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AN OVERVIEW ON CERVICAL CANCER

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ABSTRACT

Globally cervical cancer is the second most common malignancy in women and a major cause of morbidity and mortality.Recently, the greatest strides in reducing cervical cancer mortality have occurred with the advent and implementation of screening programs. Many important advances have also taken place in the diagnosis and treatment of cervical cancer. This review article will highlight diagnostic and staging considerations with an emphasis on newer imaging modalities and how they might augment approved The International Federation of Gynecology and Obstetrics (FIGO) clinical staging. One third of all cervical carcinomas occur during the reproductive period. Cervical carcinoma is the second greatest cause of death due to cancer during this phase. The aim here was to provide information about in diagnosing and managing cervical cancer in women.

KEYWORDS: Cervical cancer, FIGO, mortality.

INTRODUCTION

Worldwide, cervical cancer is second only to breast cancer in incidence and approximately three fourths of cases occur in developing countries. Cervical cancer has a major impact on

the lives of Women globally. The elderly, the economically disadvantaged, and those who do not participate in screening programs are disproportionately represented among women who develop and die from this disease. Approximately 80% of cervical cancers are squamous cell, and 15%are adenocarcinomas. Although there are lingering concerns that patients with adenocarcinomas may have a worse prognosis, there are no data showing they should be managed differently. Epidemiologic risk factors for the development of carcinoma of the cervix include young age at first coitus, multiple sexual partners, high parity, and history of other sexually transmitted diseases. Among women with one lifetime sexual partner, high risk sexual behaviors [1] by the male partner contribute to the development of cervical cancer.Hence male circumcision [2] is associated with a reduced prevalence of penile human papillomavirus [3] (HPV) infection and a reduced risk of cervical cancer among current sexual partners. Several studies have clearly linked exposure to cigarette smoke to an increased risk for cervical cancer. Carcinogens present in cigarette smoke [4] are concentrated in cervical mucus and may interfere with local immunity. The long recognized association between sexual behaviors and cervical cancer has suggested a sexually transmissible agent as a causative factor. Evidence implicating HPV in the pathogenesis of cervical cancer includes epidemiologic studies showing HPV infection to be the most important risk factor for the development of intraepithelial lesions and invasive squamous carcinomas, prevalence of HPV DNA in more than 90% of preinvasive and invasive lesions, HPV transcriptional activity identified in cervical neoplasia. Papanicolaou test has been the most cost-effective [5] cancer screening test ever developed. However the degree to which further reductions in mortality can be attained through screening is uncertain. In underdeveloped countries, screening women once in their lifetime (at age 35 years) with a simplified strategy of visual inspection of the cervix with acetic acid or HPV testing in cervical cell samples is predicted to reduce the lifetime risk of cancer by 25–36%. The cost-effectiveness of this strategy may be appealing in areas where resources are scarce. The eventual development of an HPV vaccine offers future promise in primary prevention.

Cervical cancer

Cervical cancer starts in the cells lining the cervix the lower part of the uterus (womb).This is also called the uterine cervix. The fetus grows in the body of the uterus (the upper part). The cervix connects the body of the uterus to the vagina (birth canal). The part of the cervix closest to the body of the uterus is called the endocervix. The part next to the vagina is the exocervix (or ectocervix). The two main types of cells covering the cervix are squamous cells

(on the exocervix) and glandular cells (on the endocervix). These two cell types meet at a place called the transformation zone. Most cervical cancers begin in the cells in the transformation zone. These cells do not suddenly change into cancer. Instead, the normal cells of the cervix first gradually develop pre-cancerous changes that turn into cancer. Doctors use several terms to describe these precancerous changes, including cervical intraepithelial neoplasia (CIN), squamous intraepithelial lesion (SIL), and dysplasia. These changes can be detected by the Pap test and treated to prevent cancer from developing .Cervical cancers and cervical pre-cancers are classified by how they look under a microscope. The main types of cervical cancers are squamous cell carcinoma and adenocarcinoma.Most (up to 9 out of 10) cervical cancers are squamous cell carcinomas. These cancers form from cells in the exocervix and the cancer cells have features of squamous cells under the microscope. Squamous cell carcinomas most often begin in the transformation zone (where the exocervix joins the endocervix).Most of the other cervical cancers are adenocarcinomas. Adenocarcinomas are cancers that develop from gland cells. Cervical adenocarcinoma develops from the mucus-producing gland cells of the endocervix. Cervical adenocarcinomas seem to have become more common in the past 20 to 30 years. Less commonly, cervical cancers have features of both squamous cell carcinomas and adenocarcinomas. These are called adenosquamous carcinomas or mixed carcinomas.Although cervical cancers start from cells with precancerous changes (precancers), only some of the women with pre-cancers of the cervix will develop cancer. It usually takes several years for cervical pre-cancer to change to cervical cancer, but it can happen in less than a year. For most women, pre-cancerous cells will go away without any treatment. Still,in some women precancers turn into true (invasive) cancers. Treating all cervical precancers can prevent almost all true cervical cancers. Although almost all cervical cancers are either squamous cell carcinomas or adenocarcinomas, other types of cancer also can develop in the cervix. [6] These other types,such as melanoma, sarcoma, and lymphoma, occur more commonly in other parts of the body. [7]

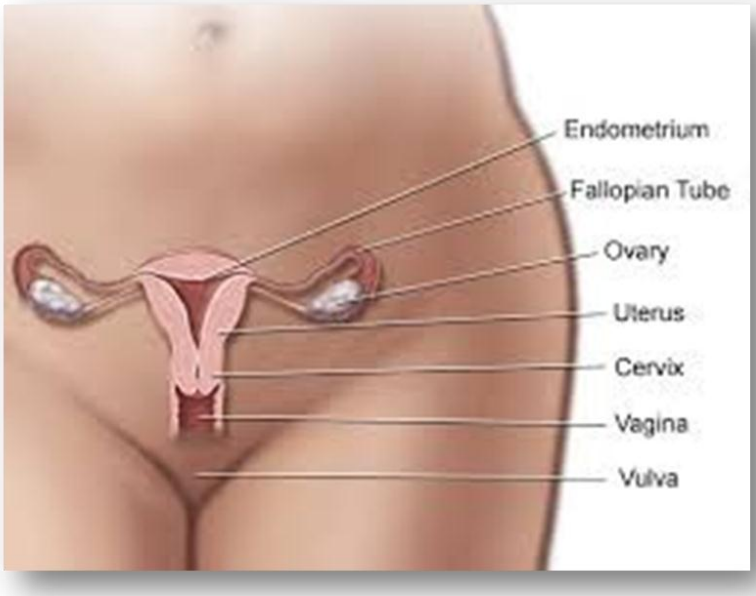

Figure-1.Anatomy of cervix

Risk factors for cervical cancer[8]

Human papilloma virus infection

The most important risk factor for cervical cancer is infection by the human papilloma virus (HPV). HPV is a group of more than 150 related viruses, some of which cause a type of growth called papillomas, which are more commonly known as warts. HPV [9] can infect cells on the surface of the skin, and those lining the genitals, anus, mouth and throat, but not the blood or internal organs such as the heart or lungs. HPV can be spread from one person to another during skin-to-skin contact. One way HPV is spread is through sex, including vaginal, anal, and even oral sex. Different types of HPVs cause warts on different parts of the body. Some cause common warts on the hands and feet; others tend to cause warts on the lips or tongue. Certain types of HPV may cause warts on or around the female and male genital organs and in the anal area. These are called low-risk types of HPV because they are seldom linked to cancer. Other types of HPV are called high-risk types because they 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. Doctors believe that a woman must be infected with HPV in order to develop cervical cancer. Although this can mean infection with any of the high-risk types, about two-thirds of all cervical cancers are caused by HPV 16 and 18.Infection with HPV is common, and in most people the body can clear the infection by itself. Sometimes, however, the infection does not go away and becomes chronic. Chronic infection, especially when it is caused by certain high-risk HPV

types, can eventually cause certain cancers, such as cervical cancer.Although there is currently no cure for HPV infection, there are ways to treat the warts and abnormal cell growth that HPV causes. [10]

Smoking: [11-13] When someone smokes, they and those around them are exposed to many cancer-causing chemicals that affect organs other than the lungs. These harmful substances are absorbed through the lungs and carried in the bloodstream throughout the body. Women who smoke are about twice as likely as non-smokers to get cervical cancer. Tobacco by-products have been found in the cervical mucus of women who smoke. Researchers believe that these substances damage the DNA of cervix cells and may contribute to the development of cervical cancer. Smoking also makes the immune system less effective in fighting HPV infections.

Immunosuppression

Human immunodeficiency virus [14] (HIV), the virus that causes AIDS, damages the immune system and puts women at higher risk for HPV infections. This might explain why women with AIDS have a higher risk for cervical cancer. The immune system is important in destroying cancer cells and slowing their growth and spread. In women with HIV, a cervical pre-cancer might develop into an invasive cancer faster than it normally would. Another group of women at risk of cervical cancer are those taking drugs to suppress their immune response, such as those being treated for an autoimmune disease (in which the immune system sees the body's own tissues as foreign and attacks them, as it would a germ) or those who have had an organ transplant.

Chlamydia infection

Chlamydia is a relatively common kind of bacteria that can infect the reproductive system. It is spread by sexual contact. Chlamydia infection can cause pelvic inflammation, leading to infertility. Some studies have seen a higher risk of cervical cancer in women whose blood test results show evidence of past or current chlamydia infection (compared with women who have normal test results). Women who are infected with chlamydia often have no symptoms In fact, they may not know that they are infected at all unless they are tested for Chlamydia during a pelvic exam. 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.

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. In one study, the risk of cervical cancer was doubled in women who took birth control pills longer than 5 years, but the risk returned to normal 10 years after they were stopped. The 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.

Use of intrauterine device

A recent study found that women who had ever used an intrauterine device (IUD) had a lower risk of cervical cancer. The effect on risk was seen even in women who had an IUD for less than a year, and the protective effect remained after the IUDs were removed.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.

Multiple fullterm pregnancies

Women who have had three or more full-term pregnancies have an increased risk of developing cervical cancer. One theory is that these women had to have had unprotected intercourse to get pregnant, so they may have had more exposure to HPV. 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 two times more likely to get cervical cancer later in life than women who waited to get pregnant until they were 25 years or older.

Poverty

Poverty is also a risk factor for cervical cancer. Many low-income women do not have ready access to adequate health care services, including Pap tests. This means they may not get screened or treated for cervical pre-cancers.

Diethylstilbestrol (DES)

DES is a hormonal drug that was given to some women to prevent miscarriage between 1940 and 1971. 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. This type of cancer is extremely rare in women who haven't been exposed [15] to DES. There is about one case of this type of cancer in every 1,000 women whose mothers took DES during pregnancy. This means that about 99.9% of DES daughters do not develop these cancers. DES-related clear cell adenocarcinoma is more common in the vagina than the cervix. The risk appears to be greatest in women whose mothers took the drug during their first 16 weeks of pregnancy. The average age of women when they are diagnosed with DES related clearcell adenocarcinoma is 19 years. Since the use of DES during pregnancy was stopped by the FDA in 1971 even the youngest DES daughters are older than 35 past the age of highestrisk. Still, there is no age cut-off when these women are safe from DES related cancer. [15,16] DES daughters may also be at increased risk of developing squamous cell cancers and precancers of the cervix linked to HPV.

Family history

Cervical cancer may run in some families. If in a family mother or sister had cervical cancer, there chances of developing the disease are 2 to 3 times higher than if no one in the family had it.

Some researchers suspect that some instances of this familial tendency are caused by an inherited condition that makes some women less able to fight off HPV infection than others.

Causes of cervical cancer

Genes (packets of our DNA) have instructions for controlling when cells grow and divide. Certain genes that promote cell division are called oncogenes. Others that slow down cell division or cause cells to die at the right time are called tumor suppressor genes. Cancers can be caused by DNA mutations (gene defects) that turn on oncogenes or turn off tumor suppressor genes.HPV causes the production of two proteins known as E6 and E7 which turn off some tumor suppressor genes. This may allow the cervical lining cells to grow too much and to develop changes in additional genes, which in some cases will lead to cancer. But HPV does not completely explain what causes cervical cancer. Most women with HPV don't get cervical cancer, and certain other risk factors, like smoking and HIV infection, influence which women exposed to HPV are more likely to develop cervical cancer.

Prevention of cervical cancer

Finding cervical precancers

A well-proven way to prevent cervix cancer is to have testing to find pre-cancers before they can turn into invasive cancer. The Pap test (or Pap smear) and the human papilloma virus (HPV) test are used for this. If a pre-cancer is found it can be treated, stopping cervical cancer before it really starts. Most invasive cervical cancers are found in women who have not had regular Pap tests. The Pap test (or Pap smear) is a procedure used to collect cells from the cervix so that they can be looked at under a microscope to find cancer and pre-cancer. These cells can also be used for HPV testing. A Pap test can be done during a pelvic exam, but not all pelvic exams include a Pap test. An HPV test can be done on the same sample of cells collected for the Pap test.Things to be done to prevent precancers such as avoiding exposure to HPV,getting an HPV vaccine and avoiding smoke.

Signs and symptoms of cervical cancer

The most common symptoms are

- Abnormal vaginal bleeding, such as bleeding after vaginal intercourse, bleeding after menopause, bleeding and spotting between periods, and having (menstrual) periods that are longer or heavier than usual. Bleeding after douching or after a pelvic exam may also occur.
- An unusual discharge from the vagina the discharge may contain some blood and may occur between your periods or after menopause.
- Pain during intercourse.

Diagnosis of cervical cancer [17,18]

The first step in finding cervical cancer is often an abnormal Pap test result. This will lead to further tests which can diagnose cervical cancer.Cervical cancer may also be suspected if the patient has symptoms like abnormal vaginal bleeding or pain during intercourse.

Medical history and physical exam

First, the doctor will ask to patient about the personal and family medical history. This includes information related to risk factors and symptoms of cervical cancer. A complete physical exam will help evaluate patient's general state of health. The doctor will do a pelvic exam and may do a Pap test if one has not already been done. In addition patient's lymph nodes will be checked closely for evidence of metastasis (cancer spread).The Pap test is a

screening test, not a diagnostic test. An abnormal Pap test result may mean more testing, sometimes including tests to see if a cancer or a pre-cancer is actually present.The tests that are used include colposcopy (with biopsy) and endocervical scraping. If a biopsy shows a pre-cancer, doctors will take steps to keep an actual cancer from developing.

Colposcopy: A speculum will be placed in the vagina to help the doctor see the cervix. The doctor will use a colposcope to examine the cervix. The colposcope is an instrument (that stays outside the body) that has magnifying lenses (like binoculars). It lets the doctor see the surface of the cervix closely and clearly. The doctor will apply a weak solution of acetic acid (similar to vinegar) to patient's cervix to make any abnormal areas easier to see. Colposcopy itself causes no more discomfort than any other speculum exam. It has no side effects and can be done safely even if patient is pregnant. Like the Pap test, it is better not to do it during patient's menstrual period. If an abnormal area is seen on the cervix, a biopsy will be done. For a biopsy, a small piece of tissue is removed from the area that looks abnormal. The sample is sent to a pathologist to look at under a microscope. A biopsy is the only way to tell for certain whether an abnormal area is a pre-cancer, a true cancer, or neither. Although the colposcopy procedure is usually not painful, the cervical biopsy can cause discomfort,cramping, or even pain in some women.

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

For this type of biopsy, first the cervix is examined with a colposcope to find the abnormal areas. Using a biopsy forceps, a small (about 1/8-inch) section of the abnormal area on the surface of the cervix is removed. The biopsy procedure may cause mild cramping, brief pain, and some slight bleeding afterward. A local anesthetic is sometimes used to numb the cervix before the biopsy.

Endocervical curettage (endocervical scraping)

Sometimes the transformation zone (the area at risk for HPV infection and pre-cancer) cannot be seen with the colposcope and something else must be done to check that area for cancer. 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). The curette is used to scrape the inside of the canal to remove some of the tissue, which is then sent to the laboratory for examination. After this procedure, patients may feel a cramping pain, and they may also have some light bleeding.

Cone biopsy: In this procedure, also known as conization, the doctor removes a cone-shaped piece of tissue from the cervix. The base of the cone is formed by the exocervix (outer part of the cervix), and the point or apex of the cone is from the endocervical canal. The tissue removed in the cone includes the transformation zone (the border between the exocervix and endocervix, where cervical pre-cancers and cancers are most likely to start).A cone biopsy can also be used as a treatment to completely remove many pre-cancers and some very early cancers. Having had a cone biopsy will not prevent most women from getting pregnant, but if a large amount of tissue has been removed, women may have a higher risk of giving birth prematurely.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)**

In this method, the tissue is removed with a thin wire loop that is heated by electrical current and acts as a scalpel.For this procedure, a local anesthetic is used. It takes only about 10 minutes. The patient may have mild cramping during and after the procedure, and mild-to-moderate bleeding for several weeks.

- **Cold knife cone biopsy**

This method uses a surgical scalpel or a laser instead of a heated wire to remove tissue. Patient will receive anesthesia during the operation (either a general anesthesia, where you are asleep, or a spinal or epidural anesthesia, where an injection into the area around the spinal cord makes patient numb below the waist) and is done in a hospital, but no overnight stay is needed. After the procedure, you might have cramping and some bleeding for a few weeks.

RESULTS OF BIOPSY

Pre-cancerous changes in a biopsy are called cervical intraepithelial neoplasia (CIN).Sometimes the term dysplasia is used instead of CIN. CIN is graded on a scale of 1 to

3 based on how much of the cervical tissue looks abnormal when viewed under the microscope.

- 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).

If a cancer is found on a biopsy, it will be identified as either squamous cell carcinoma or adenocarcinoma.

Cystoscopy, proctoscopy, and examination under anesthesia

These are most often done in women who have large tumors. They are not necessary if the cancer is caught early.In cystoscopy a slender tube with a lens and a light is placed into the bladder through the urethra. This lets the doctor check patient's bladder and urethra to see if cancer is growing into these areas. Biopsy samples can be removed during cystoscopy for pathologic (microscopic) testing. Cystoscopy can be done under a local anesthetic, but some patients may need general anesthesia. Proctoscopy is a visual inspection of the rectum through a lighted tube to check for spread of cervical cancer into patient's rectum.

Imaging studies

These include magnetic resonance imaging (MRI) and computed tomography (CT) scans. These studies can show whether the cancer has spread beyond the cervix.

- **Computed tomography (CT)** [19]

The computed tomography (CT) scan is an x-ray procedure that produces detailed crosssectional images of patient's body. Instead of taking one picture, like a conventional x-ray, a CT scanner takes many pictures as it rotates around patient. A computer then combines these pictures into an image of a slice of patient's body (think of a loaf of sliced bread). The machine takes pictures of multiple slices of the part of patient's body that is being studied. CT scans can help tell if patient's cancer has spread to the lymph nodes in the abdomen and pelvis. They can also be used to see if the cancer has spread to the liver, lungs, or elsewhere in the body. A CT scanner has been described as a large donut, with a narrow table in the middle opening. Before the test patient may be asked to drink 1 to 2 pints of a liquid called

oral contrast. Patient may also receive an IV (intravenous) line through which a different kind of contrast is injected.

- **Magnetic resonance imaging (MRI)** [20-22]

Magnetic resonance imaging (MRI) scans use radio waves and strong magnets instead of x rays to take pictures. The energy from the radio waves is absorbed and then released in a pattern formed by the type of tissue and by certain diseases. A computer translates the pattern of radio waves given off by the tissues into a very detailed image of parts of the body. Not only does this produce cross sectional slices of the body like a CT scanner, it can also produce slices that are parallel with the length of patient's body.MRI images are particularly useful in examining pelvic tumors. They are also helpful in detecting cancer that has spread to the brain or spinal cord. A contrast material might be injected into a vein just as with CT scans, but is used less often.MRI scans take longer than CT scans often up to an hour. Also, patient has to be placed inside a tube-like piece of equipment, which is confining and can upset people with claustrophobia (a fear of enclosed spaces). Special, open MRI machines that are not so confining may be an option for some patients; the downside of these is that the images may not be as good. The machine also makes a thumping noise that some find disturbing. Some places provide headphones with music to block this noise out. A mild sedative is helpful for some people.

- **Intravenous urography**

Intravenous urography (also known as intravenous pyelogram, or IVP) is an x-ray of the urinary system taken after a special dye is injected into a vein. This dye is removed from the bloodstream by the kidneys and passes through the ureters and into the bladder (the ureters are the tubes that connect the kidneys to the bladder). This test finds abnormalities in the urinary tract, such as changes caused by spread of cervical cancer to the pelvic lymph nodes,which may compress or block a ureter. IVP is rarely used currently to evaluate patients with cervical cancer.

- **Positron emission tomography**

Positron emission tomography [23] (PET) scans uses glucose (a form of sugar) that contains a radioactive atom. Cancer cells in the body absorb large amounts of the radioactive sugar and a special camera can detect the radioactivity. This test can help see if the cancer has spread to lymph nodes. PET scans can also be useful if the doctor thinks the cancer has spread but

doesn't know where. PET scans can be used instead of other types of x-rays because they scan patient's whole body. PET scans are often combined with CT scans using a machine that can do both at the same time. The CT/PET test is rarely used for patients with early cervical cancer, but may be used to look for more advanced disease.

Staged of cervical cancer: [24, 25] The two systems used for staging most types of cervical cancer, the FIGO (International Federation of Gynecology and Obstetrics) system and the AJCC (American Joint Committee on Cancer).

- **AJCC (American Joint Committee on Cancer)**

The AJCC system classifies cervical cancer on the basis of 3 factors: the extent of the tumor (T), whether the cancer has spread to lymph nodes (N) and whether it has spread to distant sites (M). The FIGO system uses the same information. The system described below is the most recent AJCC system, which went into effect January 2010.

Tumor extent (T)

Tis: The cancer cells are only found on the surface of the cervix (in the layer of cells lining the cervix), without growing into deeper tissues. (Tis is not included in the FIGO system)

T1: The cancer cells have grown from the surface layer 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.

T1a: There is a very small amount of cancer, and it can be seen only under a microscope.

- **T1a1**: The area of cancer is less than 3 mm (about 1/8-inch) deep and less than 7 mm (about 1/4-inch) wide.
- **T1a2**: 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.

  T1b: This stage includes stage I cancers that can be seen without a microscope. This stage also includes 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.
- **T1b1**: The cancer can be seen but it is not larger than 4 cm (about 1 3/5 inches).
- **T1b2**: The cancer can be seen and is larger than 4 cm.

  T2: In this stage, 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. The cancer may have grown into the upper part of the vagina.

T2a: The cancer has not spread into the tissues next to the cervix (called the parametria).

- **T2a1**: The cancer can be seen but it is not larger than 4 cm (about 1 3/5 inches).
- **T2a2**: The cancer can be seen and is larger than 4 cm.

T2b: The cancer has spread into the tissues next to the cervix (the parametria)

T3: The cancer has spread to the lower part of the vagina or the walls of the pelvis. The cancer may be blocking the ureters (tubes that carry urine from the kidneys to the bladder).

- **T3a**: The cancer has spread to the lower third of the vagina but not to the walls of the pelvis.
- **T3b**: The cancer has grown into the walls of the pelvis and/or is blocking one or both ureters (this is called hydronephrosis).

T4: The cancer has spread to the bladder or rectum or it is growing out of the pelvis

Lymph node spread (N)

NX: The nearby lymph nodes cannot be assessed

N0: No spread to nearby lymph nodes

N1: The cancer has spread to nearby lymph nodes

Distant spread (M)

M0: The cancer has not spread to distant lymph nodes, organs, or tissues

M1: The cancer has spread to distant organs (such as the lungs or liver), to lymph nodes in the chest or neck, and/or to the peritoneum (the tissue coating the inside of the abdomen).

FIGO Staging Classification: Cervical Carcinoma

Stage 0 Carcinoma in situ

Stage IA1 Invasive carcinoma, confined to cervix, diagnosed only by microscopy. Stromal invasion <3 mm in depth and < 7 mm in horizontal spread.

Stage IA2 Invasive carcinoma, confined to cervix, diagnosed only by microscopy. Stromal invasion >3 mm and <5 mm in depth and < 7 mm in horizontal spread.

Stage IB1 Invasive carcinoma, confined to cervix, microscopic lesion > IA2 or clinically visible lesion > 4 cm in greatest dimension.

Stage IB2 Invasive carcinoma, confined to cervix, clinically visible lesion >4 cm in greatest dimension.

Stage IIA Tumor extension beyond cervix to vagina but not to lower third of vagina. No parametrial invasion.

Stage IIB Tumor extension beyond cervix. Parametrial invasion but not to pelvic sidewall and not to lower third of vagina.

Stage IIIA Tumor extension to lower third of vagina but not to pelvic sidewall.

Stage IIIB Tumor extension to pelvic sidewall or causing hydronephrosis or nonfunctioning kidney.

Stage IVA Tumor invasion into bladder or rectum.

Stage IVB Distant metastasis.

Treatment of cervical cancer

Surgery for cervical cancer

- **Cryosurgery**

A metal probe cooled with liquid nitrogen is placed directly on the cervix. This kills the abnormal cells by freezing them. This can be done in a doctor's office or clinic. After cryosurgery, the patient may have a lot of watery brown discharge for a few weeks. Cryosurgery is used to treat carcinoma in situ of the cervix (stage 0), but not invasive cancer.

- **Laser surgery**

A focused laser beam, directed through the vagina, is used to vaporize (burn off) abnormal cells or to remove a small piece of tissue for study. It is done under local anesthesia (numbing medicine).Laser surgery is used to treat carcinoma in situ of the cervix (stage 0). It is not used to treat invasive cancer.

- **Conization**

A cone-shaped piece of tissue is removed from the cervix. This is done using a surgical or laser knife (cold knife cone biopsy) or using a thin wire heated by electricity (the loop electrosurgical, LEEP or LEETZ procedure). After the procedure, the tissue removed (the cone) is examined under the microscope. If the margins (outer edges) of the cone contain cancer (or pre-cancer) cells (called positive margins), some cancer (or pre-cancer) may have

been left behind, so further treatment is needed. A cone biopsy may be used to diagnose the cancer before additional treatment with surgery or radiation. It can also be used as the only treatment in women with early (stage IA1) cancer who want to preserve their ability to have children (fertility).

- **Hysterectomy** [26]

This is surgery to remove the uterus (both the body of the uterus and the cervix) but not the structures next to the uterus (parametria and uterosacral ligaments). The ovaries and fallopian tubes are usually left in place unless there is another reason to remove them. When the uterus is removed through a surgical incision in the front of the abdomen, it is called an abdominal hysterectomy. When the uterus is removed through the vagina, it is called a vaginal hysterectomy. When the uterus is removed using laparoscopy, it is called a laparoscopic hysterectomy. Laparoscopy allows the inside of the abdomen and pelvis to be seen through a thin tube with a camera at the end (the laparoscope) that is inserted into one or more very small surgical incisions. Small instruments can be controlled through the tube, so the surgeon makes cuts and removes tissue through the tubes without making a large cut in the abdomen. The laparoscope can also make it easier for the doctor to remove the uterus, ovaries, and fallopian tubes through the vaginal incision. This is called a laparoscopic assisted vaginal hysterectomy. In some cases, laparoscopy is performed with special tools to help the surgeon see better and with instruments that are controlled by the surgeon. This is called robotic-assisted surgery.General or epidural (regional) anesthesia is used for all of these operations. The recovery time and hospital stay tends to be shorter for a laparoscopic or vaginal hysterectomy than for an abdominal hysterectomy. For a laparoscopic or vaginal hysterectomy, the hospital stay is usually 1 to 2 days followed by a 2- to 3-week recovery period. A hospital stay of 3 to 5 days is common for an abdominal hysterectomy, and complete recovery takes about 4 to 6 weeks. Any type of hysterectomy results in infertility (inability to have children). Complications are unusual but could include excessive bleeding, wound infection, or damage to the urinary or intestinal systems. Hysterectomy is used to treat stage IA1 cervical cancers. It is also used for some stage 0 cancers (carcinoma in situ), if cancer cells were found at the edges of the cone biopsy (this is called positive margins). A hysterectomy is also used to treat some non-cancerous conditions. The most common of these is leiomyomas, a type of benign tumor commonly known as fibroids.Hysterectomy does not change a woman's ability to feel sexual pleasure. A woman does not need a uterus or cervix

to reach orgasm. The area around the clitoris and the lining of the vagina remain as sensitive as before after a hysterectomy.

- **Radical hysterectomy** [27-29]

For this operation, the surgeon removes the uterus along with the tissues next to the uterus (the parametria and the uterosacral ligaments) and the upper part (about 1 inch) of the vagina next to the cervix. The ovaries and fallopian tubes are not removed unless there is some other medical reason to do so. This surgery is usually performed through an abdominal incision. Often, some pelvic lymph nodes are removed as well.Another surgical approach is called laparoscopic-assisted radical vaginal hysterectomy. This operation combines a radical vaginal hysterectomy with a laparoscopic pelvic node dissection. Laparoscopy allows the inside of the abdomen and pelvis to be seen through a thin tube with a camera at the end (the laparoscope) that is inserted into one or more very small surgical incisions. Small instruments can be controlled through the tube, so the surgeon can make cuts and remove tissue through the tubes without making a large cut in the abdomen. The laparoscope can make it easier for the doctor to remove the uterus, ovaries, and fallopian tubes through the vaginal incision. Laparoscopy can also be used to perform a radical hysterectomy through the abdomen. Lymph nodes are removed as well. This is called laparoscopically assisted radical hysterectomy with lymphadenectomy. Robot-assisted laparoscopic surgery is also sometimes used to perform radical hysterectomies. The advantages are lower blood loss and a shorter stay in the hospital after surgery (compared to surgery using regular incisions). However, this way of treating cervical cancer is still relatively new, and its ultimate role in treatment is still being studied.More tissue is removed in a radical hysterectomy than in a simple one, so the hospital stay can be longer, about 5 to 7 days. Because the uterus is removed, this surgery results in infertility. Because some of the nerves to the bladder are removed, some women have problems emptying their bladder after this operation and may need a catheter for a time.Complications are unusual but could include excessive bleeding, wound infection, or damage to the urinary and intestinal systems.A radical hysterectomy and pelvic lymph node dissection are the usual treatment for stages IA2, IB, and less commonly IIA cervical cancer, especially in young women.Radical hysterectomy does not change a woman's ability to feel sexual pleasure. Although the vagina is shortened, the area around the clitoris and the lining of the vagina is as sensitive as before. A woman does not need a uterus or cervix to reach orgasm. When cancer has caused pain or bleeding with intercourse, the hysterectomy may actually improve a woman's sex life by stopping these symptoms.

- **Trachelectomy** [30]

Most women with stage IA2 and stage IB cervical cancer are treated with hysterectomy.Another procedure, known as a radical trachelectomy, allows women be treated without losing their ability to have children. This procedure removes the cervix and the upper part of the vagina but not the body of the uterus. The surgeon places a purse-string stitch to act as an artificial opening of the cervix inside the uterine cavity.The nearby lymph nodes are also removed using laparoscopy which may require another incision (cut). The operation is done either through the vagina or the abdomen.After trachelectomy, some women are able to carry a pregnancy to term and deliver a healthy baby by cesarean section. In one study, the pregnancy rate after 5 years was more than 50%,but the women who had this surgery had a higher risk of miscarriage than what is seen in normal healthy women. The risk of the cancer coming back after this procedure is low.

- **Pelvic exenteration** [31]

This is a more extensive operation that may be used to treat recurrent cervical cancer. In this surgery, all of the same organs and tissues are removed as in a radical hysterectomy with pelvic lymph node dissection. In addition, the bladder, vagina, rectum, and part of the colon may also be removed, depending on where the cancer has spread. If the bladder is removed, a new way to store and eliminate urine will be needed. This usually means using a short segment of intestine to function as a new bladder. The new bladder may be connected to the abdominal wall so that urine is drained periodically when the patient places a catheter into a urostomy (a small opening). Or urine may drain continuously into a small plastic bag attached to the front of the abdomen If the rectum and part of the colon are removed, a new way to eliminate solid waste must be created. This is done by attaching the remaining intestine to the abdominal wall so that fecal material can pass through a colostomy (a small opening) into a small plastic bag worn on the front of the abdomen. It may be possible to remove the cancerous part of the colon (next to the cervix) and reconnect the colon ends so that no bags or external appliances are needed. If the vagina is removed, a new vagina can be surgically created out of skin, intestinal tissue,or muscle and skin (myocutaneous) grafts.Recovery from total pelvic exenteration takes a long time. Most women don't begin to feel like themselves again for 6 months after surgery. Some say it takes a year or two to adjust completely.Nevertheless, these women can lead happy and productive lives. With practice and determination, they can also have sexual desire, pleasure, and orgasms.

- **Pelvic lymph node dissection**

Cancer that starts in the cervix can spread to lymph nodes in the pelvis (lymph nodes are peasized collections of immune system tissue). To check for lymph node spread, the surgeon might remove some of these lymph nodes. This procedure is known as a lymph node dissection or lymph node sampling. It is done at the same time as a hysterectomy (or trachelectomy). Removing lymph nodes can lead to fluid drainage problems in the leg. This can cause severe swelling in the leg, a condition called lymphedema.

Radiation therapy for cervical cancer [32]

- **External beam radiation**

One way to give radiation is to aim x-rays at the cancer from outside the body. This is called external beam radiation therapy (EBRT). Treatment is much like getting a regular x-ray, but the radiation dose is stronger. Each treatment lasts only a few minutes, although the setup timegetting patient into place for treatment usually takes longer. The procedure itself is painless, but does result in some side effects. When radiation is used as the main treatment for cervical cancer, EBRT is usually combined with chemotherapy (called concurrent chemoradiation). Often, this is a low dose of a drug called cisplatin, but other chemotherapy drugs can be used as well. The radiation treatments are given 5 days a week for 6 to 7 weeks to complete.EBRT can also be used by itself to treat areas of cancer spread or as the main treatment of cervical cancer in patients who can't tolerate chemoradiation. Common side effects of external beam radiation therapy include fatigue (tiredness),upset stomach,diarrhea or loose stools (if radiation is given to the pelvis or abdomen),nausea and vomiting,skin changes.As the radiation passes through the skin to the cancer, it can damage the skin cells. This can cause irritation ranging from mild, temporary redness to peeling. The skin may release fluid, which can lead to infection, so the area exposed to radiation must be carefully cleaned and protected.Radiation to the pelvis can also irritate the bladder (radiation cystitis), causing discomfort and an urge to urinate often.Radiation can affect the vulva and vagina, making them sensitive and sore, and sometimes causing a discharge.Pelvic radiation can also affect the ovaries, leading to menstrual changes and even early menopause.Radiation can also lead to low blood counts, which can cause anemia (low red blood cells), which can cause you to feel tired, leukopenia (low white blood cells), which increases the risks of serious infection.

- **Brachytherapy/ internal radiation therapy** [32,33]

This involves placing a source of radiation in or near the cancer. For the type of brachytherapy that is used most often to treat cervical cancer, intracavitary brachytherapy, the radiation source is placed in a device that is in the vagina (and sometimes the cervix). This is often used in addition to EBRT as a part of the main treatment for cervical cancer.To treat cervical cancer in women who have had a hysterectomy, the radioactive material is placed in a cylinder in the vagina.To treat a woman who still has a uterus, the radioactive material can be placed in a small metal tube called a tandem that goes in the uterus, along with small round metal holders called ovoids placed near the cervix. This is sometimes called tandem and ovoid treatment.Another option is called tandem and ring. For this, a round holder (like a disc) is placed close to the uterus. Which one is used depends on what type of brachytherapy is planned.Low-dose rate brachytherapy is completed in just a few days. During that time, the patient remains in bed the hospital with instruments holding the radioactive material in place. High-dose rate brachytherapy is done as an outpatient over several treatments (often at least a week apart). For each high-dose treatment, the radioactive material is inserted for a few minutes and then removed. The advantage of high-dose rate treatment is that patient does not have to stay still for long periods of time.In brachytherapy, radiation only travels a short distance, so the main effects of the radiation are on the cervix and the walls of the vagina. The most common side effect is irritation of the vagina. It may become red and sore and there may be a discharge. The vulva may become irritated as well. Brachytherapy can also cause many of the same side effects as external beam radiation, such as fatigue, diarrhea, nausea, irritation of the bladder, and low blood counts. Often brachytherapy is given right after external beam radiation (before the side effects can go away), so it can be hard to know which type of treatment is causing the side effect.

Side effects of radiation therapy

Both external beam radiation to the pelvis and brachytherapy can cause scar tissue to form in the vagina. The scar tissue can make the vagina more narrow (called vaginal stenosis), less able to stretch, or even shorter, which can make vaginal intercourse painful. A woman can help prevent this problem by stretching the walls of her vagina several times a week.Although this can be done by having sexual intercourse 3 to 4 times a week, most women find that hard to do during (or in the weeks after) treatment. The other way to stretch out the walls of the vagina is by using a vaginal dilator (a plastic or rubber tube used to stretch out the vagina). A woman getting radiation does not have to start using the dilator

during the weeks that radiation is being given, but she should start by 2 to 4 weeks after treatment ends.Because it can take a long time to see the effects of radiation and because the radiation effects are long lasting, it is recommended that the dilator be used indefinitely.Vaginal dryness and painful intercourse can be long-term side effects from radiation (both brachytherapy and external beam radiation). Vaginal (local) estrogens may help with vaginal dryness and changes to the vaginal lining, especially if radiation to the pelvis damaged the ovaries, causing early menopause. Radiation to the pelvis can also weaken the bones, leading to fractures. Hip fractures are the most common, and might occur 2 to 4 years after radiation. Bone density studies are recommended.If pelvic lymph nodes are treated with radiation, it can lead to fluid drainage problems in the leg. This can cause severe swelling in the leg, a condition called lymphedema. It is important to know that smoking increases the side effects from radiation and can make treatment less effective.

Chemotherapy for cervical cancer [34-36]

Chemo is often given in cycles, with each period of treatment followed by a recovery period.There are a few situations in which chemo may be recommended.

- **For the main treatment**

For some stages of cervical cancer, the preferred treatment is radiation and chemo given together (called concurrent chemoradiation). The chemo helps the radiation work better. Options for concurrent chemoradiation include:Cisplatin given weekly during radiation. This drug is given into a vein (IV) about 4 hours before the radiation appointment.Cisplatin plus 5-fluorouracil (5-FU) given every 4 weeks during radiation.Sometimes chemo is also given (without radiation) before and/or after chemoradiation.

- **To treat recurrent cervical cancer**

Chemo may also be used to treat cancers that have spread to other organs and tissues. It can also be helpful when cancer comes back after treatment with chemoradiation.Drugs most often used to treat advanced cervical cancer include:Cisplatin,Carboplatin,Paclitaxel (Taxol®),Topotecan,Gemcitabine (Gemzar®) Often combinations of these are used.Some other drugs can be used as well, such as docetaxel (Taxotere®), ifosfamide (Ifex®), 5-fluorouracil (5-FU), irinotecan (Camptosar®, CPT-11), and mitomycin.

Side effects of chemotherapy: Common side effects of chemotherapy can include nausea and vomiting, loss of appetite, loss of hair, mouth sores, fatigue (tiredness).Because

chemotherapy can damage the blood-producing cells of the bone marrow, the blood cell counts might become low. This can result in an increased chance of infection (from a shortage of white blood cells),bleeding or bruising after minor cuts or injuries (because of a shortage of blood platelets) and shortness of breath (due to low red blood cell counts).When chemo is given with radiation, the side effects are often more severe. The nausea and fatigue are often worse. Diarrhea can also be a problem if chemo is given at the same time as radiation. Problems with low blood counts can also be worse. Some drugs used to treat cervical cancer, including paclitaxel and cisplatin, damage nerves outside of the brain and spinal cord. This (called peripheral neuropathy) can sometimes lead to symptoms (mainly in the hands and feet) like numbness, pain, burning or tingling sensations, sensitivity to cold or heat, or weakness.

- **HPV vaccines** [37,38]

Vaccines have been developed to prevent infection with some of the HPV types associated with cervical cancer.Any woman who is sexually active is at risk of infection from human papillomavirus (HPV). Over 100 subtypes of HPV have been identified. A significant proportion of HPV disease is attributed to four subtypes; 6,11,16 and 18. HPV subtypes 16 and 18 cause approximately 70% of cervical cancer cases worldwide. HPV subtypes 6 and 11 infections are responsible for genital warts.One or more co-factors that increase the likelihood of persistence of HPV infection are also needed for cervical cancer to develop.Two HPV vaccines have been developed: Cervarix®, a bivalent HPV (types 16,18) vaccine and Gardasil®, a quadrivalent HPV (types 6,11,16,18) vaccine. Both are prophylactic vaccines that have been shown to be effective in young women prior to HPV exposure.These vaccines attempt to produce an immune reaction to the parts of the virus (E6 and E7 proteins) that make the cervical cancer cells grow abnormally. It is hoped that this immunity will kill the cancer cells or stop them from growing.

- **Sentinel lymph node biopsy** [39,40]

During surgery for cervical cancer, lymph nodes in the pelvis may be removed to check for cancer spread. Instead of removing many lymph nodes, a technique called sentinel lymph node biopsy can be used to target just the few lymph nodes most likely to contain cancer. In this technique a blue dye containing a radioactive tracer is injected into the cancer and allowed to drain into lymph nodes. Then, during surgery, the lymph nodes that contain radiation and the blue dye can be identified and removed. These are the lymph nodes most

likely to contain cancer if it had spread. If these lymph nodes don't contain cancer, the other lymph nodes don't need to be removed. Removing fewer lymph nodes may lower the risk of later problems. A clinical trial is looking at a different way of doing a sentinel node biopsy procedure. It maps the lymph nodes using with robotic (laparoscopic) assisted near infrared imaging after injecting indocyanine green (ICG) dye into the cervix.

- **Targeted therapy**

As researchers have learned more about the gene changes in cells that cause cancer, they have been able to develop newer drugs that specifically target these changes. These targeted drugs work differently from standard chemotherapy drugs. They often have different (and less severe) side effects. These drugs may be used alone or with more traditional chemotherapy.Pazopanib is a type of targeted therapy drug that blocks the effect of certain growth factors on cancer cells. In studies of patients with advanced cervical cancer, it helped them live longer.

Recurrent cervical cancer

Cancer that comes backs after treatment is called recurrent cancer. Cancer can come back locally (in or near where it first started, such as cervix, uterus or nearby the pelvic organs) or come back in distant areas (spread through the lymphatic system and/or the bloodstream to organs such as the lungs or bone).If the cancer has recurred in the pelvis only, extensive surgery (by pelvic exenteration) may be an option for some patients. This operation may successfully treat 40% to 50% of patients.Sometimes radiation or chemo may be used to help relieve symptoms, but they aren't expected to cure the cancer.

CONCLUSION

The prevalence and natural history studies is that both HPV based preventive strategies, whether for screening or vaccination, should effectively target all cases of cervical cancer. The most important point remains that women and clinicians need to be informed of the usually benign nature of an HPV infection to minimize the anxiety that may accompany a positive HPV test result, and this should be at the forefront of all communication messages.

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