# Cervical Cancer Study Notes

Cervical cancer is the second most prevalent cancer in women globally and continues to be a major cause of cancer-related mortality in women residing in developing nations. Among women in the United States, it ranks as the fourth most prevalent malignant neoplasm, following breast, colorectal, and endometrial carcinomas. In the United States, the occurrence of invasive cervical cancer has consistently decreased over the past few decades. However, in numerous developing nations, it is still increasing. The shift in the epidemiological pattern in the United States has been ascribed to widespread screening using Papanicolaou testing (Pap smears).

**Incidence**: In the United States, cervical cancer has a higher prevalence among Hispanic, African American, and Native American women compared to white women.
**Gender**: Cervical cancer exclusively affects individuals who are assigned female at birth.
**Age**: Cervical cancers typically impact women in their middle age or beyond, although it can be detected in women of reproductive age as well.

## Historical background:

Due to regular screening of women, the most prevalent outcome is an abnormal Pap smear test.

From a clinical perspective, the initial indication is atypical vaginal bleeding, typically occurring after sexual intercourse.

Vaginal discomfort, foul-smelling discharge, and painful urination are frequently observed.

The tumor has vertical growth, expanding into the endometrial cavity, downward towards the vagina, and laterally towards the pelvic wall. It has the ability to immediately infiltrate the bladder and rectum.

Manifestations such as constipation, hematuria, fistula, and ureteral obstruction, with or without hydroureter or hydronephrosis, indicate the presence of local organ involvement.

The presence of leg edema, discomfort, and hydronephrosis indicates the involvement of the pelvic wall.

The typical locations for distant metastasis are lymph nodes outside the pelvic region, liver, lungs, and bones.

Physical examination findings in patients with early-stage cervical cancer may appear reasonably unremarkable.

As the disease advances, the cervix may exhibit atypical visual characteristics, such as extensive erosion, ulceration, or the presence of a tumor. The anomalies can also affect the vaginal region.

A rectal examination can detect the presence of an external mass or the presence of visible blood resulting from the erosion of a tumor.

Pelvic metastases is frequently detected during bimanual examination.

The presence of leg edema indicates the possibility of a tumor causing obstruction in the lymphatic or vascular system.

In cases where the disease affects the liver, certain patients may experience hepatomegaly.

Detecting pulmonary metastases through physical examination is typically challenging, unless there are clear signs of pleural effusion or bronchial obstruction.

## Causes:

Initial epidemiological evidence has established a clear cause-and-effect connection between cervical cancer and sexual activity. Significant risk factors identified include early sexual debut, engaging in sexual activity with several partners, having promiscuous male partners, and a previous history of sexually transmitted infections. Nevertheless, the quest for a potential sexually transmitted carcinogen had yielded no results until the past decade, when a significant advancement in molecular biology allowed scientists to identify viral genetic material in cervical cells.

HPVs are now strongly implicated as the main suspects based on compelling data. HPV viral DNA has been identified in over 80% of squamous intraepithelial lesions (SILs) and invasive cervical malignancies, although controls continuously exhibit a lower percentage of HPV viral DNA detection. Both animal data and molecular biologic evidence unequivocally demonstrate the capacity of papilloma virus–induced lesions to undergo malignant transformation. Squamous intraepithelial lesions (SILs) are primarily observed in younger women, but invasive malignancies are more frequently diagnosed in women who are approximately 10-15 years older. This pattern suggests a gradual development of cancer over time.

A significant proportion of sexually active women experience HPV infection. The majority of these infections resolve spontaneously within a few months to a couple of years, and just a small percentage advance to malignancy. Therefore, it is necessary for other essential variables to be included in the process of carcinogenesis.

Three primary elements have been hypothesized to impact the advancement of low-grade SILs to high-grade SILs. These factors encompass the specific type and duration of viral infection, where a high-risk HPV type and persistent infection indicate a greater likelihood of progression. Additionally, host conditions that weaken the immune system, such as multiple pregnancies or inadequate nutritional status, as well as environmental factors like smoking, use of oral contraceptives, or deficiencies in vitamins, also contribute to the risk. Furthermore, other gynecologic characteristics, such as the onset of menstruation, the age at which sexual activity begins, and the number of sexual partners, substantially elevate the likelihood of developing cervical cancer.

## Human papillomavirus

HPV is a diverse collection of viruses that possess closed circular double-stranded DNA. The genetic material of the virus contains 6 initial open reading frame proteins (E1, E2, E3, E4, E6, E7), which serve as regulatory proteins, and 2 subsequent open reading frame proteins (L1, L2), which

constitute the viral capsid.

So far, scientists have discovered and replicated 77 distinct genotypes of HPV. Out of these, types 6, 11, 16, 18, 26, 31, 33, 35, 39, 42, 43, 44, 45, 51, 52, 53, 54, 55, 56, 58, 59, 66, and 68 are more inclined to infect anogenital tissues.

The human papillomaviruses (HPVs) that infect the human cervix can be classified into two main types. The low-risk varieties encompass HPV 6b and 11, which are linked to low-grade SILs but are never detected in invasive malignancy. The high-risk variants, predominantly HPV 16 and 18, are present in 50-80% of SILs and in as many as 90% of invasive malignancies.

The primary distinction between the two types is in the post-infection behavior. Specifically, low-risk HPVs persist as extrachromosomal DNA episomes, whereas high-risk HPVs integrate their genome into the host cellular DNA. Recombination frequently results in the direct connection of E6 and E7 to the viral promoter and enhancer regions, enabling their persistent expression following integration. The binding and inactivation of the Rb protein by E7, as well as the binding of p53 by E6 and its subsequent destruction, result in the functional loss of both TP53 and the RB genes. This loss leads to resistance to apoptosis, which in turn causes uncontrolled cell proliferation following DNA damage. Consequently, this leads to the development of cancer.
Human immunodeficiency virus (HIV)

The exact relationship between human immunodeficiency virus (HIV) infection and the development of cervical cancer remains unclear. Research has indicated that there is a greater occurrence of HPV in women who are HIV-positive compared to those who are HIV-negative. Furthermore, the prevalence of HPV is directly linked to the degree of weakened immune system function, as evaluated by CD4 levels.
It has been suggested that a decrease in the normal functioning of lymphocytes can increase the activity of latent or subclinical HPV, leading to a higher likelihood of chronic infection.
The potential synergistic effect of HIV on HPV infection, whether through direct molecular interaction or indirect immunologic mechanisms, is still uncertain.

## Differentials

**Cervicitis**
Endometrial Carcinoma refers to a type of cancer that develops in the lining of the uterus.
Pelvic Inflammatory Disease (PID)
Uterine cancer
Vaginitis is an inflammation of the vagina.

## Laboratory investigations:

Performing a Pap smear is recommended for every patient suspected of having cervical cancer.
It is recommended to refer the patient to a gynecologist for the procedures of colposcopy, direct biopsies, and endocervical curettage.
Once the diagnosis is confirmed, it is advisable to request a comprehensive blood cell count and serum chemistry analysis to assess any abnormalities related to potential metastatic disease.

### Radiological examinations:

After the diagnosis is confirmed, imaging studies are conducted to determine the stage of the condition.
It is advisable to have a regular chest radiograph in order to assist in excluding the possibility of pulmonary metastases.
A computed tomography (CT) scan of the abdomen and pelvis is conducted to detect the presence of metastases in the liver, lymph nodes, or other organs, as well as to assist in excluding the possibility of hydronephrosis/hydroureter.

In patients with a sizable primary tumor, barium enema investigations can determine whether the cervical mass is causing external rectal compression.

**Methods**:

For patients with a large primary tumor, it is advisable to conduct cystoscopy and proctoscopy in order to exclude the possibility of local invasion in the bladder and colon.
Clinical staging procedures may be inadequate in detecting pelvic and aortic lymph node involvement in 20-50% and 6-30% of patients, respectively. Therefore, surgical staging is often advised. Pretreatment surgical staging is the most precise approach for assessing the scope of the disease. Nevertheless, there is scant evidence indicating an enhancement in overall survival through the implementation of regular surgical staging. Hence, it is necessary to personalize the pretreatment surgical staging based on a comprehensive evaluation that excludes metastatic disease using fine-needle aspiration of lymph nodes when other non-surgical methods have been inconclusive.

Histologic findings of precancerous lesions in the cervix are typically identified during Pap smear tests. The Pap smear classification system has undergone evolutionary changes over time. The conventional numerical system categorized class I as representing typical cells, class II as denoting aberrant cells, class III as indicating cervical dysplasia, class IV as signifying carcinoma in situ, and class V as representing invasive malignancy. The numerical method was superseded by the cervical intraepithelial neoplasia (CIN) system in 1972. CIN I denotes a condition of mild dysplasia, CIN II signifies moderate dysplasia, and CIN III represents severe dysplasia or cancer in situ. Since 1988, the National Cancer Institute (NCI) has organized a workshop with the aim of establishing standardized protocols for reporting Pap smear results.

**AS-CUS (Atypical Squamous Cells of Undetermined Significance)**

ASCUS, which stands for Atypical Squamous Cells of Undetermined Significance, are seen in around 5% of Pap smear findings. Typically, they indicate the presence of squamous metaplasia and HPV lesions. Around 50% of cases with ASCUS naturally resolve on their own. As a result, it is recommended to do repeat smears every 4-6 months for a duration of 2 years until three consecutive smears show no abnormalities. Colposcopy and biopsy should be conducted for individuals who do not adhere to therapy or those who continue to have persistent ASCUS. Topical estrogens should be administered to postmenopausal women for a duration of 2 months prior to the subsequent Pap smear. Any detected infection must be promptly treated.

**Low-grade squamous intraepithelial lesions**

Approximately 5-40% of Pap smears showing low-grade squamous intraepithelial lesions (LGSIL) exhibit CIN II-III. Most of these cases (78.3%) have spontaneous regression. The management

choices consist of either promptly conducting colposcopy with biopsy or conducting a repeat Pap smear every 4-6 months. Colposcopy is recommended if there are persistent low-grade squamous intraepithelial lesions (LGSILs).

**Severe squamous intraepithelial lesions**

Patients exhibiting high-grade squamous intraepithelial lesions on smears should be subjected to colposcopy and direct biopsies. If the complete extent of the lesion and transforming zone is observed, either excisional or ablative therapy is recommended. If the complete extent of the lesion or the transition zone is not visible, a cone biopsy is recommended.
Indeterminate presence of abnormal glandular cells

Glandular cells exhibiting abnormalities that beyond those associated with a reactive or inflammatory process, however do not reach the level of severity required for classification as neoplasia, are referred to as atypical glandular cells of unclear significance. The origin of these cells can be traced back to the endocervix, endometrium, fallopian tubes, or ovaries.

**Overall considerations**

A comprehensive assessment should encompass Pap smear utilizing a cytobrush, as well as obtaining samples from the endocervix and endometrium. If the smear test indicates the presence of adenocarcinoma in situ, it is recommended to proceed with a cone biopsy. If the underlying cause of the disease remains uncertain following the aforementioned investigation, it is recommended that the patient has a procedure known as dilatation and curettage.

Prior to performing uterine curettage, it is important to get ultrasound findings that accurately delineate the fallopian tubes and ovaries. This will assist in the identification of primary cancers in these organs.
In relation to invasive cervical cancer, the histology of malignant growth in the cervix is primarily derived from epithelial cells, with squamous cell carcinoma being the main type, accounting for 85% of cases. Uncommon histologies encompass adenocarcinoma, small cell carcinoma, melanoma, and lymphoma.
Medical Care: The management of cervical cancer is contingent upon the specific stage of the illness. Surgery is the preferred treatment for early invasive cancer. For more complex situations, the current accepted practice is to use a combination of radiation and chemotherapy. Chemotherapy or radiation therapy can alleviate symptoms in patients with disseminated illness. Surgery is the preferred treatment for stage Ia illness.

**Stage IB or IIA**

Patients diagnosed with stage IB or IIA illness have two treatment options: combination external beam radiation with brachytherapy or total hysterectomy with bilateral pelvic lymphadenectomy.The majority of retrospective investigations have demonstrated comparable survival rates for both operations, however these studies are sometimes marred by patient selection bias and other confounding variables. Nevertheless, a recent randomized research demonstrated equivalent overall and disease-free survival rates.There is a limited amount of data available on the quality of life, especially in relation to psychosexual aspects.Administering radiation therapy to the pelvic region after surgery reduces the likelihood of the cancer returning in people who have high-risk characteristics.A recent randomized trial demonstrated that patients

who have parametrial involvement, positive pelvic nodes, or positive surgical margins experience advantages from a postoperative regimen that combines cisplatin-containing chemotherapy and pelvic radiotherapy.

**Stage IIB-IVA refers to the advanced stages of a medical condition or disease.**
Radiation therapy has long been the preferred treatment for locally advanced cervical cancer, namely stages IIB, III, and IVA.The reported 5-year survival rates for stages IIB, III, and IVA when treated solely with radiation are 65-75%, 35-50%, and 15-20%, respectively.The treatment starts with a series of external beam radiation sessions to decrease the size of the tumor, allowing for the administration of intracavitary treatment afterwards. Brachytherapy is administered by inserting afterloading applicators into the uterus and vagina.

**Chemoradiotherapy for cervical cancer**

Three meticulously executed studies on concurrent chemoradiation have recently altered the standard of therapy for this particular patient population.Within the Radiation Therapy Oncology Group experiment, a total of 403 patients diagnosed with large stage IB and IIB-IVA tumors were randomly assigned to receive either irradiation targeting the pelvic and paraaortic regions or pelvic radiation in combination with cisplatin and fluorouracil. The group that got combination treatment had considerably higher rates of both disease-free survival and overall survival.Rose and his colleagues ran a study as part of the Gynecologic Oncology Group (GOG) to see how well radiation therapy worked when combined with three different types of chemotherapy (cisplatin alone, cisplatin/5-fluorouracil/hydroxyurea, and hydroxyurea alone) in people with stage IIB, III, or IVA cancer.

The groups that received cisplatin-containing regimens exhibited considerably greater overall survival rates.In a separate GOG experiment, individuals with large stage IB illness were randomly assigned to receive either radiation therapy alone or a combination of weekly cisplatin and radiation therapy. Every patient underwent adjuvant hysterectomy. The combined-therapy group had significantly higher rates of disease-free survival and overall survival after 4 years of follow-up.According to the study results described earlier, it is now justifiable to consider employing cisplatin-based chemotherapy along with radiation as a viable choice for patients with locally advanced cervical cancer.

## Surgical care:

Stage 0 carcinoma, also known as carcinoma in situ, is managed using local ablative techniques such as cryosurgery, laser ablation, and loop excision.
Hysterectomy should only be performed on patients who have additional gynecologic indications that can support the need for the treatment.
Following local therapy, many patients have ongoing lifelong monitoring.

The primary approach to managing widespread cervical cancer is predominantly palliative, as achieving a cure is not feasible.
The use of individual chemotherapeutic drugs like cisplatin or ifosfamide leads to response rates of around 20%. Combining several treatment regimens results in increased rates of response and can extend the period of time without disease recurrence. Nevertheless, the level of toxicity is heightened without any corresponding improvement in survival rates. Furthermore, the response length is typically brief.

Palliative radiotherapy is frequently employed as a standalone treatment to manage hemorrhaging, pelvic discomfort, or urinary or partial blockages of the large bowel caused by pelvic illness.
In this particular group of patients, invasive operations such as nephrostomy or diverting colostomy are occasionally carried out to enhance their quality of life.It is crucial to prioritize the provision of comprehensive palliative care, which encompasses sufficient pain management, for these patients.

Total hysterectomy is the recommended treatment for microinvasive illness (stage IA).
If the depth of invasion is less than 3 mm and there is no lymphovascular invasion, there is no need for lymph node dissection.Patients who have stage IA1 illness without lymphovascular space invasion and wish to preserve their fertility may undergo therapeutic conization. They will be closely monitored with cytology, colposcopy, and endocervical curettage.

Radiation therapy can effectively treat patients with medical comorbidities who are not suitable for surgery.

**Advisory sessions:**

The management of cervical cancer often necessitates a multidisciplinary strategy that involves the collaboration of a gynecologic oncologist, radiation oncologist, and medical oncologist.

Nutritional regimen:

Optimal diet is crucial for individuals diagnosed with cervical cancer. Efforts should be exerted to promote and ensure sufficient consumption of food through the mouth.
Nutritional supplements like Ensure or Boost are administered to patients who have had substantial weight loss or are unable to consume regular diet owing to sickness induced by radiation or chemotherapy.
Megace, an appetite stimulant, may be administered for patients suffering from severe anorexia.
Percutaneous endoscopic gastrostomy tubes are inserted to provide nutritional supplementation for patients who cannot consume any food orally.
Hyperalimentation is occasionally employed in patients suffering from metastatic cancer-induced severe intestinal blockage.

**Drug Category: Chemotherapy agents** -- These drugs hinder the growth and multiplication of cells.
The drug, **Cisplatin (Platinol),** works by causing intrastrand cross-linking of DNA and inhibiting DNA precursors. These are the proposed mechanisms of action. Utilized in conjunction with radiation therapy.
The recommended dosage for adults is 50-100 mg/m2 administered intravenously every 3 weeks.
Administer 40 milligrams per square meter intravenously once a week for a duration of 5 weeks.
The appropriate dosage for pediatric patients has not been determined.
Contraindications for this medication include documented hypersensitivity, renal failure, peripheral neuropathy, and bone marrow suppression.
Interactions: Impairs the excretion of bleomycin
Pregnancy: This medication is considered unsafe and should not be used during pregnancy.
Precautions: Peripheral neuropathy and myelosuppression may occur. Intravenous hydration reduces the risk of kidney damage. Selective serotonin antagonists and steroids can be used to prevent nausea and vomiting.

T**he drug 5-Fluorouracil,** sometimes known as Efudex, Adrucil, or Fluoroplex, is a pyrimidine antagonist. Multiple methods of action have been suggested, such as the suppression of thymidylate synthase and the hindrance of RNA synthesis. Additionally, it possesses strong radiosensitizing properties.
The recommended dosage for adults is 225 mg/m2/d administered continuously via intravenous infusion for a duration of 5 weeks.
The appropriate dosage for pediatric patients has not been determined.
Contraindications include a documented hypersensitivity, myelosuppression, and acute active infection.
Interactions: This medication may enhance the effects of anticoagulants, immunosuppressives, NSAIDs, platelet inhibitors, and thrombolytics.
Pregnancy: This medication is contraindicated during pregnancy.
Precautions: Inflammatory reactions may arise when using occlusive dressings. However, the use of porous gauze dressings for cosmetic purposes does not lead to an increase in such reactions.

**Ifosfamide (Ifex) i**s a drug that forms connections throughout DNA, both between strands and within strands, which disrupts the process of protein synthesis.
The recommended dosage for adults is 5 grams per square meter administered intravenously over a period of 24 hours every 3 weeks.
The appropriate dosage for pediatric patients has not been determined.
Contraindications include a confirmed hypersensitivity, renal or hepatic insufficiency, and bone marrow suppression.

**Phenobarbital, phenytoin, chloral hydrate,** and other medicines that disrupt the activity of cytochrome P-450 may change the effects.
Pregnancy: This medication is considered unsafe during pregnancy.
Precautions: This medication may lead to hemorrhagic cystitis and severe myelosuppression. Use cautiously if you have impaired renal function or limited bone marrow reserve.

**Paclitaxel (Taxol**) acts by promoting tubulin polymerization and stabilizing microtubules.
The recommended adult dosage is 175 mg/m2 administered intravenously over a period of 3 hours every 3 weeks. Alternatively, a dosage of 135 mg/m2 can be administered intravenously over a period of 24 hours every 3 weeks.

The appropriate dosage for pediatric patients has not been determined.
Contraindications include a confirmed allergic reaction to paclitaxel or polyoxyethylated castor oil, peripheral neuropathy, bone marrow suppression, liver failure, and serious heart illness.
Co-administering cisplatin may intensify myelosuppression.

Pregnancy: This medication is considered unsafe and should not be used during pregnancy.
To reduce the likelihood of hypersensitivity reactions, it is recommended to administer steroids, H1 blockers, and H2 blockers as a precaution. Possible side effects include myelosuppression, alopecia, arthralgia/myalgias, and cardiac arrhythmia.

## Deterrence/Prevention:

Cervical cancer screening
Retrospective studies indicate that the utilization of a Pap smear for screening purposes results in a reduction of the occurrence rate of cervical cancer by 60-90% and a decrease in the mortality

rate by 90%.
Since 1988, the American Cancer Society and the National Cancer Institute have advised that a Pap smear and pelvic examination should be conducted every year following the start of sexual activity or in women who are 18 years old and above. If there are 3 consecutive negative results, the physician and patient may choose to extend the screening interval. Pap smear screening should be continued for women aged 60 and above.
In 1995, the American College of Obstetricians and Gynecologists advised that women with risk factors such as HIV or HPV infection, cervical abnormalities, and many sexual partners should have annual Pap smear screening.
The Pap smear has a false-negative rate of 20%, primarily due to sampling error. To minimize sample error, physicians should ensure that sufficient material is collected from both the endocervical canal and the ectocervix. Smears without endocervical or metaplastic cells should be repeated. Cervical lesions that appear suspicious or highly abnormal during a physical examination should be biopsied, regardless of the results of cytologic testing.

Complexities:

Adverse effects resulting only from radiation exposure

During the acute stage of pelvic radiation, the adjacent healthy tissues, including the intestines, bladder, and perineum skin, are frequently impacted.
Immediate negative effects on the digestive system include diarrhea, abdominal cramps, discomfort in the rectal area, or bleeding. Diarrhea is typically managed with either loperamide (Imodium) or atropine sulfate (Lomotil). Proctitis symptoms can be relieved by prescribing little enemas that contain steroids.

Cystourethritis may also manifest, resulting in dysuria, increased frequency of urination, and nocturia. Antispasmodics frequently provide relief from symptoms.
It is necessary to analyze urine for potential infection. If a urinary tract infection is discovered, treatment should be promptly initiated.
It is important to maintain proper skin hygiene for the perineum, and if redness or peeling of the skin occurs, a topical lotion should be applied.

The delayed consequences of radiation often manifest 1-4 years following the completion of treatment. The primary consequences encompass rectal or vaginal narrowing, obstruction of the small intestine, impaired nutrient absorption, and persistent inflammation of the bladder.

## Surgical complications

Urinary dysfunction is the most common complication following radical hysterectomy, which occurs due to partial denervation of the detrusor muscle.
Additional complications encompass a shorter vagina, a fistula connecting the ureter and vagina, excessive bleeding, infection, blockage of the bowel, narrowing and scarring of the intestine or rectosigmoid colon, as well as fistulas connecting the bladder and rectum to the vagina.

The prognosis of cervical cancer is contingent upon the stage of the disease. Typically, the survival rate for stage I disease exceeds 90%, for stage II ranges from 60-80%, for stage III is roughly 50%, and for stage IV disease is less than 30%.

**Medical instruction for patients:**

Underserved and minority communities in the United States have a higher incidence of cervical cancer. It is crucial to enhance awareness regarding the advantages of Pap smear screening in these specific demographics.
To access high-quality educational materials for patients, please visit eMedicine's Cancer and Tumors Center, Women's Health Center, and Procedures Center. Additionally, please refer to eMedicine's patient education articles on Cervical Cancer, Pap Smear, and Colposcopy.