinvasive lesion with an unknown natural history may be significant and should be studied. Data are also needed regarding quality-of-life issues related to the selection of radical hysterectomy versus definitive radiation treatment in patients with early invasive cervical cancer.

The optimal role for chemotherapy in the treatment of early or advanced invasive cervical cancer is unknown. In the area of concomitant chemotherapy and radiation, a number of clinical trials have been completed or are under way, but at this time there is no proven benefit to combining chemotherapy with radiation. Additional studies are warranted, including quality-of-life studies.

Several issues related to radiation therapy for cervical cancer need to be addressed. The impact of p53 status and HPV subtypes on radiation responsiveness is a promising area of research that may allow optimization of treatment strategies. Dose-response relationship, time/dose relationship, improvements in technical instrumentation, and optimization of brachytherapy techniques need further study.

Predictive assays for tumor and/or normal tissue radiation sensitivity would allow for individualization of radiation prescriptions, while addressing the influence of hypoxia and anemia could improve the radiation responsiveness of the tumor. Studies in these areas are ongoing and should be supported.

Support should also be given to research to develop topical microbicides designed to prevent HPV infection as well as HIV infection and other sexually transmitted diseases.

One of the most exciting areas of research in the prevention and treatment of cervical cancer is the development and testing of prophylactic and therapeutic vaccines against HPV. The firmly established causal relationship between HPV infection and cervical neoplasia makes vaccine strategies uniquely appealing as a prophylactic and therapeutic approach. Research efforts in this area should be given the highest priority.

Conclusions

Carcinoma of the cervix is a substantial public health issue worldwide and remains an important issue for women's health in the United States, especially when one considers the totality of invasive disease and its precursor lesions. The evidence presented at this Consensus Development Conference has led to the following conclusions:

- Carcinoma of the cervix is causally related to infection with HPV. Reducing the rate of HPV infection by encouraging changes in the sexual behavior of young people and/or through developing an effective HPV vaccine would reduce the incidence of this disease.
- Screening with the Pap smear remains the best currently available method of reducing the incidence and mortality of invasive cervical cancer. Inability of women to adhere to screening guidelines and failure of many health care providers to recommend screening to their patients are issues that need to be studied further and remedied. Specific attention should be paid to populations known to be underscreened, including the elderly; the uninsured; ethnic minorities, especially Hispanics and blacks; and poor women, particularly those in rural areas. Women with cervical cancer should have access to appropriate specialists and clinical trials.
- Microinvasive squamous carcinoma with 3 mm or less of invasion and 7 mm or less of lateral spread (stage IA1) is highly curable with either simple hysterectomy or, in cases where preservation of fertility is an issue, by cone biopsy with clear margins.
- Seventy to 85 percent of patients with other stage I and stage IIA disease are cured. Treatment with radical surgery or radiation is equally effective. Selection criteria for treatment with a particular modality should be established to ensure treatment with one modality or the other, but not both. The combined use of radical surgery followed by radiation increases the cost and morbidity of treatment substantially.

- Patients with more advanced, nonmetastatic disease are treated with radiation. Although 5-year survival rates in the range of 40–60 percent are reported, there is clearly room for improvement. The addition of systemic chemotherapy in this subset of patients is an active area of investigation.
- Recurrent cervical cancer confined to the pelvis is treated with the modality that the patient has not previously received; i.e., if the patient has received radiation, she is treated with surgery and vice versa. Radiation may be useful in the palliation of symptoms due to metastases. The efficacy of chemotherapy in those with metastatic disease is best evaluated in the context of a clinical trial.
- Additional research efforts are needed to improve detection, staging, treatment, and quality of life for cervical cancer patients. Included among these are investigations into optimal pre- and posttreatment imaging, improved screening compliance and technical evaluation of Pap smears, prognostic markers to improve treatment selection, laparoscopic surgical techniques, radiobiology, and systemic chemotherapy. Cervical cancer can, in theory, be prevented and treated by HPV vaccine therapy; this research holds promise for a profound impact on this disease.

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CERVICAL CANCER

A Continuing Medical Education Activity Sponsored by the National Institutes of Health

OBJECTIVE

The objective of this NIH Consensus Statement is to inform the biomedical research and clinical practice communities of the results of the NIH Consensus Development Conference on Cervical Cancer. The statement provides state-of-the-art information regarding preventive approaches and appropriate management of cervical cancer and presents the conclusions and recommendations of the consensus panel regarding these issues. In addition, the statement identifies those areas of study that deserve further investigation. Upon completing this educational activity, the reader should possess a clear working clinical knowledge of the state-of-the-art regarding this topic.

ACCREDITATION

The National Institutes of Health is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. The National Institutes of Health designates this continuing medical education activity for 1 credit hour in Category I of the Physician's Recognition Award of the American Medical Association. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

EXPIRATION

This form must be completed and **postmarked by December 31, 1997**, for eligibility to receive continuing medical education credit for this continuing medical education activity. The expiration date for this test may be extended beyond December 31, 1997. Beginning January 1, 1998, please check the NIH Consensus Development Program web site (http://consensus.nih.gov) or call the NIH Office of Medical Applications of Research at 301-496-1144 for information regarding an extended expiration date for this continuing medical education activity.

INSTRUCTIONS

The consensus statement contains the correct answers to the following 10 questions. Select your answer(s) to each question and write the corresponding letter(s) in the answer space provided. Mail the completed test by the expiration date shown above to the address at the end of this test. You will receive notification of your test results within 2 to 3 weeks. If you have successfully completed the test (7 or more correct answers), you will receive a certificate for 1 hour of CME credit along with your test results. Photocopies of this form are acceptable. There is no fee for participating in this continuing education activity.

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1. Among women worldwide, breast cancer is the most common malignancy, both in terms of incidence and mortality. The second most common cancer among women worldwide is:

   a. lung
   b. cervix
   c. ovary
   d. colon
   ANSWER _____

2. Invasive cervical cancer and precursor lesions are firmly associated with the presence of:

   a. Epstein-Barr virus
   b. herpes simplex virus
   c. human papillomavirus
   d. helicobacter pylori
   ANSWER _____

3. The virus responsible for cervical cancer is transmitted by:

   a. sexual intercourse
   b. maternal-fetal transmission during pregnancy and labor
   c. blood transfusions
   d. fomites
   ANSWER _____

4. Populations with low rates of screening for cervical cancer include:

   a. older women
   b. rural women
   c. Hispanic women
   d. poor women
   e. all of the above
   ANSWER _____

5. Primary prevention of infection with the virus responsible for cervical cancer may require ALL BUT the following:

   a. education of adolescents about the causal links between sexually transmitted disease and the development of cervical cancer
   b. delayed onset of sexual activity
   c. development of an effective prophylactic vaccine
   d. promotion of regular exercise
   e. development of effective vaginal microbicides
   ANSWER _____

6. Patients with stages IB and IIA cervical cancer may be treated appropriately with either radical hysterectomy and pelvic lymphadenectomy or radiation therapy, with equivalent results.

   a. true
   b. false
   ANSWER _____

7. In patients found to have metastatic disease in pelvic lymph nodes at the time of radical hysterectomy, postoperative radiation therapy has been proven to increase overall survival.

   a. true
   b. false
   ANSWER _____

8. Patients with advanced stages of cervical cancer (FIGO stages IIB–IVA) are placed at increased risk of developing persistent or recurrent disease after definitive radiation therapy with all but one of the following factors:

   a. large-volume primary tumor
   b. low hemoglobin values
   c. nodal metastasis
   d. BRCA1 mutation
   e. poor performance status
   ANSWER _____

9. The chemotherapeutic agent with the best documented single-agent activity in cervical cancer is:

   a. carboplatin
   b. cisplatin
   c. paclitaxel
   d. hydroxyurea
   e. doxorubicin
   ANSWER(S) _____

10. Brachytherapy, when given in addition to external beam radiation, has not been shown to improve local control and long-term survival in women with advanced-stage cervical cancer (FIGO stage IIB–IVA).

    a. true
    b. false
    ANSWER(S) _____

Your response to the following two questions is optional and will have no effect on the grading results of this test.

Was the objective of this continuing education activity clearly stated?

a. not at all
b. very little
c. somewhat
d. considerably
e. completely

ANSWER _____

Did the activity planners provide the necessary information to meet the stated goals and objectives?

a. not at all
b. very little
c. somewhat
d. considerably
e. completely

ANSWER _____

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