Cervical Cancer

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1. Prevention

Consider educating patients about measures that may decrease the risk of cervical cancer.

1.1 Consider educating patients about safe sexual practices to decrease the risk of cervical cancer.

Recommendations

- Advise patients to:
  - Limit their number of sexual partners
  - Avoid intercourse at an early age
  - Use condoms to decrease the risk of acquiring HPV
- See module Human Papillomavirus.

Evidence

- Epidemiologic studies have shown that women with multiple sexual partners have an increased risk of developing cervical cancer. Relative risk is 2.1 [CI, 1.1 to 2.7] for ≥6 lifetime sexual partners (1).
- Epidemiologic studies have shown that women who have had intercourse at an early age have an increased risk of developing cervical cancer. Relative risk is 2.9 [CI, 1.3 to 2.4] for ages 14 to 15 at first sexual intercourse (1).

Rationale

- HPV is sexually transmitted and can cause cervical dysplasia and cervical cancer.
- Increasing the number of sexual partners increases exposure to HPV.
- Intercourse at an early age (under ages 13 to 15) exposes the cervix to HPV when it is most vulnerable.
- Intercourse with the use of condoms helps decrease the exposure to HPV.

Comments

- Although HPV is sexually transmitted and can cause cervical dysplasia and cervical cancer, HPV infection is very common. Most women who have had sexual intercourse have been exposed to HPV; therefore, care must be taken when counseling patients about HPV infection because it does not carry the same connotations as other sexually transmitted diseases (i.e., HPV on a Pap smear does not signify infidelity in the relationship).
- There are multiple types of HPV. The major high-risk types are 16 and 18.
- There is considerable controversy regarding the association between use of oral contraceptives and cervical cancer.
- According to a meta-analysis of 28 studies including 12,531 women with cervical cancer, the relative risk of cervical cancer increases with duration of oral contraceptive use. Compared with women who never used oral contraceptives, those who used oral contraceptives for less than 5 years had a relative risk of 1.1 (CI, 1.1 to 1.2), those who used them for 5 to 9 years had a relative risk of 1.6 (CI, 1.4 to 1.7), and those who used them for 10 years or more had a relative risk of 2.2 (CI, 1.9 to 2.4) (2).

1.2 Consider advising patients to avoid smoking to decrease the risk of cervical cancer.

Recommendations

- Advise patients not to smoke in an effort to decrease their risk of developing cervical cancer.
- See module Smoking Cessation.
Evidence
- Epidemiologic studies have shown that women who have smoked are at increased risk of developing cervical cancer. Smokers have a relative risk of 3.4 [CI, 2.1 to 5.6] (3).
- Mean nicotine in the cervical mucus of smokers was 1056 ng/mL vs. 43 ng/mL in nonsmokers (4).

Rationale
- Women who smoke have an increased risk of developing cervical dysplasia and cancer because of the carcinogenic and immunosuppressive effect that smoking has on the cervix.

Comments
- Second-hand smoke is also a risk factor for cervical cancer (5). Nonsmokers exposed to second-hand smoke for ≥3 hours a day have a relative risk of 3.0 [CI, 1.3 to 7.0] (3).

1.3 Vaccinate young women against HPV to reduce the risk of cervical cancer.

Recommendations
- Recommend the quadrivalent HPV vaccine for females aged 11 to 12 years.
- Give three doses of the vaccine, with the second dose 2 months after the initial dose and the third dose 6 months after the initial dose
- Recommend catch-up vaccination for females aged 13 to 26 years who have not been previously vaccinated.

Evidence
- A 2007 statement from the Advisory Committee on Immunization Practices of the CDC recommended the HPV vaccine for cervical cancer prevention for girls age 11 to 12, noting that the vaccine could be given as early as age 9, and as late as age 26 (6).
- Clinical trials indicate that the vaccine has high efficacy in preventing persistent HPV infection and cervical cancer precursor lesions caused by HPV types 16 and 18 and genital warts caused by HPV types 6 and 11 among females who have not already been infected with the respective HPV type (7; 8).

Rationale
- Sequelae of infection of the female genital tract with high-risk HPV subtypes include cervical dysplasia and squamous cell carcinoma.
2. Screening

Screen all women at risk for cervical cancer using cervical cytology.

2.1 Screen women between the ages of 21 and 65 for cervical cancer every 3 years using cervical cytology.

Recommendations

- Initiate screening with cervical cytology at age 21 and conduct screening every 3 years with cervical cytology.
- In women ages 30 to 65, consider screening every 5 years with cervical cytology plus HPV testing.
- Screen high-risk women more often including women who have been exposed to DES, are HIV positive, have a history of CIN 2/3, or are otherwise immunocompromised.
- **High-value care**: Discontinue screening in women older than age 65 who have had prior adequate screening unless they have history of high-grade dysplasia (CIN2 or worse).
- **High-value care**: Discontinue screening in women who have had hysterectomy with removal of the cervix unless they have history of high-grade dysplasia (CIN2 or worse).
- If cervical cytology result is:
  - Satisfactory and negative for intraepithelial lesion or malignancy, repeat cervical cytology at the scheduled interval
  - Unsatisfactory, repeat within 3 to 6 months
  - ASC-US, refer for colposcopy, obtain HPV DNA testing, or repeat cytology at 6 and 12 months
  - ASC-H, HSIL, squamous cell cancer, or atypical glandular cells, refer for colposcopy
  - Repeat the Pap test in 1 year in females under age 20 with ASC-US or LSIL instead of following the adult recommendations noted above.
  - See table [The Bethesda System for Reporting Results of Cervical Cytology](#).
  - See module [Papanicolaou Smear](#).

Evidence

- Recommendations are based on the 2012 guideline from the U.S. Preventive Services Task Force (9) and the 2012 consensus guideline from the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology, which recommended every 5-year screening of women over age 30 with cytology plus HPV testing as a preferred strategy (10). The 2009 guidelines from the American Congress of Obstetricians and Gynecologists are similar (11).
- A 2011 systematic review found that liquid-based cytology and conventional cytology have equivalent sensitivity and specificity (12).
- Multiple epidemiologic studies have shown that women who are screened with cervical cytology have a significant reduction (95%) in developing cervical cancer and dying of cervical cancer (13). In a retrospective study, the implementation of cervical cytology screening programs in British Columbia resulted in the incidence of cervical cancer decreasing by 85% between 1955 and 1988 (14).
- One study evaluated 128,805 women who initially had a normal Pap smear result. The incidence of HSIL suggestive of cancer was 25 per 10,000 women who had a second smear performed within 9 to 12 months of the first. This figure increased to 29 per 10,000 women for patients who had their second smear at 13 to 24 months and to 33 per 10,000 women for patients whose second Pap smear was performed 25 to 36 months after initial screening. These differences did not reach statistical significance (15).
- The effect of screening interval was evaluated in 938,576 women under age 65. In patients who had three or more negative test results, the excess risk for cervical cancer if screening were to be performed every 3 years instead of annually was 3 in 100,000 (16).
• After 3 consecutive, yearly, negative cytology smears, the risk of cervical cancer is reduced to approximately 1/100,000/years (13).
• National consensus guidelines from the American Society for Colposcopy and Cervical Pathology recommend less aggressive follow-up for adolescents with ASC-US and LSIL due to the extremely low risk of malignancy in this population (17).

Rationale
• Women who have annual cervical cytology decrease their risk of dying of cervical cancer by 95%.

2.2 Consider screening women ages 30 to 65 every 5 years using the combination of cervical cytology and HPV DNA testing.

Recommendations
• Consider combining cervical cytology and HPV DNA testing every 5 years in women ages 30 to 65:
  • If both test results are negative, repeat combination screening every 5 years but not more frequently
  • If cytology is negative and HPV testing is positive, defer colposcopy but repeat both tests in 6 to 12 months
  • If cytology shows atypical cells of undetermined significance and HPV testing is negative, defer colposcopy and repeat both tests, but repeat cytology in 12 months
  • If cytology shows atypical cells of undetermined significance and HPV testing is positive, defer colposcopy
  • If cytology shows atypical squamous cells-high grade, LSIL, or HSIL and HPV testing is negative, refer for colposcopy

Evidence
• A 2012 guideline from the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology recommended testing every 5 years with cervical cytology and HPV testing as the preferred screening strategy in women aged 30 to 65 (18).
• A systematic review of the accuracy of screening tests for cervical cancer found that the addition of HPV testing to cytology increases sensitivity but decreases specificity slightly compared with cytology alone. HPV testing alone had performance characteristics similar to those of HPV testing with cytology (12).
• Testing for high-risk HPV identifies more women with high-grade dysplasia than does a single cervical cytology sample (19; 20; 21; 22).
• The sensitivity obtained by combining the two methods of screening exceeds 95% in most studies (19; 20; 21; 22).
• Prevalence of HPV DNA positivity falls after the late teens and early twenties. In contrast, the incidence of high-grade dysplasia rises and peaks among women in their late twenties and early thirties (23; 24).
• There is a high NPV for underlying high-grade dysplasia in women with negative HPV and negative cytology results. Prospective studies indicate that the incidence of high-grade dysplasia during the subsequent 3 years is less than 2.0 per 1000 women whose results are negative on both tests (25).
• The addition of an HPV test to the Pap test to screen women in their mid-30s for cervical cancer reduces the incidence of grade 2 or 3 cervical intraepithelial neoplasia or cancer detected by subsequent screening examinations (26).
• National consensus guidelines indicate that colposcopy should be performed in women who are HPV high risk DNA positive and have a cytology result of atypical cells of undetermined significance (23).
• Recommendations are based on the 2012 guideline from the U.S. Preventive Services Task Force (9) and the 2012 consensus guideline from the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology (10).
• National consensus guidelines indicate that women who are high-risk HPV DNA negative and have a cytology result of ASC-US can be followed with repeated cytology in 12 months (23).
Rationale

- The addition of HPV testing to cervical cytology increases the diagnostic accuracy of cervical cancer screening.
3. Diagnosis

Use history, physical, and laboratory results to make a diagnosis of cervical cancer.  

3.1 Use history to elicit risk factors or symptoms of cervical cancer.  

Recommendations

- Ask about factors that increase risk of cervical cancer:
  - Multiple sexual partners
  - Early age of first intercourse
  - Smoking
- Ask about factors that can indicate cervical cancer:
  - Postcoital bleeding, which is commonly the first symptom of cervical cancer
  - The “terrible triad” of advanced cervical cancer (sciatic back pain, hydroureter, leg swelling)
  - Foul-smelling vaginal discharge
  - Change in urinary or bowel habits

Evidence

- Early age of first intercourse (RR, 1.8 [CI, 1.3 to 2.4]), multiple sexual partners (RR, 2.1 [CI, 1.1 to 2.7]) (1), and smoking (RR, 3.4 [CI 2.1 to 5.6]) (3) increase the chance of HPV causing cervical dysplasia and cancer.
- Epidemiologic studies have shown that postcoital bleeding is the most common symptom of invasive cervical cancer. Sixty percent of patients with cervical cancer present with abnormal vaginal bleeding (27).
- Epidemiologic studies have also shown that other symptoms of cervical cancer include the “terrible triad” (9%), foul-smelling vaginal discharge (4%), and changes in urinary or bowel habits (4%) (27).

Rationale

- A careful history may be helpful in identifying patients at high risk for developing cervical cancer.
- Early age of first intercourse, multiple sexual partners, and smoking increase the chance of HPV causing cervical dysplasia and cancer.
- As cancer grows on the cervix, the first symptom is frequently bleeding after intercourse because of direct trauma.
- As cervical cancer invades through the parametrium to the pelvic sidewall, it can cause blockage of the ureter (hydroureter), infiltrate nerves along the uterosacral ligament and sacrum (sciatic back pain) and cause pressure on the iliac vessels (leg swelling).
- Large exophytic tumors and large ulcerative lesions can become necrotic and produce a foul-smelling vaginal discharge that is usually slightly green or pink in color.
- Advanced cervical cancer may impinge on the urinary bladder, ureters, or rectosigmoid, causing change in urinary or bowel habits.

Comments

- Although postcoital bleeding is the most common symptom of cervical cancer, most women with postcoital bleeding do not have cervical cancer. It is frequently caused by glands on the cervix (such as in pregnancy or women taking birth control pills), cervicitis, or lack of estrogen in the postmenopausal woman.
- Although other causes of vaginal discharge such as cervicitis and vaginitis are much more common than cervical cancer, examination of the cervix and a Pap smear must be performed in any patient with persistent vaginal discharge.
3.2 Use physical examination to look for signs of cervical cancer.

Recommendations
- On physical examination look for:
  - Exophytic or ulcerative lesion on the cervix
  - Firmness in the parametrium
  - Leg swelling
  - Right upper quadrant mass and tenderness
  - Left supraclavicular lymphadenopathy (Virchow's node)
- See figure Cervical Cancer.

Evidence
- Recommendations are based on consensus in a review article (14).

Rationale
- Most cervical cancers are easily identified on speculum exam by the presence of a red exophytic or ulcerative lesion on the cervix.
- As cervical cancer advances, it spreads to the lateral tissue around the cervix called the parametrium; frequently, this can be detected on bimanual rectovaginal exam by feeling firmness in the parametrium.
- Advanced cervical cancer approaching the pelvic sidewalls may cause leg swelling by compressing the iliac vessels and by lymphatic blockage.
- Metastatic disease to the liver may present with right upper quadrant abdominal mass and tenderness.
- Metastatic disease may be detected by lymphadenopathy in the left supraclavicular area (Virchow's node).

Comments
- Physical examination alone is not an effective screening tool for cervical cancer.

3.3 Obtain appropriate laboratory testing to help diagnose cervical cancer.

Recommendations
- Perform:
  - Pap smear in any patient with postcoital bleeding
  - Colposcopy in any patient with an abnormal Pap smear showing HSIL, microinvasive, or invasive cancer
  - Biopsy on any grossly visible abnormality of the cervix
- See table Laboratory and Other Studies for Cervical Cancer.

Evidence
- The Pap smear is an excellent screen for cervical cancer. Epidemiologic studies have shown that yearly Pap smears reduce the risk of developing and dying of cervical cancer by 95% (13).
- In a meta-analysis of nine studies including 6281 patients, colposcopy had a sensitivity of 96% and specificity of 69% in differentiating normal cervix from high-grade dysplasia and cancer (28).

Rationale
- A Pap smear can detect precancer (cervical dysplasia) and microinvasive and small invasive cancers of the cervix.
- Colposcopic examination of the cervix can detect early cervical cancer.
- Most precancers (cervical dysplasia) and some early cancers are not visible to the naked eye.
- The colposcope is a low-powered magnification device that permits the identification of mucosal abnormalities characteristic of dysplasia or invasive cancer.
• Biopsy should be performed on grossly abnormal lesions of the cervix to determine the histologic diagnosis and to exclude invasive cancer.

Comments
• Even if the Pap test result does not show squamous intraepithelial lesion or cancer, biopsy should be performed on grossly abnormal lesions of the cervix.

3.4 Obtain imaging studies to help stage cervical cancer.

Recommendations
• Obtain the following in all patients with cervical cancer:
  • Chest x-ray
  • IVP or abdominal/pelvic CT
  • Examination under anesthesia with cystoscopy and proctoscopy
  • See table Laboratory and Other Studies for Cervical Cancer.
  • See table FIGO Staging of Cervical Cancer.

Evidence
• The recommended staging of cervical cancer includes chest x-ray, IVP, and examination under anesthesia with cystoscopy and proctoscopy (29).
• In a retrospective study of 817 patients, 1% of patients with invasive cervical cancer with no pulmonary symptoms had pulmonary metastasis (30).
• CT can help in the evaluation of lymph node metastasis. In a prospective study of 320 patients, evaluation of nodal metastasis by CT had a sensitivity of 34%, specificity of 96%, and false-negative rate of 18% (31).

Rationale
• Cervical cancer is clinically staged and the recommended staging includes chest x-ray, IVP, and examination under anesthesia with cystoscopy and proctoscopy.
• Proper staging of any cancer helps with prognosis, tailoring of treatment, and gives a small survival advantage.
• Chest x-ray is required to detect asymptomatic lung metastasis.
• Invasion of the parametrium with cervical cancer can result in hydroureter, which can be detected by IVP and would stage the cancer as a 3B.
• Abdominal/pelvic CT can also detect hydroureter as well as suspicious hepatic or pelvic/aortic lymph node metastasis.
• Anesthesia is needed for proper relaxation so adequate examination of the vagina and parametrium can be performed along with cystoscopy and proctoscopy.

Comments
• Patients with 1A or small 1B1 tumors may undergo renal ultrasound instead of IVP as a less expensive and safer examination for hydronephrosis.
• In the U.S., a CT of the abdomen and pelvis is frequently performed instead of IVP in patients with apparent advanced cervical cancer; however, for clinical staging, only the presence of hydroureter on the CT can be used. Routine CT scanning of the abdomen and pelvis cannot be used in the clinical staging of cervical cancer because the staging system is international and the cost of performing CT on all patients with cervical cancer in developing countries is prohibitive. Asymptomatic liver metastasis or lymph node metastasis identified on CT would be used for treatment but would not change the clinical staging.
• Because CT scanning fails to detect periaortic metastasis in approximately 25% of patients with advanced cervical cancer (stage 2B to 4A), gynecologic oncologists are routinely performing retroperitoneal or laparoscopic pelvic and periaortic lymphadenectomies to better help surgically stage patients. Again, because cervical cancer is clinically staged, the results of periaortic lymph node assessment will be used for tailoring treatment but would not change the clinical stage (31).
3.5 Consider diagnoses other than cervical cancer in patients with an abnormal Pap smear result, postcoital bleeding, or lesions on the cervix. 

**Recommendations**

- Consider:
  - Dysplasia as a differential diagnosis for a high-grade Pap smear result
  - Glands on the cervix (pregnancy or use of birth control pills), cervicitis, or lack of estrogen in postmenopausal women as differential diagnoses for postcoital bleeding
  - Cervical polyps, cervical cysts (Nabothian cyst), leiomyomas, or metastatic spread of other cancers to the cervix (such as endometrial cancer) as differential diagnoses for lesion on the cervix
- See table [Differential Diagnosis of Cervical Cancer](#).

**Evidence**

- Consensus.

**Rationale**

- There are other possible causes of an abnormal Pap test result, postcoital bleeding, and a lesion on the cervix besides cervical cancer.
4. Consultation

Consider consultation for diagnosis and proper clinical staging of cervical cancer. Consult appropriate specialists for help in managing patients with cervical cancer.

4.1 Consider consultation with a gynecologist for diagnosis and a gynecologic oncologist for clinical staging of cervical cancer.

Recommendations
- Consider consultation with:
  - A gynecologist for colposcopy for women with a Pap smear showing HSIL or cancer
  - A gynecologic oncologist for proper clinical staging of cervical cancer

Evidence
- Colposcopy has a sensitivity of 96% and specificity of 69% differentiating normal cervix from high-grade cervical dysplasia and cancer (28).

Rationale
- Pap smear is a screening test and must be verified by colposcopy and biopsy.
- Precancers (cervical dysplasia) and some early cancers are not visible to the naked eye.
- The colposcope is a low-powered magnification device that permits the identification of mucosal abnormalities characteristic of dysplasia or invasive cancer.
- Expertise is needed for proper clinical staging of cervical cancer to determine prognosis, tailor treatment, and allow a small survival advantage.

4.2 Consider referral to a gynecologic oncologist or medical oncologist as needed for management of patients with documented cervical cancer.

Recommendations
- Obtain consultation with a gynecologic oncologist for women with documented cervical cancer to:
  - Perform proper and cost-efficient staging
  - Perform the specific surgery
  - Assist the radiation oncologist in radiation treatment
  - Administer radiation sensitizing chemotherapy during external beam radiation
  - Administer primary chemotherapy in patients with distant recurrence or distant metastasis
  - Consult a medical oncologist to administer radiation sensitizing or primary chemotherapy.

Evidence
- Consensus.

Rationale
- Cervical cancer needs to be properly staged and managed by a subspecialist who is well informed and trained in all aspects of management.
5. Hospitalization

Consider hospitalizing patients with symptoms of cervical cancer that cannot be treated on an outpatient basis or for surgery.

5.1 Consider hospitalizing women with cervical cancer with excessive vaginal bleeding, uncontrolled pain, serious infection, or for surgery.

Recommendations
- Hospitalize women with:
  - Excessive vaginal bleeding from cervical cancer causing hemodynamic instability for blood transfusions and for control of hemorrhage; vaginal packing to control hemorrhage; and additional steps as needed such as suturing, embolization, radiation therapy, or surgery
  - Severe pelvic and back pain from cervical cancer for intravenous narcotics for control of pain, to be followed by long-acting oral or transdermal pain medication
  - Stage 3B disease and hydronephrosis who develop pyelonephritis, sepsis, or both for ureteral decompression along with antibiotic treatment
  - Stage 1 and 2 cervical cancer who require hysterectomy for postoperative inpatient care

Evidence
- Consensus.

Rationale
- Women with hemodynamic instability for bleeding require supportive care.
- Patients with severe pain require acute pain control with intravenous narcotics.
- Patients whose hydronephrosis causes pyelonephritis, sepsis, or both require decompression and antibiotics.
- Patients requiring hysterectomy need postoperative hospitalization.

Comments
- Vaginal packing to control hemorrhage from cervical cancer must be firm. Loose packing will only temporarily conceal active bleeding.
- Of the gynecologic malignancies, advanced and recurrent cervical cancer tends to be the most painful. Invasion through the cardinal ligament to the pelvic sidewall or through the uterosacral ligaments to the sacrum tends to cause severe pelvic and low back pain radiating down the buttocks.
6. Therapy

Consider surgery and radiation to be the main treatments for cervical cancer; consider chemotherapy concurrent with external beam radiation for treatment of cervical cancer and in patients with distant metastasis.

6.1 Consider surgery in patients with stage 1A1 to 2A cervical cancer.

Recommendations

- Consider:
  - LEEP or cone, abdominal or vaginal hysterectomy, or modified radical hysterectomy in patients with stage 1A1 cancer
  - Modified radical hysterectomy in patients with stage 1A2 cervical cancer
  - Radical hysterectomy in patients with stage 1B1, 1B2 and 2A cervical cancer

Evidence

- Stage 1A1 cancers have a small chance of lymph node metastasis and recurrence, allowing for conservative surgical resection such as abdominal or vaginal hysterectomy. Patients desiring to preserve fertility may be treated with cervical cone or LEEP providing the margins are free of disease. In a retrospective Medline literature search of 2369 cases of stage 1A1 cervical cancer, the incidence of lymph node metastasis and recurrence and death were <1% (32).
- Patients with stage 1A2 cervical cancer have an increased chance of recurrence and nodal metastasis and therefore require definitive cancer treatment. However, because their cervical disease is still microscopic, a modified radical hysterectomy rather than a radical hysterectomy can be performed to decrease morbidity. In a retrospective Medline review of 422 cases of stage 1A2 disease, lymph node metastases were found in 8% of patients and recurrence and death occurred in 3% of patients (32).
- Patients with stage 1B and 2A tumors may undergo radical hysterectomy with lymphadenectomy. The overall cure rate is approximately 85%. In a prospective surgical pathologic study by the Gynecologic Oncology Group of 732 patients, there was an 86% survival rate following radical hysterectomy (33).
- In a prospective randomized trial of 343 patients comparing surgery to primary radiation for stage 1B to 2A cancer, overall survival rate was 83% in both groups (34).

Rationale

- Stage 1A1 cancers have a small chance of recurrence and lymph node metastasis, and thus younger women wishing fertility may be treated with LEEP or conization instead of hysterectomy to preserve childbearing.
- Patients who have finished childbearing, especially those who have had repeated dysplasias or microinvasive cancers in the past, may undergo vaginal, abdominal or modified radical hysterectomy to decrease the chance of recurrence.
- Once cervical cancer has extended to stage 1A2 or above, LEEP, cone or abdominal or vaginal hysterectomy alone cannot cure the patient because an adequate margin and lymphadenectomy has not been performed.
- Patients with stage 1A2 cervical cancer may undergo modified radical hysterectomy, which has fewer complications than a radical hysterectomy.
- Once a tumor has become grossly invasive, (stage 1B and 2A) a radical hysterectomy is required to insure that the tumor is removed en bloc with an adequate margin and regional lymphadenectomies (the modified Halsted philosophy of cancer surgery).

Comments
Newer techniques of radical hysterectomy include using surgical staples (35) and laparoscopic radical hysterectomy (36). In a prospective study of 100 consecutive radical hysterectomies performed by the surgical stapling technique, operative time and blood loss were significantly reduced, although survival, recurrence, and complication rates were similar to the traditional technique (35). In a retrospective review, 19 patients underwent laparoscopic radical hysterectomy with a 90% success rate. Blood loss and hospital stay were reduced whereas operative time was increased with the laparoscopic approach (36).

6.2 Consider primary radiation therapy with radiation sensitizing chemotherapy for any stage of cervical cancer.

Recommendations

- Consider primary radiation therapy for patients with:
  - Stage 1 and 2 cervical cancers who are not surgical candidates or who do not want surgery
  - Stage 2B to 4A cervical cancer
- Administer daily external beam radiotherapy delivered to the entire pelvis, including the pelvic nodes, for 5 to 6 weeks followed by an intracavitary treatment of brachytherapy radiation to give a higher local dose to the mid pelvis (see information on radiation sensitizing chemotherapy).
- Administer weekly cisplatin, 40 mg/m², during the 4 to 6 weeks of external beam radiation.
- See table Drug Treatment for Cervical Cancer.

Evidence

- In a prospective randomized trial of 343 patients comparing surgery to primary radiation for stages 1B to 2A cancer, overall survival rate was 83% in both groups (34).
- Prospective randomized trials have shown approximately a 10% to 15% increased survival with the addition of radiation sensitizing chemotherapy. Of 388 patients with stage 1B2 to 4A disease treated with cisplatin and 5-FU vs. radiation alone, the overall survival was increased to 73% with chemotherapy vs. 58% with radiation alone (37).
- In a similar prospective study of 526 patients, weekly cisplatin increased survival to 65% vs. 47% with radiation alone (38).
- In a similar group of 368 patients, cisplatin and 5-FU increased survival to 67% vs. 57% with radiation alone (39).
- In high-risk stage 1 and 2A disease, radiation sensitizing chemotherapy has also been shown to be effective (40).
- In a prospective randomized trial of 243 high-risk stage 1A2 to 2A patients, the addition of cisplatin and 5-FU increased survival to 87% from 77% with radiation alone (40).
- In a similar group of 369 patients, weekly cisplatin increased survival to 83% from 74% with radiation alone (41).
- A systematic review of 24 trials including 4921 patients showed that chemoradiation improved overall survival by 10% and progression-free survival by 13%, regardless of whether platinum was used (42).
- A multicenter study of 526 women with locally advanced cervical cancer randomized to one of three chemotherapy regimens during pelvic radiation—single-agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea—showed increased survival with single-agent cisplatin or cisplatin-based combination chemotherapy (43).

Rationale

- Patients with early cervical cancer who are not surgical candidates or who do not wish surgery may undergo primary radiation therapy.
- Once a tumor has grown into the parametrium or lower vagina (stage 2B to 4A), adequate margins cannot be obtained by surgery; therefore, patients need to be treated with radiotherapy.
- Radiation-sensitizing chemotherapy increases the response to radiation by facilitating additional tumor cell killing.
• Chemotherapy helps in redistribution, which encourages cells in the resting phase (G0, which are not sensitive to radiation) to be recruited into the active phase of the cell cycle and which would therefore be more sensitive to radiation.
• Because of the direct killing of tumor cells by chemotherapy, the tumor tends to shrink more rapidly, and thus the hypoxic tumor cells (which are relatively resistant to radiation) receive more blood supply and oxygenation, becoming more sensitive to radiation.
• Radiation-sensitizing chemotherapy is not regarded as an adequate systemic therapy because the drugs are given in too low a dose and over too short a time period.

Comments
• Although platinum and the combination of platinum and 5-FU are relatively equivalent, weekly cisplatin is the preferred radiation sensitizer because of ease of administration and decreased toxicity.
• In younger, sexually active patients, radical hysterectomy is generally preferred over primary radiotherapy because radiotherapy obliterates ovarian function and causes scarring of the upper vagina resulting in painful intercourse.
• The charge for external beam and brachytherapy radiation is significantly greater than radical hysterectomy.

6.3 Consider pelvic exenteration for patients who develop midline pelvic recurrence after radiation therapy for cervical cancer.

Recommendations
• Consider pelvic exenteration for patients:
  • With recurrent or persistent cancer of the cervix after radiation therapy
  • Who are good surgical candidates
  • With no evidence of metastatic disease

Evidence
• In a review of 100 patients undergoing pelvic exenteration, 61% of patients were cured at 5 years (44).

Rationale
• Pelvic exenteration consists of resection of the uterus, vagina, bladder, and rectosigmoid.
• The only chance for cure in patients with recurrent or persistent cancer of the cervix in the midpelvis after radiation therapy is exenteration; these patients have already received the maximum dose of radiation and therefore additional radiation would cause excessive morbidity.
• Chemotherapy is not effective following high-dose radiation because radiation fibrosis prevents adequate drug delivery.

Comments
• Reconstructive surgery techniques have been added to total pelvic exenterations to improve quality of life. These techniques include vaginal reconstruction, colonic J pouch rectal reanastomosis, and continent urinary conduits.

6.4 Consider special management of patients with cervical cancer diagnosed in pregnancy.

Recommendations
• Base management of patients with cervical cancer in pregnancy on cancer stage and duration of pregnancy, e.g.:
  • Stage 1A1 disease, follow until term and deliver vaginally
  • Stage 1A2 to 2A disease with pregnancy <20 weeks, consider immediate treatment or follow to fetal maturity before treatment
Stage 2B to 4A disease with pregnancy <20 weeks, consider immediate treatment without regard to the pregnancy

Any stage with pregnancy >24 weeks, follow to fetal maturity before treatment

Evidence

Consensus.

Rationale

Of cancers occurring during pregnancy, cervical cancer is one of the most common.

Treatment is based on stage, but the timing of treatment is influenced by the duration of the pregnancy.

Comments

Full informed consent should be given to the mother and father about the risks to both mother and fetus. Some mothers are willing to put their health at risk in order to allow the fetus to progress to maturity.

Patients with stage 1B to 4A tumors should not be delivered vaginally because of increased hemorrhage, infection, and spread of tumor.

6.5 Consider chemotherapy for patients with distant recurrence and with stage 4 disease with distant metastasis.

Recommendations

Consider chemotherapy for patients with recurrence outside the pelvis and with stage 4 disease with distant metastasis.

Give cisplatin, 50 mg/m² intravenously, every 3 weeks.

Consider other active agents, including:

- Paclitaxel, 135 mg/m², every 3 weeks
- 5-FU, 1000 mg/m²-d, for 4 days every 4 weeks
- Topotecan, 1.5 mg/m²-d, for 5 days every 4 weeks
- Ifosfamide, 1.2 to 1.5 g/m²-d, for 5 days every 4 weeks

Consider combination chemotherapy such as cisplatin/paclitaxel, cisplatin/topotecan, and cisplatin/ifosfamide to increase response rate.

See table Drug Treatment for Cervical Cancer.

Evidence

In a review of 968 patients, the overall response rate to cisplatin was 25% (45).

In a prospective study of 52 patients, paclitaxel had a response rate of 17% (46).

In a review of 270 patients, the response rate to 5-FU was 13% (45).

In a prospective trial of 49 patients, topotecan had a response rate of 19% (47).

In a prospective trial of 56 patients, ifosfamide had a response rate of 16% (48).

In a prospective randomized trial of 438 patients, cisplatin and ifosfamide had a response rate of 31% vs. 18% with cisplatin alone (49).

Rationale

Once cervical cancer has spread from the pelvis, pelvic surgery and pelvic radiation are no longer options, and chemotherapy is needed to treat distant disease.

Cisplatin is the most active chemotherapeutic agent in treating cervical cancer.

Comments

In general, when cervical cancer recurs in the pelvis following radiation, there is no response to chemotherapy because the fibrosis and scarring from the previous radiation prohibits drug delivery.
7. Patient Education

Inform patients about the management, course, and prognosis of cervical cancer. 

7.1 Provide patients with cervical cancer with details of treatment and subsequent follow-up and prognosis.

Recommendations

- Initiate discussions about:
  - Stage of disease
  - Prognosis
  - Therapeutic options
  - Benefits and risks of surgery, radiation, and chemotherapy
  - Need for follow-up

Evidence

- Consensus.

Rationale

- Patient education is a key component in adherence to treatment and optimizing management.
8. Follow-up

Schedule periodic posttreatment surveillance for all patients with cervical cancer.

8.1 Schedule periodic posttreatment cancer surveillance at regular intervals during the first 5 years after diagnosis and perform frequent Pap smears.

Recommendations

- Schedule regular follow-ups every 3 months for the first year, every 4 months for the second year, then every 6 months until 5 years.
- At follow-up visits include history, physical examination, and vaginal cuff Pap smear.
- Note that patients with advanced disease may require chest x-rays, CT scans, or both of the abdomen and pelvis.

Evidence

- In a retrospective review of 249 patients, 89% of recurrences occur within the first 2 years after treatment (50).
- A Pap smear should be obtained at each visit because in a retrospective review of 1847 cases, 72% of vaginal recurrences are asymptomatic and are detected by abnormal cytologic smears (51).

Rationale

- Routine examination may allow for early detection of recurrence.
References


Glossary

5-FU
5-fluorouracil

ASC-H
atypical squamous cells; cannot exclude a high-grade squamous intraepithelial lesion

ASC-US
atypical squamous cells of undetermined significance

BUN
blood urea nitrogen

CBC
complete blood count

CDC
Centers for Disease Control and Prevention

CI
confidence interval

CT
computed tomography

DES
diethylstilbestrol

DNA
deoxyribonucleic acid

FIGO
International Federation of Gynecology and Obstetrics

GO
Gap 0; resting phase of the cell cycle

HIV
human immunodeficiency virus

HPV
human papillomavirus

HSIL
high-grade squamous intraepithelial lesion(s)

IVP
intravenous pyelogram

LEEP
loop electrical excision procedure

LSIL
low-grade squamous intraepithelial lesion(s)

RR
relative risk

SEER
Surveillance, Epidemiology, and End Results program

Terms

Brachytherapy
Radiation sources inserted directly onto the tumor
Cervical dysplasia
Precancerous cervical lesion on biopsy

Conization
Surgical excision of the cervix

External beam radiation
Outpatient daily radiation treatments to the pelvis, usually consisting of 25 sessions over 5 weeks

Parametrium
Ligaments and adipose tissue around the cervix

Radical hysterectomy
An extended type of hysterectomy which includes removing the uterus along with the parametrium

Squamous intraepithelial lesion, high grade
Possible precancerous cervical lesion on Pap smear
### Laboratory and Other Studies for Cervical Cancer

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap smear</td>
<td></td>
<td></td>
<td>Annual Pap smears reduce the risk of dying from cervical cancer by 95% (13)</td>
</tr>
<tr>
<td>Colposcopy</td>
<td>96</td>
<td>69</td>
<td>Used to direct cervical biopsies after Pap smear that show HSIL or cancer (28)</td>
</tr>
<tr>
<td>Cervical biopsy</td>
<td></td>
<td></td>
<td>Helps differentiate cervical dysplasia from microinvasive and invasive cancer</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td></td>
<td></td>
<td>Used in staging of cervical cancer to detect asymptomatic lung metastasis (1%) (30)</td>
</tr>
<tr>
<td>IVP</td>
<td></td>
<td></td>
<td>Used in staging to determine hydroureter, which would mean the tumor is stage 3B</td>
</tr>
<tr>
<td>Renal ultrasound</td>
<td></td>
<td></td>
<td>May be used as a substitute for IVP in apparent early cancers</td>
</tr>
<tr>
<td>CT scan of abdomen and pelvis</td>
<td>34</td>
<td>96</td>
<td>May be used to help direct therapy but is not used as a part of staging (31)</td>
</tr>
<tr>
<td>Exam under anesthesia with cystoscopy and proctoscopy</td>
<td></td>
<td></td>
<td>Used to help determine stage to detect regional spread</td>
</tr>
</tbody>
</table>

CT = computed tomography; HSIL = high-grade squamous intraepithelial lesion(s); IVP = intravenous pyelogram.
## Differential Diagnosis of Cervical Cancer

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysplasia</td>
<td>Abnormal Pap test result</td>
</tr>
<tr>
<td></td>
<td>Needs colposcopy and biopsy</td>
</tr>
<tr>
<td>Normal cervical glands</td>
<td>Glands on the cervix (such as in pregnancy or women on birth control pills).</td>
</tr>
<tr>
<td></td>
<td>Associated with postcoital bleeding</td>
</tr>
<tr>
<td></td>
<td>Obtain Pap smear</td>
</tr>
<tr>
<td>Cervicitis</td>
<td>Postcoital bleeding</td>
</tr>
<tr>
<td></td>
<td>There are no discrete lesions on the cervix, but rather the cervix is red and</td>
</tr>
<tr>
<td></td>
<td>inflamed. Needs biopsy if Pap smear result is abnormal</td>
</tr>
<tr>
<td>Cervical atrophy</td>
<td>Postcoital bleeding</td>
</tr>
<tr>
<td></td>
<td>Vagina and cervix tend to be pale and atrophic. Needs to have Pap smear</td>
</tr>
<tr>
<td>Cervical polyp</td>
<td>Abnormal-appearing cervix</td>
</tr>
<tr>
<td></td>
<td>Tends to be discrete, movable lesion. Needs biopsy</td>
</tr>
<tr>
<td>Cervical cysts</td>
<td>Abnormal-appearing cervix</td>
</tr>
<tr>
<td></td>
<td>Tend to be well-circumscribed lesions on the cervix. If diagnosis is</td>
</tr>
<tr>
<td></td>
<td>questionable, needs biopsy</td>
</tr>
<tr>
<td>Metastatic disease to the cervix</td>
<td>Abnormal-appearing cervix</td>
</tr>
<tr>
<td></td>
<td>The cervix tends to be normal in color and appearance but is firm on palpation.</td>
</tr>
<tr>
<td></td>
<td>Needs biopsy</td>
</tr>
</tbody>
</table>
## Drug Treatment for Cervical Cancer

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Dosing</th>
<th>Side Effects</th>
<th>Precautions</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>40 mg/m² IV weekly during external beam radiation. 50 mg/m² IV every 3 weeks as primary chemotherapy</td>
<td>Risk of infection or bleeding. SIADH, hyperuricemia, alopecia, peripheral neuropathy, visual impairment, injection site reactions, secondary malignancy, elevated hepatic enzymes, cardiac or vascular toxicity, TLS</td>
<td>■ Severe nephrotoxicity, severe myelo-suppression, severe nausea and vomiting, ototoxicity, anaphylactic reactions. Avoid overdose and confusion with carboplatin. Avoid with: CrCl&lt;30, pregnancy. Decrease dose if CrCl&lt;60. Give IV hydration when administered</td>
<td>Cisplatin is the most active chemotherapeutic agent for cervical cancer</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>135 mg/m² IV every 3 weeks</td>
<td>Myelosuppression, risk of infection or bleeding. Peripheral neuropathy, alopecia, edema, fever, asthenia, injection site reactions, myalgia, arthralgia, hypotension, ECG abnormalities, vomiting, diarrhea, stomatitis, radiation recall reaction, elevated hepatic enzymes</td>
<td>■ Treatment facility required. Anaphylaxis. Avoid with low neutrophil counts. Avoid with pregnancy. Avoid extravasation. Must premedicate. Decrease dose with hepatic disease. Metabolized by CYPs 3A4, 2C8 and P-gp.</td>
<td></td>
</tr>
<tr>
<td>Fluorouracil, 5-FU</td>
<td>1000 mg/m²·d continuous IV infusion for 4 days every 4 weeks</td>
<td>Myelosuppression, risk of infection or bleeding. Vomiting, diarrhea, anorexia, GI bleeding, stomatitis, hand and foot syndrome, neurotoxicity, lacrimation, cardiotoxicity, injection site reactions, photosensitivity</td>
<td>■ Hospitalize for first course of therapy due to severe toxic reactions. Avoid with pregnancy. Consider dose reduction with hepatic disease</td>
<td></td>
</tr>
<tr>
<td>Ifosfamide (Ifex)</td>
<td>1.2-1.5 g/m² IV qd for 5 days every 4 weeks</td>
<td>Risk of infection or bleeding. Alopecia, vomiting, renal insufficiency, cardiotoxicity, secondary malignancy</td>
<td>■ Hemorrhagic cystitis, CNS toxicity, severe myelosuppression. Avoid with pregnancy. Decrease dose if CrCl&lt;60. Substrate of CYPs 3A4 and 2B6. Give vigorous hydration and mesna</td>
<td></td>
</tr>
<tr>
<td>Topotecan (Hycamtin)</td>
<td>1.5 mg/m² qd for 5 days every 4 weeks</td>
<td>Risk of infection or bleeding. Vomiting, diarrhea, constipation, abdominal pain, anorexia, stomatitis, alopecia, fever, asthenia, pain, dyspepsia, fatigue, rigors, rash, ILD, infertility</td>
<td>■ Myelosuppression. Avoid with pregnancy. Avoid extravasation. May need to decrease dose with CKD.</td>
<td></td>
</tr>
</tbody>
</table>

■ = black box warning; bid = twice daily; CKD = chronic kidney disease; CNS = central nervous system; CrCl = creatinine clearance; CV = cardiovascular; CYP = cytochrome P450 isoenzyme; ECG = electrocardiogram; GI = gastrointestinal; ILD = interstitial lung disease; IM = intramuscular; IV = intravenous; P-gp = P-glycoprotein; PO = oral; q12hr = every 12 hours; qd = once daily; qid = four times daily; SC = subcutaneous; SCr = serum creatinine; SIADH = syndrome of inappropriate secretion of antidiuretic hormone; tid = three times daily; TLS = tumor lysis syndrome

PIER provides key prescribing information for practitioners but is not intended to be a source of comprehensive drug information.
### The Bethesda System for Reporting Results of Cervical Cytology

<table>
<thead>
<tr>
<th>Specimen adequacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfactory</td>
</tr>
<tr>
<td>Unsatisfactory</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interpretation/result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative for intraepithelial lesion or malignancy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epithelial cell abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cells</td>
</tr>
<tr>
<td>ASC-H</td>
</tr>
<tr>
<td>LSIL</td>
</tr>
<tr>
<td>HSIL</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glandular cell abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical glandular cells</td>
</tr>
<tr>
<td>Atypical glandular cells, favor neoplastic</td>
</tr>
<tr>
<td>Endocervical adenocarcinoma in situ</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
</tbody>
</table>

ASC-H = atypical squamous cells; cannot exclude a high-grade squamous intraepithelial lesion; ASC-US = atypical squamous cells of undetermined significance; HSIL = high-grade squamous intraepithelial lesion(s); LSIL = low-grade squamous intraepithelial lesion(s).
## FIGO Staging of Cervical Cancer

<table>
<thead>
<tr>
<th>Stage 1A</th>
<th>Microscopic cervical cancer which is measured &lt; 3 mm depth of invasion and &lt; 7 mm horizontal spread</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1A 2</td>
<td>Microscopic cervical cancer with a depth between 3 to 5 mm and &lt; 7 mm horizontal spread</td>
</tr>
<tr>
<td>Stage 1B1</td>
<td>Microscopic cervical cancer with dimensions &gt; stage 1A2 or any gross lesion &lt; 4 cm in width</td>
</tr>
<tr>
<td>Stage 1B2</td>
<td>Gross lesion &gt; 4 cm in width</td>
</tr>
<tr>
<td>Stage 2A</td>
<td>Cervical cancer extending to the upper 2/3 of the vagina</td>
</tr>
<tr>
<td>Stage 2B</td>
<td>Cervical cancer extending into the parametrium but not to the pelvic sidewall</td>
</tr>
<tr>
<td>Stage 3A</td>
<td>Cervical cancer extending to the lower 1/3 of the vagina</td>
</tr>
<tr>
<td>Stage 3B</td>
<td>Cervical cancer extending to the pelvic sidewall and/or causing hydronephrosis</td>
</tr>
<tr>
<td>Stage 4A</td>
<td>Cervical cancer extending into the mucosa of the bladder or the rectum</td>
</tr>
<tr>
<td>Stage 4B</td>
<td>Cervical cancer with metastatic spread to distant organs</td>
</tr>
</tbody>
</table>

FIGO = International Federation of Gynecology and Obstetrics.
Cervical Cancer

This patient presented with erosion to her cervix due to low grade cervical carcinoma. The most common signs of cervical cancer are vaginal bleeding between menstrual periods or after menopause, postcoital vaginal bleeding, and abnormal vaginal discharge. Direct examination usually shows an abnormal cervix, although a tumor in the cervical canal may be difficult to see. The diagnosis is usually established by punch biopsy of obvious lesions or by colposcopy with directed biopsy. The image is reproduced from the CDC Public Health Image Library.