EVERYONE'S GUIDE FOR CANCER THERAPY
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Cervix
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Invasive cervical cancer accounts for six percent of all cancers that afflict women in the United States. About 16,000 cases of invasive carcinoma of the cervix are diagnosed in the United States each year, while there are at least 500,000 new cases of a pre-invasive cancer-known as squamous intraepithelial lesions-where the cancer cells are confined to the surface skin of the cervix.

Since 1940, there has been a steady decrease in the incidence of carcinoma of the cervix because most women with no symptoms are screened with cervical and vaginal Pap smears. The probability at birth that a white woman will eventually develop cervical cancer dropped from 1.1 percent in 1975 to 0.7 percent in 1985. Similarly, for African-American women, the probability dropped from 2.3 percent in 1975 to 1.6 percent in 1985.

Types Over 90 percent of cervical carcinomas start in the surface cells lining the cervix and are called squamous cell carcinoma. About 5 to 9 percent start in glandular tissue (adenocarcinoma). Adenocarcinomas are more difficult to diagnose, but they are treated the same way as squamous cell carcinomas and the survival rate, stage for stage, is similar.

There are several types of adenocarcinoma. About 60 percent are the endocervical cell type, 10 percent each are of endometrioid and clear cell carcinomas, and 20 percent are adenosquamous carcinoma.

There are two rare types of cervical carcinoma known as small cell carcinoma and cervical sarcoma. Both have a poor prognosis.

How It Spreads Most scientists believe that pre-invasive cervical cancer may develop over a period of months or years after the cervix is infected with the human papilloma virus (HPV). This early lesion-known as mild dysplasia or cervical intraepithelial neoplasia (CIN) Grade 1 or now called low-grade squamous intraepithelial lesion (LGSIL)-can progress to moderate dysplasia (CIN-2), then to severe dysplasia and carcinoma in situ (CIN-3) or collectively known now as a high-grade squamous intraepithelial lesion (SIL) and eventually to invasive carcinoma. Most physicians believe that about two-thirds of all cases of high-grade SIL progress to invasive cancer if left untreated. This transformation takes anywhere from 2 to 30 years, about 10 years on the average.

Once the cervical cancer becomes invasive, it can spread locally to the upper vagina and into the tissues surrounding the upper vagina and the cervix (the parametrium). Eventually it grows toward the pelvic sidewall, obstructing the tubes (ureters) that drain urine from the kidney to the bladder. It can also spread to the bladder and rectum.

Cervical tumor cells can invade the lymphatic system and spread to the lymph nodes around the vessels on the pelvic wall. Eventually they may spread to the iliac lymph nodes higher in the pelvis, the aortic lymph nodes, and the nodes above the collarbone and occasionally to the groin nodes.

Metastases can also spread through the bloodstream to the lower vagina, vulva, lungs, liver and brain. Distant metastases are more common in women with cancer spread to the lymph nodes or higher stage cancer. Invasion of the pelvic nerves is common in advanced cases. There may also be spread within the abdomen when the tumor penetrates the full thickness of the cervix.

What Causes It There is significant evidence that cervical carcinoma is sexually transmitted. Most researchers believe that the human papilloma virus is the cause or a strong cofactor in the development of pre-invasive and invasive carcinomas of the cervix, as well as pre-invasive and invasive squamous cell cancer of the vagina and vulva. Ninety-five percent of squamous cell carcinomas of the cervix contain human papilloma virus DNA. There are many types of human papilloma virus (HPV) that infect humans. Types 6 and 11 usually cause genital warts, while types 16, 18, 31, and 33 usually result in high-grade SIL (dysplasia, CIN-2 and 3) and carcinomas. Genital warts are associated with cervical, vaginal, and vulvar dysplasia and invasive carcinoma in about 25 percent of cases.

RISK FACTORS

The average age of women with invasive cervical cancer in the United States is between 45 and 50, while the average age of women with carcinoma in situ is between 25 and 35. The difference is attributed to the long latent period of progression of a lesion confined to the cervical skin to an invasive cervical cancer.

The risk factors for pre-invasive cervical cancer (cervical dysplasia) and cervical cancer are the same. Circumcision is no longer believed to lower the risk of cervical carcinoma.

At Significantly Higher Risk

- Suppression of the immune system from corticosteroids, kidney transplants, therapy for other cancers, or HIV.
- A history of genital warts.
- A history of herpes simplex virus infection.
- Low socioeconomic status.
- Early age at first intercourse.
- Multiple sexual partners.
- Women whose male partner(s) either have had penile warts, have had multiple sexual partners or whose previous partners had cervical cancer.

At Slightly Higher Risk

- Multiple pregnancies.
- Cigarette smoking.

SCREENING

The American College of Obstetricians and Gynecologists recommends that a Pap smear be done for all women by age 18 or who are sexually active, regardless of age. Women who have multiple sexual partners should be screened annually, but those in long-term, stable relationships who have had negative Pap smears three years in a row may be screened less often.

A major problem with the Pap smear is that it is often thought to be normal when it is actually abnormal. The pathologist examining the cells can make an error, the health care provider may not sample the cervix adequately or an infection might obscure the results. The estimated false negative rate is about 20 percent, half of which can be attributed to faulty sampling techniques.

Adenocarcinomas and adenosquamous carcinomas are also more difficult to detect on Pap smears since they start high up in the cervical canal and may not be sampled by the Pap smear. Because of the high false negative rate, routine annual screening is strongly recommended to decrease the likelihood that cervical warts, dysplasia or cancer will be missed.

COMMON SIGNS AND SYMPTOMS

In many cases-and in almost all cases of pre-invasive cancer-there are no symptoms. The most common symptoms in women with cancer include abnormal vaginal bleeding or discharge, bleeding after intercourse and pain.

DIAGNOSIS

Physical Examination

- Most women with cervical cancer will have a normal general physical examination.
- Careful evaluation of the external genitalia.
- Lymph nodes in the groin and above the collarbone should be examined to detect any enlargement.
- Examination of the abdomen to look for an enlarged liver, a mass or excessive abdominal fluid (ascites).
- A gynecologic pelvic and rectal examination is important to detect disease in the tissue surrounding the cervix and vagina and the pelvic lymph nodes.

Blood and Other Tests

- Complete blood count.
- Liver function chemistries.
- Kidney function chemistries.
- The levels of the serum squamous cell carcinoma antigen (SCCA) and the serum carcinoembryonic antigen (CEA) in the blood should be measured in women with advanced cancer. SCCA is elevated in 50 percent of all women with cervical cancer. CEA is elevated in about 20 percent of all women with cervical carcinomas. Although CEA and SCCA are not accurate enough to use for screening, they are useful to monitor the response to treatment and for follow up to detect recurrent disease.

Imaging

- Chest x-ray.
- CT or MRI scans of the abdomen and pelvis.

Endoscopy and Biopsy

- Cystoscopy in advanced cases.
- Sigmoidoscopy in advanced cases.
- All women with an abnormal Pap smear or cervical lesions should undergo an office colposcopic examination. A colposcope is an instrument that can magnify the cervix from 7.5 to 15 times.
- The definitive diagnosis is made on a biopsy. Early cancers are occasionally diagnosed by a large biopsy of the cervix, known as a LEEP or cold knife cone biopsy. A cervical LEEP or conization should be done when: colposcopy cannot determine if there is an invasive cancer, when there are no obvious lesions on the cervix, and the Pap smear is consistently abnormal, when a colposcopically-directed biopsy does not adequately account for abnormal cells found on a Pap smear, when a diagnosis of microinvasion (early invasion) is found on the biopsy, when a squamous intraepithelial lesion is identified by a scraping from the cervical canal (endocervical curettage), or when there is a diagnosis of adenocarcinoma in situ of the cervix.

STAGING

Most gynecologic oncologists use the FIGO (International Federation of Gynecologists and Obstetricians) classification. This divides the disease into five stages, with further divisions in each stage. A carcinoma in situ is Stage 0. The cancer is confined to the cervix in Stage I. In

Stage II, the disease either extends beyond the cervix but not to the pelvic sidewall, or involves the vagina but not the lower third. A Stage III carcinoma extends to the pelvic sidewall involves the lower third of the vagina or obstructs one or both of the ureters. In Stage IV, the cancer has spread to distant organs beyond the true pelvis or involves the lining of the bladder or rectum.

TREATMENT OVERVIEW

Squamous cell carcinoma and adenocarcinoma are generally treated in similar ways. Radical surgery and radiation therapy are equally effective treatments for early stage disease (Stage Ib and a small IIa).

For carcinomas more advanced than Stage IIa, treatment is with radiation therapy and chemotherapy. Higher stages are generally treated with higher doses of radiation therapy as well.

Surgery For younger women surgery is usually recommended because it allows the ovaries to still function and it avoids the vaginal scarring that can result from radiation. There is also a small chance that women who survive many years after radiation therapy will develop a second malignancy in the radiated area.

Radical exenterative surgery-removal of the rectum and/or bladder and the cervix, uterus and vagina-is usually reserved for recurrent carcinoma confined to the central pelvis.

Surgery may also be used to stage cervical cancer since other methods, even CT and MRI scans, are notoriously inaccurate in detecting lymph node metastasis and intra-abdominal spread in the more advanced stages. Unfortunately, there is no reliable way to diagnose microscopic metastases to the pelvic and para-aortic nodes without removing them. So many gynecologic oncologists will recommend a surgical staging procedure before radiation therapy is given to evaluate the intra-abdominal surfaces and the status of the pelvic and aortic lymph nodes. It can be done laparoscopically or through an abdominal incision.

Surgical staging is done, if possible, through an approach outside the lining of the abdominal cavity (extraperitoneal). This avoids the manipulation of the intra-abdominal organs as much as possible (as in intra-abdominal operation) and results in fewer complications following radiation therapy.

The incidence of cancerous pelvic and para-aortic nodes increases with more advanced disease and there may be a survival advantage to removing the involved nodes. Women with microscopic metastases to the pelvic and aortic nodes can be cured if the nodes are removed and radiation therapy and chemotherapy is then given (two-thirds and one-third chance respectively).

Women with positive para-aortic nodes may have distant metastases to the lymph nodes above the collarbone (10 to 20 percent of cases). If the neck nodes are positive, then only palliative therapy is warranted.

Radiation Several radiation techniques may be used depending on the stage of the disease-external beam therapy and intracavitary therapy: the insertion of radioactive substances around the tumor or into the tumor (interstitial radiation). Intracavitary radiation may be of two types: low-dose rate and high-dose rate (*see Radiation Therapy chapter*).

Chemotherapy It is now standard therapy to give chemotherapy simultaneously with radiation therapy in women with advanced cervical cancers. This treatment is currently being investigated for women at high risk for recurrent disease (regardless of the stage) or for those with multiple pelvic lymph node or aortic lymph node metastases.

TREATMENT BY STAGE

STAGE 0 (Squamous cell carcinoma)

Carcinoma in situ (intraepithelial carcinoma) High-grade SIL.

Standard Treatment There are four treatment options for this early-stage tumor.

A LEEP (Loop Electrosurgical Excision Procedure) is similar to a cone biopsy and is for both diagnostic and therapeutic indications. It is usually performed in the office with a local anesthesia with only rare side effects. A cervical cold-knife conization is performed when a LEEP is not appropriate-usually for recurrent disease or difficult anatomy.

Laser vaporization therapy is usually done for larger lesions.

Freezing the cervix (cryotherapy) can be performed in the doctor's office and has a negligible complication rate.

STAGE O (Adenocarcinoma)

Standard Treatment Adenocarcinoma in situ (confined to the surface of the cervix) is often difficult to diagnose. The diagnosis is usually made with a cervical biopsy or endocervical curettage. In all cases a conization is required to rule out a truly invasive lesion. For women who may want to have children, a LEEP or cone biopsy may cure the disease if the surgical margins, or edges, do not show any evidence of disease. Even so, adenocarcinoma in situ or an invasive adenocarcinoma is occasionally found in the residual cervix even if the cone biopsy has negative margins. For those who have completed childbearing, the treatment of choice is a simple vaginal or abdominal hysterectomy.

Five-Year Survival 100 percent.

STAGE I is cancer confined to the cervix.

STAGE IA1

Stage Ia involves a carcinoma of the cervix diagnosed only microscopically. All visible lesions, even those with minimal invasion, are Stage Ib. Stage I is further divided into two stages based on the depth of invasion of the cervix. In Stage Ia there is less than 3 mm of invasion and the invasion is less than 7 mm wide. When the depth of invasion is less than 3 mm from the surface and there is no vascular space involvement, a hysterectomy is often recommended. However, a cervical LEEP or conization may be

curative if the edges (margins) of the cone biopsy are free of disease and if there is no vascular space involvement. This is appropriate therapy for those women who want to preserve their fertility or who want to avoid a hysterectomy.

Standard Treatment Women with this stage of disease are usually treated with a cone biopsy (a large cone-shaped biopsy of the cervix) or a vaginal or abdominal hysterectomy, with or without removal of the ovaries.

Five-Year Survival 100 percent.

STAGE IA2

The depth of stromal invasion is greater than 3 mm and less than 5 mm from the surface of the cervix. It also must be less than 7 mm wide.

Standard Treatment In the United States, women with cancer invading greater than 3 mm into the cervix or those with invasive cancer less than that, but with blood vessel involvement, are treated like those women with Stage Ib1 disease.

Five-Year Survival 85 to 95 percent.

STAGE IB

Lesions are larger than Stage Ia2, but are still confined to the cervix.

STAGE IB1

Cervical cancer confined to the cervix, but no greater than 4.0 cm in size.

STAGE IB2

Cervical cancer confined to the cervix, but greater than 4 cm in size.

Standard Treatment There are two options for treatment. A radical hysterectomy may be done, with removal of the lymph nodes from the blood vessels from both sides of the pelvis and from around the aorta. An alternative is external beam radiation (given in divided doses five days a week for five weeks) followed two weeks later by intracavitary or interstitial radiation (low-dose or high-dose rate). Both options result in an equal rate of cure. The choice depends on available local expertise, the age of the patient and ones medical condition. Small lesions (stage IB1) are usually operated on while large ones are often treated with surgery or radiation. Women who have metastasis disease in the removed lymph nodes are frequently treated with external beam radiation therapy to the affected area following surgery.

A radical abdominal hysterectomy and a bilateral pelvic and aortic lymph node dissection are usually performed through either a midline abdominal incision or a large lower transverse abdominal incision. However, more recently, a number of gynecologic oncologists are performing the same operation using minimally invasive surgical techniques (laparoscopy). The entire procedure is performed through four to five small incisions in the abdominal wall. One just below, the second above the naval, the third just above the pubic bone, and the other two on opposite sides of the pelvis. Although this procedure is still investigational, as the technique is learned by more laparoscopists, it will become more widely available. Its limitations are primarily based on the patient's weight as obese women are not good candidates. There are also a number of gynecologic

oncologists who believe that the lymph nodes should be removed laparoscopically and the radical hysterectomy performed through the vagina. Cervical cancers greater than 4 cm (stage Ib2) confined to the cervix may be treated with surgery alone, radiation therapy followed by surgery six weeks later, or radiation therapy and chemotherapy alone, or chemotherapy followed by radical hysterectomy.

Five-Year Survival 70 to 95 percent.

STAGE II The cancer is one that either extends beyond the cervix (but not to the pelvic sidewall) or involves the vagina (but not the lower third).

STAGE IIA

In Stage IIa there is no obvious involvement of the tissue surrounding the cervix (parametrium), but there is involvement of up to the inner two-thirds of the vagina.

Standard Treatment Treatment with either a radical hysterectomy and removal of the lymph nodes or external beam radiation therapy followed by intracavitary or interstitial radiation with chemotherapy is standard.

Women with large lesions of the cervix are sometimes managed with preoperative radiation therapy, hysterectomy and lymph node dissection.

Women who have metastatic disease in the lymph nodes are often given external beam radiation therapy to the pelvis and sometimes the para-aortic region after surgery with or without chemotherapy.

Five-Year Survival Approaching 70 to 95 percent.

STAGE IIB

There is obvious parametrial involvement, but no extension to the pelvic sidewall.

Standard Treatment External beam radiation therapy may be given in divided doses over five weeks with concurrent chemotherapy, followed by intracavitary or interstitial radiation.

Five-Year Survival 65 to 80 percent.

Investigational

- A new radiation technique that is currently being studied is known as high-dose rate brachytherapy, which allows for shorter treatment times in an outpatient or office setting.
- Hyperthermia, a technique using radiation therapy and heat, is also being studied.

STAGE IIIA or IIIB

Stage III is defined as carcinoma that extends to the pelvic sidewall involves the lower third of the vagina or obstructs one or both ureters. Stage IIIa means there is no extension to the pelvic sidewall, but the tumor involves the lower third of the vagina. In Stage IIIb, there is extension to the pelvic sidewall, obstruction of one or both ureters, or there is a non-functioning kidney.

Standard Treatment External beam radiation therapy with chemotherapy followed by intracavitary or interstitial radiation therapy is the standard therapy.

Five-Year Survival 40-60 percent.

Investigational Same as for Stage IIb.

STAGE IV

Stage IV is defined as cancer that has spread to distant organs beyond the true pelvis or involves the lining of the bladder or rectum.

STAGE IVA means that a biopsy has shown that either the lining of the bladder or the rectum is involved with cancer.

Standard Treatment This stage is usually treated with radiation therapy and chemotherapy or by the surgical removal of the uterus, the vagina and the bladder and/or rectum (pelvic exenteration).

Five-Year Survival 20 to 30 percent.

STAGE IVB

In Stage IVb there is spread to distant organs.

Standard Treatment Radiation may be used to relieve the symptoms of pelvic disease or isolated distant metastases. Several chemotherapy drugs are useful for treating cervical cancer, but they are rarely curative. They include cisplatin or carboplatin, which has a response rate of 15 to 25 percent, and ifosfamide, which has a response rate of 30 percent. Combination chemotherapy, including cisplatin + etoposide + bleomycin, has a response rate of about 50 percent. Other drug combinations that have been used in women with metastatic disease include mitomycin-C + bleomycin + cisplatin, carboplatin + ifosfamide, cisplatin + ifosfamide with or without bleomycin.

Investigational Many of the drugs used in the standard treatment are being tested in different combinations and doses.

TREATMENT FOLLOW-UP

A Pap smear and careful examination of the pelvis, abdomen and lymph nodes is performed every three months for the first two years after treatment, and then every six months for three more years. Routine chest x-rays and pelvic and abdominal CT scans are not warranted in the absence of symptoms.The serum levels of carcinoembryonic antigen and/or squamous cell carcinoma antigen in the blood should be measured at each visit if they were elevated before treatment.

RECURRENT CANCER

Symptoms of recurrent cervical carcinoma may include vaginal bleeding or discharge, pain in the pelvis, back or legs, leg swelling (edema), chronic cough and weight loss.

- Cervical cancer can recur in the vagina, pelvis, lymph nodes, lung, or liver.
- If radiation was not given previously, recurrences that are confined to the pelvis may be treated with external beam radiation with chemotherapy and intracavitary or interstitial radiation therapy.
- If radiation therapy was already given, the only option is the removal of the vagina, uterus, and the bladder and/or rectum with the creation of an artificial bladder-a pelvic exenteration. The five-year survival rate after a pelvic exenteration is about 50 percent.
- Women with recurrent tumors that cannot be surgically removed or with metastatic disease are usually treated with chemotherapy. Commonly used drugs include single agent cisplatin or carboplatin. Other regimens include cisplatin or

carboplatin + ifosfamide, vincristine + mitomycin-C + bleomycin + cisplatin and bleomycin + mitomycin-C + 5-fluorouracil.

- Those with unresectable pelvic disease may be re-irradiated with interstitial radiation or given pelvic arterial chemotherapy.

THE MOST IMPORTANT QUESTIONS YOU CAN ASK

- What qualification do you have for treating cancer? Will a specialist in gynecologic oncology be involved in my care?
- What is the advantage of surgery versus radiation therapy?
- Why or why not, will a staging surgery be performed?
- Is there a benefit of using high-dose rate radiation therapy?