

# Cervical Cancer Tests and Treatment

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Advances in screening and treatment of cervical cancer have been made in recent years. Here we discuss tests, stages of disease, and strategies for treatment.

Cervical cancer is the third most common cause of cancer death among women worldwide. In the United States, there are more than 12,000 cases each year.<sup>1</sup> The incidence of cervical cancer has decreased by 75% over the past 3 decades with the implementation of the Pap test for cervical cancer screening.<sup>1</sup>

Human papillomavirus (HPV) is the cause of cervical cancer. HPV is a sexually transmitted DNA virus that infects human skin and mucous membranes. High-risk types (16, 18) are responsible for approximately 70% of cervical cancers. At increased risk for cervical cancer are women who have had multiple sexual partners, an early age at first sexual intercourse, high parity, as well as those who use oral contraceptives, smoke cigarettes, or are immunocompromised.

With the introduction and widespread utilization of prophylactic HPV vaccines, the incidence of cervical cancer will decrease in the future. The HPV vaccine is 100% effective

at preventing high-grade cervical dysplasia caused by HPV types 16 and 18. Two different vaccines are approved by the FDA. Cervarix® (GlaxoSmithKline), approved for females ages 9 to 26, protects against HPV 16 and 18. Gardasil® (Merck), approved for females and males ages 9 to 26, protects against HPV 6, 11, 16, and 18.

## SCREENING FOR CERVICAL CANCER

The Pap test uses cytologic interpretation of cervical cells to screen for cervical dysplasia and cervical cancer, with a sensitivity of 81% and specificity of 77% for the detection of severe cervical dysplasia. Conventional cytology and liquid-based cytology have similar sensitivity for the detection of cervical dysplasia, but liquid-based cytology has a higher false-positive rate and results in fewer unsatisfactory specimens. The addition of HPV testing (molecular assays that detect HPV infection) to liquid-based cytology improves the sensitivity for the detection of cervical dysplasia.<sup>2</sup>

The current recommendations for cervical cancer screening are to initiate cervical cytology screening at age 21 regardless of the age of first sexual intercourse. Women ages 21 to 29 should be screened with conventional or liquid-based cytology every 2 years. Women 30 or older who have had 3 consecutive normal cytology tests, have no history of cervical intraepithelial neoplasia (CIN) 2-3, are not immunocompromised, and were not exposed to diethylstilbestrol in utero may undergo screening every 3 years.<sup>3</sup>

Screening by HPV cotesting with cytology may be performed in women 30 and older, and if negative in low-risk women, should not be repeated more often than every 3 years. HPV testing is used to stratify risk in

## FOCUSPOINT

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women 21 and older with atypical cells of undetermined significance (ASC-US) cytology results and in postmenopausal women with low-grade squamous intraepithelial lesion cytology results. Cervical cytology screening may be discontinued in women ages 65 to 70 with 3 consecutive normal cytology results and no abnormal results in the past 10 years.<sup>3</sup>

Several studies have reported the impact of HPV testing as a replacement of Pap test, or in combination with Pap testing. In general these show that HPV testing for high-risk types is more effective at preventing cervical cancer than are Pap tests.<sup>4,5</sup> It appears that cervical cancer screening programs based primarily on HPV testing provide better assessment of the risk of cervical cancer (the presence of CIN 2 or CIN 3) and may make cytological screening more efficient and cost-effective.<sup>6,7</sup> HPV testing may become a more important component of cytology-based screening or even replace it.

Several recent clinical trials investigating HPV DNA testing for cervical cancer screening will play a role in determining future recommendations for Pap testing and cervical cancer screening programs. There are 2 types of cervical HPV testing approved by the FDA for clinical practice. *Digene*<sup>®</sup> hybrid capture 2 (HC2) High-Risk HPV DNA testing (Qiagen Inc, Gaithersburg, MD) uses liquid hybridization followed by signal amplification to detect 13 high-risk types of HPV by an RNA cocktail probe, which does not distinguish individual HPV types. Cervista<sup>®</sup> HPV HR and Cervista<sup>®</sup> HPV 16/18 (Hologic, Inc, Marlborough, MA) are both sensitive and specific for the detection of CIN 3; this gives clinicians another option in HPV testing and should be used in accordance with current guidelines for management and triage of Pap test results.

The Cervista HPV HR identifies 14 high-risk types of HPV and is designed to be used similarly to the *digene* HC2 High-Risk HPV DNA test to triage colposcopy patients who have ASC-US cytology results, and to be used adjunctively with cytology in women 30 and older.<sup>8</sup> The Cervista HPV 16/18 test is the first FDA-approved test to specifically identify HPV types (HPV 16 and 18). This test may help clinicians make treatment plans for women with abnormal Pap results, in consideration of the cancer risk associ-

ated with the type of HPV with which she is infected.<sup>8,9</sup>

## TREATMENT OF CERVICAL CANCER

Treatment strategies for cervical cancer are dependent on the stage of disease. The International Federation of Gynecology and Obstetrics (FIGO) staging system is based on clinical exam and relies on pelvic exam, chest radiography, and sometimes imaging to evaluate for ureteral obstruction. Imaging for evaluation of lymph node involvement is not included in the FIGO staging system; however, management decisions are often made based on the suspicion for lymph node involvement seen on CT, MRI, or PET scan.

In 2009, FIGO made minor changes in the staging system by adding stage IIA1 (lesions beyond the uterus but not to the pelvic sidewall or to the lower third of the vagina, that are clinically visible and  $\leq 4$  cm) and IIA2 (lesions beyond the uterus but not to the pelvic sidewall or to the lower third of the vagina, that are clinically visible and  $>4$  cm) (Table).<sup>10</sup>

Early-stage cervical cancer may be treated with surgery or radiotherapy. Stage IA1 may be treated with a cold knife cone biopsy or simple hysterectomy. Generally speaking, women with cervical cancer stages IA2 to IIA can be treated with modified radical hysterectomy with pelvic lymph node dissection. Fertility-sparing surgery can be performed in the form of radical trachelectomy and pelvic lymph node dissection in carefully selected women with stages IA2 to IB1 disease.

Radiotherapy is the treatment of choice in locally advanced disease. Radiotherapy consists of external-beam therapy and intracavitary brachytherapy with concurrent cisplatin-based chemotherapy. Intensity-modulated radiotherapy is being widely adapted for external beam radiation, which allows radiation treatment volumes to be shaped specifically for target volumes of interest, thereby reducing toxicity to surrounding organs and increasing tumor dose.

Brachytherapy for cervical cancer has traditionally been performed with low-dose-rate systems, in which the 2 separate insertions of tandem and ovoids are performed under general anesthesia and radiation is given as an inpatient. High-dose-rate and

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**In general, several studies show that HPV testing for high-risk types is more effective at preventing cervical cancer than are Pap tests.**

**TABLE. FIGO Staging for Carcinoma of the Cervix<sup>10</sup>**

|                  |   |
|------------------|---|
| <b>Stage I</b>   | <b>The carcinoma is strictly confined to the cervix</b>   |
| IA               | Invasive carcinoma that can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≤7 mm  |
| IA1              | Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm  |
| IA2              | Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm   |
| IB               | Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage IA   |
| IB1              | Clinically visible lesion ≤4.0 cm in greatest dimension   |
| IB2              | Clinically visible lesion >4.0 cm in greatest dimension   |
| <b>Stage II</b>  | <b>Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina</b>   |
| IIA              | Without parametrial invasion  |
| IIA1             | Clinically visible lesion ≤4.0 cm in greatest dimension   |
| IIA2             | Clinically visible lesion >4.0 cm in greatest dimension   |
| IIB              | With obvious parametrial invasion   |
| <b>Stage III</b> | <b>The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney</b>   |
| IIIA             | Tumor involves lower third of the vagina, with no extension to the pelvic wall  |
| IIIB             | Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney   |
| <b>Stage IV</b>  | <b>The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV</b> |
| IVA              | Spread of growth to adjacent organs   |
| IVB              | Spread to distant organs  |

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics.

pulse-dose-rate brachytherapy has more recently been adopted, in which insertions and treatments can be delivered as an outpatient with multiple insertions of fractionated radiotherapy. Disease-free survival rates with treatment with radiotherapy have been reported to be 80% to 90% for stage I, 65% for stage II, and 40% for stage III cervical cancers.<sup>11</sup>

**SUMMARY**

Cervical cancer is one of the most common causes of cancer death among women

worldwide, despite the implementation of the Pap test, which has dramatically decreased the incidence of cervical cancer in developed nations over the past 30 years. The utilization of the prophylactic HPV vaccines will likely dramatically reduce the incidence of cervical cancer in populations with access to the vaccines.

Several recent trials have shown that HPV testing may become a more important component of cervical cancer screening because it is more predictive for cervical cancer than are Pap tests. *(continued on page 37)*

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Cervical cancer treatment decisions are based on the clinical stage of the disease. The earliest stage (IA1) may be treated with simple hysterectomy or cervical cone biopsy. In general, women with stages IA2 to IIA are treated with modified radical hysterectomy and pelvic lymph node dissection. Fertility-sparing treatment is an option for carefully selected women with stages IA2 to IB1. Advanced-stage disease is treated with radiotherapy given concurrently with cisplatin-based chemotherapy. Several techniques are being adapted to reduce toxicity associated with external beam radiotherapy and to improve the tolerability of brachytherapy.

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