



Research Article

CANCER OF CERVIX

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ABSTRACT

Cervical cancer is the second most commonly diagnosed cancer and the third leading cause of cancer death among females in less developed countries. The most significant cause of cervical cancer is persistent papillomavirus infection. For many years, the papanicolaou (Pap) test has been the standard method for cervical cancer screening, reducing the incidence by 60%-90% and the death rate by 90%. Primary prevention of cervical cancer is now possible via immunisation with highly efficacious HPV vaccines secondary prevention has gained impetus with the advent of sensitive HPV DNA testing to improve traditional Pap cytology screening programmes.

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INTRODUCTION

The uterine cervix is the lowest portion of a woman's uterus (womb), connecting the uterus with the vagina. Cervical cancer occurs when the cells of the cervix grow abnormally and invade other tissues and organs of the body. Cervical cancer is slow-growing, so its progression through precancerous changes provides opportunities for prevention, early detection, and treatment.

Types of Cervical Cancer

The type of cervical cancer helps to determine the prognosis and treatment. The main types of cervical cancer are:

Squamous cell carcinoma: This type of cervical cancer begins in the thin, flat cells (squamous cells) lining the outer part of the cervix, which projects into the vagina. Most cervical cancers are squamous cell carcinomas.

Adenocarcinoma: This type of cervical cancer begins in the column-shaped glandular cells that line the cervical canal. Sometimes, both types of cells are involved in cervical cancer. Very rarely, cancer occurs in other cells in the cervix.

Causes

It isn't clear what causes cervical cancer, but it's certain that HPV plays a role. HPV is very common, and most women with the virus never develop cervical cancer. This means other factors such as environment or lifestyle choices also determine whether she will develop cervical cancer.

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Risk Factors

- **Human papillomavirus (HPV) infection:** Infection by the human papillomavirus (HPV) is the most important risk factor for cervical cancer. HPV is a group of more than 150 related viruses.

High risk type of HPV are strongly linked to cancers, including cancer of the cervix, vulva, and vagina in women, penile cancer in men, and cancers of the anus, mouth, and throat in both men and women.

- **Many sexual partners:** Greater the number of sexual partners and greater partner's number of sexual partners, there is greater chance of acquiring HPV.
- **Early sexual activity:** Having sex at an early age increases the risk of HPV.
- **Other sexually transmitted infections (STIs):** Having other STIs such as chlamydia, gonorrhoea, syphilis and HIV/AIDS increases the risk of HPV.
- **A weak immune system:** The immune system is important in destroying cancer cells and slowing their growth and spread. Human immunodeficiency virus (HIV), the virus that causes AIDS, damages a woman's immune system and puts them at higher risk for HPV infections. One may be more likely to develop cervical cancer whose immune system is weakened by autoimmune disease or by another health condition and on immunosuppressive drugs.
- **Smoking:** Women who smoke are about twice as likely as non-smokers to get cervical cancer. Researchers believe that these substances damage the DNA of cervical cells and may contribute to the development of cervical

cancer. Smoking also makes the immune system less effective in fighting HPV infections.

- **A diet low in fruits and vegetables:** Women whose diets don't include enough fruits and vegetables may be at increased risk for cervical cancer.
- **Being overweight:** Overweight women are more likely to develop adenocarcinoma of the cervix.
- **Long-term use of oral contraceptives (birth control pills):** There is evidence that taking oral contraceptives (OCs) for a long time increases the risk of cancer of the cervix. Research suggests that the risk of cervical cancer goes up the longer a woman takes OCs, but the risk goes back down again after the OCs are stopped, and returns to normal about 10 years after stopping.
- **Intrauterine device (IUD) use:** Using an IUD might also lower the risk of endometrial (uterine)cancer. However, IUDs do have some risks. Also, a woman with multiple sexual partners should use condoms to lower her risk of sexually transmitted illnesses no matter what other form of contraception she uses.
- **Having multiple full-term pregnancies:** Women who have had 3 or more full-term pregnancies have an increased risk of developing cervical cancer. No one really knows why this is true. Also, studies have pointed to hormonal changes during pregnancy as possibly making women more susceptible to HPV infection or cancer growth. Another thought is that pregnant women might have weaker immune systems, allowing for HPV infection and cancer growth.
- **Being younger than 17 at your first full-term pregnancy:** Women who were younger than 17 years when they had their first full-term pregnancy are almost 2 times more likely to get cervical cancer later in life than women who waited to get pregnant until they were 25 years or older.
- **Economic status:** Many low-income women do not have easy access to adequate health care services, including Pap tests. This means they may not get screened or treated for cervical precancers.
- **Diethylstilbestrol (DES):** DES is a hormonal drug that was given to some women between 1940 and 1971 to prevent miscarriage. Women whose mothers took DES (when pregnant with them) develop clear-cell adenocarcinoma of the vagina or cervix more often than would normally be expected. There is about 1 case of vaginal or cervical clear-cell adenocarcinoma in every 1,000 women whose mothers took DES during pregnancy. DES daughters may also be at increased risk of developing squamous cell cancers and pre-cancers of the cervix linked to HPV.
- **Having a family history of cervical cancer:** Cervical cancer may run in some families. If mother or sister had cervical cancer, chances of developing the disease are higher than if no one in the family had it.

Clinical Manifestation

Women with early cervical cancers and pre-cancers usually have no symptoms. Symptoms often do not begin until the cancer becomes invasive and grows into nearby tissue. When this happens, the most common symptoms are:

- Vaginal bleeding after intercourse, between periods or after menopause

- Watery, bloody vaginal discharge that may be heavy and have a foul odour
- Pelvic pain or pain during intercourse

Stages

Stage-I

The cancer cells have grown from the surface of the cervix into deeper tissues of the cervix. The cancer may also be growing into the body of the uterus, but it has not grown outside the uterus.

Stage-IA

- There is a very small amount of cancer, and it can be seen only under a microscope. The area of cancer invasion is between 3 mm and 5 mm (about 1/5-inch) deep and less than 7 mm (about 1/4-inch) wide.
- It might or might not have spread to nearby lymph nodes.
- It has not spread to distant sites.

Stage-IB

- This includes stage I cancers that can be seen without a microscope i.e. ≥ 4 cm as well as cancers that can only be seen with a microscope if they have spread deeper than 5 mm (about 1/5 inch) into connective tissue of the cervix or are wider than 7 mm.
- It might or might not have spread to nearby lymph nodes.
- It has not spread to distant sites.

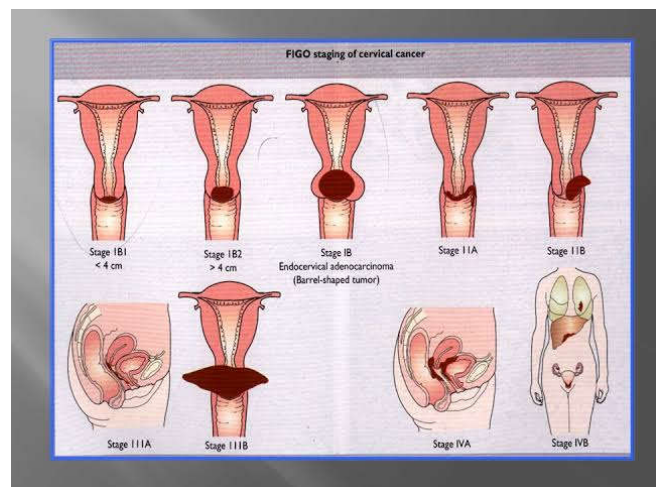


Fig Stages of cervical cancer

Stage-II

- The cancer has grown beyond the cervix and uterus, but hasn't spread to the walls of the pelvis or the lower part of the vagina.
- It might or might not have spread to nearby lymph nodes.
- It has not spread to distant sites.

Stage-III

- The cancer has spread to the lower part of the vagina or the walls of the pelvis. The cancer maybe blocking the ureters (tubes that carry urine from the kidneys to the bladder) causing kidney problems (called hydronephrosis).

- It might or might not have spread to nearby lymph nodes.
- It has not spread to distant sites.

Stage-IVA

- The cancer has spread to the bladder or rectum or it is growing out of the pelvis.
- It might or might not have spread to nearby lymph nodes.
- It has not spread to distant sites.

Stage-IVB

- The cancer has spread to distant organs beyond the pelvic area, such as distant lymph nodes, lungs, bones or liver.

Diagnostic Test

Medical history and physical exam

- Personal and family medical history which includes information related to risk factors and symptoms of cervical cancer.
- A complete physical examination will help to evaluate general state of health. Pelvic examination and in addition, lymph nodes will be felt for evidence of metastasis (cancer spread).

Colposcopy: A speculum is placed in the vagina and uses a colposcope to examine the cervix closely and clearly. The doctor will put a weak solution of acetic acid (similar to vinegar) on your cervix to make any abnormal areas easier to see and biopsy is done as needed.

Cervical biopsies: Several types of biopsies can be used to diagnose cervical pre-cancers and cancers. If the biopsy can completely remove all of the abnormal tissue, it might be the only treatment needed.

Colposcopic biopsy: Using a biopsy forceps, a small (about 1/8-inch) section of the abnormal area on the surface of the cervix is removed.

Endocervical curettage (endocervical scraping): This means taking a scraping of the endocervix by inserting a narrow instrument (called a curette) into the endocervical canal (the part of the cervix closest to the uterus) to remove some of the tissue for examination.

Cone biopsy: also known as conization, the doctor removes a cone-shaped piece of tissue from the cervix's transformation zone (the border between the exocervix and endocervix, where cervical pre-cancers and cancers are most likely to start) and may be used as treatment for many pre-cancers and some very early cancers.

The methods commonly used for cone biopsies are the loop electrosurgical excision procedure (LEEP), also called the large loop excision of the transformation zone (LLETZ), and the cold knife cone biopsy.

Loop electrosurgical procedure (LEEP, LLETZ): In this method, the tissue is removed with a thin wire loop that is heated by electricity and acts as a small knife, under local anaesthesia.

Cold knife cone biopsy: A surgical scalpel or a laser is used to remove the tissue instead of a heated wire, either with general

anaesthesia or a spinal or epidural anaesthesia in a hospital setting.

How biopsy results are reported

- In CIN1, not much of the tissue looks abnormal, and it is considered the least serious cervical pre-cancer (mild dysplasia).
- In CIN2 more of the tissue looks abnormal (moderate dysplasia)
- In CIN3 most of the tissue looks abnormal; CIN3 is the most serious pre-cancer (severe dysplasia) and includes carcinoma in situ).

Cystoscopy, proctoscopy, and examination under anesthesia:

In cystoscopy a slender tube with a lens and a light is placed into the bladder through the urethra to see if cancer is growing into these areas. Biopsy samples can be removed during cystoscopy for pathologic (microscopic) testing. Proctoscopy is a visual inspection of the rectum through a lighted tube to check for spread of cervical cancer into your rectum.

Imaging studies: Certain imaging studies may be done to show the spread, which will help to decide on a treatment plan.

Chest x-ray: To see if cancer has spread to lungs. This is very unlikely unless the cancer is far advanced.

Computed tomography (CT): CT scans are usually done if the tumour is larger or if there is concern about cancer spread.

Magnetic resonance imaging (MRI): MRI looks at soft tissue parts of the body sometimes better than other imaging tests.

Intravenous urography: Intravenous urography (also known as intravenous pyelogram, or IVP) blockage of the ureters (tubes that connect the kidneys to the bladder) by the cancer. IVP is rarely used for patients with cervical cancer because CT and MRI are also good at finding abnormal areas in the urinary tract, as well as others not seen with an IVP.

Positron emission tomography (PET scan): This test can help see if the cancer has spread to lymph nodes. PET scans are often combined with CT scans using a machine that can do both at the same time. The combined PET/CT test is rarely used for patients with early cervical cancer, but may be used to look for more advanced cancer or if radiation treatment is a possibility.

Management

Treatment Options for Cervical Cancer, by Stage

The stage of a cervical cancer is the most important factor in choosing treatment. But other factors can also affect treatment options, including exact location of the cancer within the cervix, the type of cancer (squamous cell or adenocarcinoma), age and overall health, and whether want to have children.

Stage 0 (Carcinoma in Situ)

Treatment options for squamous cell carcinoma in situ include

- Cryosurgery
- Laser surgery
- Loop electrosurgical excision procedure (LEEP/LEETZ)
- Cold knife conization

- Simple hysterectomy (as the first treatment or if the cancer returns after other treatments)

Treatment options for adenocarcinoma in situ include

- Hysterectomy
- Cone biopsy (a possible option for women who wish to have children). The cone specimen must have no cancer cells at the edges, and the woman must be closely watched after treatment. Once the woman has finished having children, a hysterectomy is recommended.

Stage IA1: Treatment for this stage depends on whether or do not want to continue to be able to have children (maintain fertility) and whether or not the cancer has grown into blood or lymph vessels (called lymphovascular invasion).

Treatment options for women who want to maintain fertility

A **cone biopsy** is the preferred procedure for women who want to have children after the cancer is treated.

- If the edges of the cone don't contain cancer cells (called negative margins), the woman can be watched closely without further treatment as long as the cancer doesn't come back.
- If the edges of the cone biopsy have cancer cells (called positive margins), then cancer may have been left behind. This can be treated with a repeat cone biopsy or a radical trachelectomy (removal of the cervix and upper vagina). A radical trachelectomy is preferred if the cancer has grown into blood or lymph vessels.

Treatment options for women who don't want to maintain fertility

- A simple (total) hysterectomy may be an option if the cancer shows no lymphovascular invasion.
- If the cancer has grown into blood or lymph vessels, women might need a radical hysterectomy along with removal of the pelvic lymph nodes.

Stage IA2: Treatment for this stage depends in part on whether or not you want to continue to be able to have children (maintain fertility).

Treatment options for women who want to maintain fertility

- Cone biopsy with removal of pelvic lymph nodes (pelvic lymph node dissection)
- Radical trachelectomy with pelvic lymph node dissection

Treatment options for women who don't want to maintain fertility

- External beam radiation therapy (EBRT) to the pelvis plus brachytherapy
- Radical hysterectomy with removal of pelvic lymph nodes and sampling of the para-aortic lymph nodes

Stages IB and IIA: The main treatment options are surgery, radiation, or radiation given with chemo (concurrent chemoradiation).

Stages IB1 and IIA1

Treatment options for women who want to maintain fertility

- Radical trachelectomy with pelvic lymph node dissection

Treatment options for women who don't want to maintain fertility

- Radical hysterectomy with removal of lymph nodes in the pelvis and some lymph nodes from the para-aortic area
- If none of the lymph nodes are found to have cancer, radiation may still be discussed as an option if the tumor is large, if the tumor has grown into blood or lymph vessels, or if the tumor is invading the surrounding connective tissue that supports organs such as the uterus, bladder, vagina (the stroma).
- If the cancer has spread to the tissues next to the uterus (called the parametria) or to any lymph nodes, or if the tissue removed has positive margins, radiation (EBRT) with chemotherapy is usually recommended. The doctor may also advise brachytherapy after the combined chemo and radiation are done.
- Radiation using both brachytherapy and external beam radiation therapy may be an option if a woman is not healthy enough for surgery or if she decides they do not want surgery
- Chemotherapy (chemo) may be given with the radiation (concurrent chemoradiation).

Stages IB2 AND IIA2

Treatment options

- **Chemoradiation:** This is usually the standard treatment. The chemo may be cisplatin or cisplatin plus fluorouracil. The radiation therapy includes both external beam radiation and brachytherapy.
- Radical hysterectomy with pelvic lymph node dissection and para-aortic lymph node sampling:

If cancer cells are found in the removed lymph nodes, or in the edges of the tissue removed (positive margins), surgery may be followed by radiation therapy, which is often given with chemo (concurrent chemoradiation).

Some doctors recommend radiation given with chemotherapy first followed by a hysterectomy.

Stages IIB, III, AND IVA

Treatment options

Chemoradiation: The chemo may be cisplatin or cisplatin plus fluorouracil. The radiation therapy includes both external beam radiation and brachytherapy.

Stage IVB: At this stage, the cancer has spread out of the pelvis to other areas of the body. Stage IVB cervical cancer is not usually considered curable. Treatment options include radiation therapy and/or chemo to try to slow the growth of the cancer or help relieve symptoms. Most standard chemo regimens include a platinum drug (cisplatin or carboplatin) along with another drug such as paclitaxel (Taxol), gemcitabine

(Gemzar), or topotecan. The targeted drug bevacizumab (Avastin) maybe added to chemo or immunotherapy alone with pembrolizumab (Keytruda®) may also be an option.

Recurrent Cervical Cancer: Cancer can come back locally (in or near where it first started, such as the cervix, uterus or nearby the pelvic organs), or it can come back in distant areas (such as the lungs or bone). If the cancer has recurred in the pelvis only, extensive surgery (pelvic exenteration) may be an option for some patients. Sometimes radiation, chemo, immunotherapy or targeted therapy may be used to slow the growth of the cancer or help relieve symptoms, but they aren't expected to cure the cancer.

Cervical Cancer in Pregnancy: A small number of cervical cancers are found in pregnant women. Most of these (70%) are stage I cancers. The treatment plan during pregnancy is determined by:

- Tumour size
- If nearby lymph nodes have cancer
- How far along the pregnancy is
- The specific type of cervical cancer
- If the cancer is at a very early stage, such as carcinoma in situ (Stage 0) or stage IA, it is safe to continue the pregnancy to term and have treatment several weeks after birth. Surgery options after birth for early-stage cancers include a hysterectomy, radical trachelectomy, or a cone biopsy.
- If the cancer is stage IB or higher, and don't want to continue pregnancy, then treatment would be radical hysterectomy and/or radiation. Sometimes chemotherapy can be given during the pregnancy (in the second or third trimester) to shrink the tumor.

If want to continue the pregnancy, the baby should be delivered by cesarean section as soon as it is able to survive outside the womb. More advanced cancers typically need be treated immediately.

Prevention

To reduce risk of cervical cancer:

- **Get vaccinated against HPV.** Vaccination is available for girls and women ages 9 to 26. The vaccine is most effective if given to girls before they become sexually active.
- **Have routine Pap tests.** Pap tests can detect precancerous conditions of the cervix, so they can be monitored or treated in order to prevent cervical cancer. Most medical organizations suggest women begin routine Pap tests at age 21 and repeat them every few years.

- **Practice safe sex.** Using a condom, having fewer sexual partners and delaying intercourse may reduce your risk of cervical cancer.
- **Quit smoke.**
- **Importance of being screened for cervical cancer:** If it's found early, cervical cancer is one of the most successfully treatable cancers. In the United States, the cervical cancer death rate declined by more than 50% over the last 30 years. This is thought to be mainly due to the effectiveness of screening with the Pap test.

Prognosis

Prognosis depends on the stage of the cancer. With treatment, the five year relative survival rate for the earliest stage of invasive cervical cancer is 92% and the overall (all stage combined) five year survival rate is about 72%.

CONCLUSION

Cervical cancer represents a major public health problem even in developed countries, screening remains an important part of a women's health care maintenance plan. Cervical canal screening should begin at age of 21yrs regardless of when the patient has her first sexual encounter.

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