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Video Case

CIN

Objectives:

- → Determine the incidence and mortality of cervical cancer
- → Discuss the etiology of cervical cancer
- → List risk factors for cervical cancer
- → Describe the primary prevention methods for cervical cancer
- → List the guidelines for screening among asymptomatic women. (The American College of Obstetrics & Gynecology)
- → Discuss how to evaluate a patient with an abnormal Pap smear
- → Discuss how to evaluate a patient with an abnormal Pap smear
- → Describe treatment options for cervical intraepithelial neoplasia and invasive cervical cancer according to stage

- → Slides
- → Important
- → Golden notes
- → Extra
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- → Reference

Female presentation

Video Case | Editing File

Cervical Disease & Neoplasia

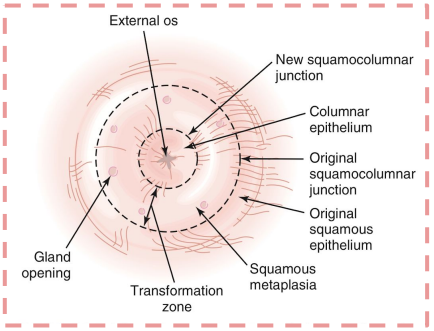
Globally, cervical cancer is the second / third most common cancer among women.

- It is the most common cause of mortality from gynecologic malignancy accounting for 250,000 deaths per year in the United States
    - Cervical cancer, incidence and mortality, have decreased substantially. In developed countries, **regular screening** has markedly decreased the incidence of the disease, and most cases now occur in women who have not had regular Papanicolaou smears.
        - It is now thought of as a most preventable gynecologic cancer
- The most common etiology of cervical cancer is the **human papillomavirus (HPV).**
    - HPV is the **most common sexually transmitted infection** (STI). Infects the lower genital tract, especially cervix in **the transformation zone.**
    - They are over 100 types of HPV and 30 affect the anal genital tract
        - 15 of these 30 are **HIGH-risk** HPV types : **ONCOGENIC**
            - **16, 18, 31 and 45** are the most common causes of cervical cancers.
        - 15 of these 30 are **LOW-risk** HPV types : are not associated with cancer "**NON-ONCOGENIC** "
            - **6 and 11** are associated with benign condyloma acuminata **/** genital warts.

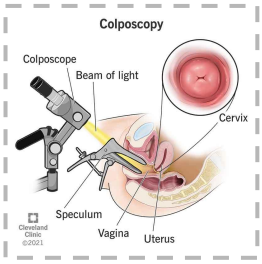
Normal Lining of The Cervix

The cervix is covered by both squamous and columnar epithelium.

- **Squamocolumnar junction or SCJ** : where these to meet is an important landmark where 90% of lower genital tract cancer arise.
    - Columnar epithelium is on **Endocervix** side of the SCJ
    - Squamous epithelium is on the vaginal side / **Ectocervix** of the SCJ



- At birth, the vagina is usually covered with squamous epithelium and the columnar epithelium is limited to the endocervix and the central portion of the exocervix (or ectocervix). In about 4% of normal female infants, the columnar epithelium extends onto the vaginal fornices. During menarche, there is an estrogen surge, and this causes the cervix to mushroom and drag the glandular or columnar epithelium of the endocervix onto the vaginal exposed portion of the cervix which form **NEW SCJ** and it will be at or close to the vaginal part of the external OS. .
    - **Transformation zone** is the area of where epithelium is replaced by squamous epithelium in a process called squamous metaplasia, it located between the original / OLD squamocolumnar junction and the NEW squamocolumnar junction. The cells that are undergoing metaplasia are vulnerable to various carcinogen, such as HPV



COLPOSCOPY is how we clinically visualize the cervical anatomy.
It's a binocular sterile microscope with magnification. Acetic acid is placed on the cervix which dehydrate cells causing those large nuclear to appear white. These white cells will be those how undergo metaplasia or dysplasia.

HPV

Risk factors

HPV Takes 3-5 years to cause cellular changes in the tissue to develop precancer (CIN) and 20-30 years to develop cancer, And this depends on 2 factors:

1. Weather it is high risk or low risk HPV type.
2. Persistence of the infection , if HPV infects a host, the host immune system will be able to eradicate the HPV before it causes change (almost 80-90 of women), **Certain risk factors will increase the likelihood that the HPV infection stay :**

- **Immunosuppression secondary to HIV or immunosuppression medication**
  - they'll be a higher incidence of infection and progression
- **Cigarette smoking**
  - the carcinogens from cigarette smoker found in high concentrations in the cervical mucus of smokers
- **Anything that will increase the chance of exposure to HPV:**
  - **Young age at first coitus** <17yr
  - Young age at first pregnancy
  - High parity
  - Multiple sexual partners
  - Sexual partner with multiple sexual partners
  - Sexually transmitted diseases.
  - Lower socioeconomic status

Women who have used oral contraceptives for 5 or more years have a higher risk of cervical cancer than women who have never used oral contraceptives.

Primary prevention

Gardasil-9

★ **The 9 valent vaccine:**
Protect against 9 HPV types (6,11, 16, 18, 31, 33, 45, 52, 58)

Gardasil

★ **The quadrivalent vaccine:**
Protects against HPV types 6, 11, 16 and 18.

Cervarix

★ **The bivalent vaccine:.**
Protects against HPV types 16 and 18.

- Quadrivalent HPV vaccine has been shown to prevent 91% of new infections.
- HPV vaccines are only indicated right now for prophylaxis
  - The vaccine is most **effective** if performed **before the onset of sexual activity.** Vaccination is still recommended after commencement of sexual activity, and even after prior abnormal cytology or CIN, but it is likely to be less effective after HPV exposure.
- The vaccine is **contraindication** during pregnant**.**
- **Women who receive the HPV vaccine should still follow regular cervical cytology screening ,** because the vaccine does not protect against all high-risk HPV viral types.

Cervical Disease & Neoplasia

Secreening / Secondary Prevention

The American College of Obstetricians and Gynecologists (ACOG) has recommended that **all women should undergo** an annual physical examination, including a Papanicolaou (Pap) smear, **within 3 years of sexual intercourse,** or **by age 21.**

- **Pap Smear (Screening test)**

The best screening test for premalignant lesions is cytology. Cytologic screening uses the Pap test. It is inexpensive and non-invasive.

- we are now able to test for HPV at the time of the pap test, adding the HPV testing has a loudest space out the interval between testing

Note : Pap test doesn't give you a diagnosis.
- **For diagnosis**, we need tissue, but we can't take tissue blindly, we need do colposcopy-guided cervical **biopsy**

What cytologies screening methods can be used ?

➔ With **conventional Pap smear,** the specimens are **smeared onto a glass slide**, which is placed in fixative and then microscopically examined.

The false-negative rate for conventional Pap smears for high-grade intraepithelial lesions is generally reported to be about 20%, but it is higher for glandular lesions and for invasive cancers. New technologies have been developed to decrease the false negative rate:

➔ With **automated liquid-based slide-preparation systems** (Thin Prep / Cytyc Corporation and Surepath / TriPath Imaging)**,** the spatula or brush taking the **smear is placed into a fixative solution**. Blood, mucus, and inflammatory cells are eliminated and a monolayer smear is then automatically prepared by a machine.

Both methods are equivalent for cancer screening but the liquid-based method has the advantage of doing reflex HPV-DNA typing. High sensitivity

Both the endocervical canal and the exocervix (or ectocervix) should be sampled when taking the pap smear. **How is it performed?**

Two specimens are obtained with the Pap smear:
- **ectocervical sample** performed by scraping the T-zone with a spatula
- **endocervical sample** obtained with a cytobrush in a nonpregnant woman or a cotton tip applicator in a pregnant woman.

Pap smear should be **started** at the following **ages**:	❖ **Age less than 20**: no Pap test or screening for HPV. ❖ **Age 21:** Start Pap test with cytology alone without HPV testing; the recommendation is the same whether HPV vaccinated or not.
The **frequency** of recommended Pap smear is as follows:	❖ **Age 21–29**: repeat Pap **every 3 years** with cytology alone; do not perform HPV testing in this age group. ❖ **Age 30–65**: ◇ repeat Pap **every 3 years** with cytology but no HPV testing ◇ repeat Pap **every 5 years** if both pap and HPV testing (the recommended option in this age group).
Pap smears should be **discontinued**:	❖ **After age 65** if she has adequate negative cytology and/or HPV tests screening, and no history of cervical dysplasia, greater than CIN2 within the last 20 years ❖ **Any age** if total hysterectomy AND no history of cervical neoplasia.

Secreening / Secondary Prevention

It is important to note that :

- More than ½ of patients to develop cervical cancer have not been screened appropriately.
- Among women diagnosed with invasive cervical cancer, ½ of them never had a Pap test.
  - Women who are highest risk of being rarely, or never screen for cervical cancer are :
    - Minority women
    - Low economic status
    - Foreign born
    - Women with no usual source of healthcare.

Classification of a Pap smear

Cervical cell **abnormalities in Pap smear can show up as either :**

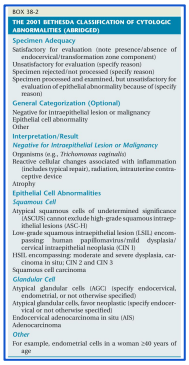
- **Atypical squamous cells / ASC** : Atypical squamous cells **look mildly atypical**, and don't necessarily develop into cervical cancer , ASC results can further be classified as :
  - **ASC-US**, where US stands for unknown significance, and there are no high grade intraepithelial lesions,
    - Patients with ASC-US found on their smear may have a **repeat smear in 6-12 months. Alternatively, HPV testing**, such as with the Hybrid Capture assay (Digene Diagnostics, Silver Spring, MD) may be used to triage such patients. , if +ve ? do colposcopy
      - About 6-10% of ASCUS patients will have high-grade CIN on colposcopy, and 90% of these can be detected by HPV testing for high-risk viral types.
      - **Possible MCQ: what's the first most common abnormal pap smear?** ASC-US
  - **ASC-H**, which is when there may be a high grade intraepithelial lesion and further testing is recommended
- **Cervical squamous intraepithelial lesions**, or CSIL, there is abnormal epithelial proliferation and maturation above the basement membrane, it's **full-blown dysplastic,** and have a greater chance of becoming cervical cancer. depending on how dysplastic the cells look it can be either :
  - Low grade squamous intraepithelial lesions, or **LSIL**,
    - LSIL often spontaneously regresses. r**epeat smear in 1 years, Alternatively, HPV testing**, if +ve ? do colposcopy
  - High grade squamous intraepithelial lesions, or **HSIL**.
    - At least 35% of patients with HSIL will develop invasive cancer within 10 yr.

- **ASC-US and LSIL** considered **low grade**, Anything else? High grade
- Any glandular lesions considered as high grade e.g. atypical glandular cells.

- **Colposcopy is the next step after abnormal Pap smear and the punch biopsies from the colposcopy will give a histologic diagnosis.**
  - Punch Biopsy is taken from the worst area or areas, together with an endocervical curettage.
    - The endocervical curettage is not performed in patients who are pregnant.

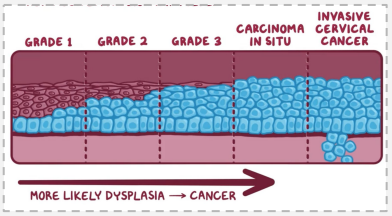
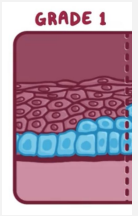
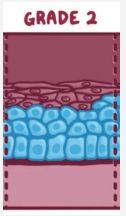
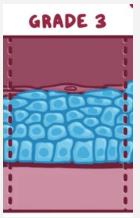
NOTE ; Any patient with a grossly abnormal cervix should have a punch biopsy performed, regardless of the results of the Papanicolaou smear.

There are two common classification systems, for describing the results of colposcopy directed biopsies :


BOX 18.2
THE 2001 BETHESDA CLASSIFICATION OF CYTOLOGIC ABNORMALITIES (ABRIDGED)
Specimen Adequacy
Satisfactory for evaluation (note presence/absence of endocervical/transformation zone component)
Unsatisfactory for evaluation (specify reason)
Specimen rejected/not processed (specify reason)
Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (specify reason)
General Categorization (Optional)
Negative for intraepithelial lesion or malignancy
Epithelial cell abnormality
Other
Interpretation/Result
Negative for Intraepithelial Lesion or Malignancy
Organisms (e.g., Trichomonas vaginalis)
Reactive cellular changes associated with inflammation (includes typical repair), radiation, intrauterine contraceptive device
Atrophy
Epithelial Cell Abnormalities
Squamous Cell
Atypical squamous cells of undetermined significance (ASCUS) cannot exclude high-grade squamous intraepithelial lesions (ASC-H)
Low-grade squamous intraepithelial lesion (LSIL) encompassing: human papillomavirus/mild dysplasia/cervical intraepithelial neoplasia (CIN 1)
HSIL encompassing: moderate and severe dysplasia, carcinoma in situ; CIN 2 and CIN 3
Squamous cell carcinoma
Glandular Cell
Atypical glandular cells (AGC) (specify endocervical, endometrial, or not otherwise specified)
Atypical glandular cells, favor neoplastic (specify endocervical or not otherwise specified)
Endocervical adenocarcinoma in situ (AIS)
Adenocarcinoma
Other
For example, endometrial cells in a woman ≥40 years of age

1. **Lower anogenital squamous terminology / LAST** : This system describes the biopsies obtained of the time of colposcopy as either LSIL or HSL mirroring the same terminology that was used for the cytology results.

2. **Bethesda system :** This system describes the biopsies obtained of the time of colposcopy as cervical intraepithelial neoplasia / CIN , and these are classified by the extent that cervical epithelium is replaced by abnormal cells

Cytology (Pap smear)	LISL	HSIL	
1- LAST system :			
Histological biopsy	LISL	HSIL	
p16 : tumor suppressor gene	-ve	+ve "means overexpression"	
2- Bethesda system :			
Histological biopsy *	CIN 1	CIN 2	CIN 3
Histological Atypica	1/3	2/3	Full thickness
Stage of dysplasia 	**Mild** dysplasia 	**Moderate** 	**Severe** 
Treatment	**Expectant management** bc it's high rate of regression and low rate of progression Pap smear and an HPV test should be done in 12 months.	**Immediate treatment** Bc of their higher rates of progression of cervical cancer	

There are two approaches to immediate **treatment :**

- **Ablation** for example : cryotherapy or laser ablation
- **Excisional methods** : cold knife cone or LEEP , both of them excise transformation zone.
- Hysterectomy is rarely necessary for the treatment of HSIL. It may be applicable when there is concomitant uterine or adnexal disease.

The principal difference between ablation and excisional methods that ablation provides no diagnostic information, additional factors to consider : a future childbearing plans and patient compliance.

Then, follow-up involves a pap smear and a reflex HPV test at 12 and 24 months, and after 2 normal results, the female can go back to routine testing,

* **NOTE : The biopsy look for cervical intraepithelial neoplasia or CIN, which comes in :**
  - **NO CIN**
  - **carcinoma in situ :** which is when the entire epithelium is made up of abnormal cells, but they don't make it past the basement membrane
  - **Invasive cervical cancer**: when the abnormal cells have made it past the basement membrane.

Diagnostic approach to an abnormal Pap smear

1a

Accelerated Repeat Pap:

1b

HPV DNA testing:

The preferred option for findings of **ASC-US in patients age ≥25** (why ? bc if pt less than 25, even if there is HPV infection the immune may clear it and these abnormalities may go away on their own within 24 months) If liquid-based cytology was used on the initial Pap, one can use this specimen for DNA testing. .

2a

Colposcopy:

- Colposcopy is a magnification of the cervix (10–12x); it is aided by acetic acid, which makes the vascular patterns more visible.
- Satisfactory or adequate colposcopy is diagnosed if the entire T-zone is visualized and no lesions disappear into the endocervical canal.

2b

Endocervical curettage (ECC):

All nonpregnant patients undergoing colposcopy that shows metaplastic epithelium entering the endocervical canal will undergo an ECC to rule out endocervical lesions.

2c

Ectocervical biopsy:

Lesions identified on the ectocervix by colposcopy (e.g., mosaicism, punctuation, white lesions, abnormal vessels) are biopsied and sent for histology.

3

Cone biopsy:

If the Pap smear is worse than the histology (suggesting the site of abnormal Pap smear cells was not biopsied), then a cone biopsy is performed. For example

1. Pap smear shows a high-grade lesion and the colposcopic examination is unsatisfactory.
2. Pap smear shows a high-grade lesion that is not confirmed on punch biopsy.
3. Pap smear shows adenocarcinoma in situ.
4. Endocervical curettings show a high-grade lesion.
5. Microinvasion is present on the punch biopsy.
6. If you have persistent CIN1 (for more than 2 years) we do it for diagnostic reason, to see if there is CIN3 hidden or other serious pathology.

Deep cone biopsies can result in an incompetent cervix. Another risk of cone biopsy is cervical stenosis, bleeding and infection.

Usually women acquire HPV in her 20s (when she becomes sexually active) and then comes with CIN in her late 20s early 30s and cancer will be in her 40s.

Cervical cancer

Premalignant lesions of the cervix are usually asymptomatic. The progression from premalignant to invasive cancer has been reported to be **approximately 8–10 years.**.

- The most common cervical cancer is squamous cell carcinoma.
- Most uterine cervical cancers are squamous in origin : Adenocarcinomas and adenosquamous carcinomas

Invasive cervical cancer

- Patients can present with **abnormal vaginal bleeding:** Postcoital,intermenstrual, or postmenopausal vaginal bleeding. Other symptoms include Persistent watery vaginal discharge, pelvic pain, leg swelling, and urinary frequency are usually seen with advanced disease.

- Usually normal general physical examination. **Weight loss** occurs **late** in the disease. There may be **enlarged inguinal** or **supraclavicular** lymph Node, **edema** of the legs, or **hepatomegaly**.
  - ◇ On pelvic examination, The cervix can appear normal and appearance, or they can be a visible cervical lesion ex.**ulcerative** or **exophytic**.

The initial diagnostic test

1. **Cervical biopsy is the initial diagnostic test.**
2. **Metastatic workup:** that includes pelvic examination, chest x-ray, intravenous pyelogram, cystoscopy, and sigmoidoscopy.
3. **Imaging studies:** An abdominal pelvic CT scan or MRI may be helpful in planning management (They **not** be used for clinical staging), Neither is particularly sensitive for detecting lymph node metastases, and PET scanning is being increasingly used for this purpose.

Invasive cervical cancer is the only gynecologic cancer that is staged clinically.
Staging is clinical **based on pelvic examination and may include an intravenous pyelogram (IVP), cystoscopy, or proctoscopy.** It does not require surgical procedure other than a biopsy. Stage 1 is the most common stage.

Stage 0:	Carcinoma in-situ (CIS). Spread limited to the cervix The basement membrane is intact.
Stage I: |A1. |A2. |B.	• Invasion is ≤3 mm deep (minimally invasive) • Invasion is >3 but ≤5 mm deep (microinvasion) • Invasion is >5 mm deep (frank invasion)
Stage II: ||A. ||B.	Spread adjacent to the cervix Involves • Upper two thirds of vagina. • Invasion of the **parametria**[1]
Stage III: IIIA. **IIIB.** IIIC.	Spread further from the cervix • Involves lower one third of vagina. • Extends to pelvic side wall and/or hydronephrosis or non functioning kidney[2] • Involvement of pelvic or paraaortic lymph nodes
Stage IV: IVA. IVB.	Spread furthest from the cervix. • Involves bladder or rectum or beyond true pelvis. • Distant metastasis

TABLE 38-1
INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS STAGING OF CARCINOMA OF THE CERVIX UTERI (2009)

Stage	
I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5.0 mm and largest extension ≤7.0 mm
IA1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm
IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm
IB	Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage IA*
IB1	Clinically visible lesion ≤4.0 cm in greatest dimension
IB2	Clinically visible lesion >4.0 cm in greatest dimension
II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA	Without parametrial invasion
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4.0 cm in greatest dimension
IIB	With obvious parametrial invasion
III	The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney
IIIA	Tumor involves lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum; a bullous edema, as such, does not permit a case to be allotted to stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

From FIGO Committee on Gynecologic Oncology: Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynecol Obst* 105:103–104, 2009.
*All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be >5.00 mm taken from the base of the epithelium of the original tissue—squamous or glandular. The depth of invasion should always be reported in mm, even in those cases with "early (minimal) stromal invasion" (=1 mm). The involvement of vascular/lymphatic spaces should not change the stage allotment.
†On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or nonfunctioning kidney are included, unless they are known to be due to another cause.

1. The fat and connective tissue that surrounds the uterus which help to connect the uterus to other tissues in the pelvis.
2. **If patient come with ureteral obstruction what's the stage? IIIB**

Management according to histology

Patients treated surgically are evaluated for risk factors for metastatic disease and tumor recurrence. These include **metastatic** disease to the lymph nodes, tumor **size >4 cm**, **poorly differentiated** lesions, or **positive margins**.
Patients with these findings offered adjuvant therapy (radiation therapy and chemotherapy).

Specific by stage:

- **Stage Ia :** when the tumor is confined to the cervix
  Cone biopsy, Radical hysterectomy, or trachelectomy.
  - Cervical conization or trachelectomy alone may suffice if the patient desires to maintain her fertility,
    - In cervical conization as long as the cone margins are free of disease and the endocervical curettings (taken after the conization) are negative.

- **Stage Ia2:**
  Radical hysterectomy we take the uterus and the tissue around the uterus

- **Stage IB or IIA:**
  Radical hysterectomy and bilateral pelvic lymphadenectomy or chemoradiation therapy.

- **Stage IIB, III, or IV A: 70-80% of the cases**
  Chemoradiation therapy
  *Although IIB is stage 2 but in case of cervical cancer is considered advanced and surgery has NO role!! So you have to know that we start **chemoradiation** from IIB and Above.

- **Stage IVB:**
  Palliative care and analgesics offered for controlling symptoms and prolong survival.

Follow up

All patients with invasive cervical cancer should be **followed up with Pap smear every three months for two years** after treatment, and **then every six months for the subsequent three years.**

Patients who have a local **recurrence** can be treated with **radiation therapy**; if they had received radiation previously, they might be considered candidates for a pelvic exenteration. Patients with distant metastases should be considered for chemotherapy treatment.

437note:
- Most common site of extrapelvic disease is LUNG.

Teaching case

A generally healthy 26 year-old G1P0 woman with a last menstrual period approximately 16 weeks ago is referred for the management of an abnormal Pap test showing High Grade Squamous Intraepithelial Lesion (HGSIL). This Pap test was obtained 10 weeks ago when she underwent an elective termination of an unplanned pregnancy at approximately six weeks of gestation. She has not had any prior Pap tests. She has never been tested for sexually transmitted infections. The combination of the undesired pregnancy and the abnormal Pap test, however, has been a "wake-up call" and today she requests testing for "everything." She received Depo-Provera at the time of the termination, and has not had a period yet. She reports a history of normal, regular menses and has used oral contraceptives inconsistently in the past. She began having sexual intercourse at the age of 17, and has had 4 lifetime partners. She is on no other medications and has no known drug allergies. Her family history is notable for a grandmother with breast cancer. She smokes ½ pack of cigarettes per day, does clerical work for a moving company, and is engaged to be married in 6 months.

Q1: According to recent guidelines published by the American College of Obstetricians and Gynecologists (2012), how many Pap tests should this patient have had given her age and clinical history.

This patient should have had only two screening pap tests by now.

Screening guidelines: Secondary prevention means the pathological change already started, but that pathology still sub- clinical (pt doesn't have any symptoms)

➢ First cytology should be obtained at age 21 regardless of coitarche.

➢ Between the ages of 21 and 29, there is no benefit of annual screening; screening with cytology alone every 3 years is recommended. It leads to harm due to overtreatment of screen detected abnormalities.

➢ Women aged 30–65 years should be screened with cytology and HPV testing; "Co Testing" every 5 years (preferred), or cytology alone every 3 years.

➢ Women over 65 years of age with evidence of adequate negative prior screening and no history of CIN within the last 20 years should not be screened for cervical cancer with any modality. Once screening is discontinued it should not resume for any reason, even if a woman reports having a new sexual partner.

Teaching case

Q2: Which historical risk factors does this patient have, for having cervical dysplasia or for having cervical dysplasia progress to cervical cancer?

- She has poor compliance with screening, early age of coitarche (< 17 years of age), and she is a cigarette smoker.
- Abnormal Pap test is presumptive evidence of HPV infection.
- She is at risk of other STIs given her lack of barrier contraception, including HIV/AIDS.
- Relatively high number of lifetime sexual partners.
- Low socio-economic status and poor access to healthcare.

Q3: What are other possible risk factors for development of cervical dysplasia?

- DES (Diethylstilbestrol) exposure -HIV infection	She probably does not have an autoimmune disease, given her generally healthy medical history.	Other diagnoses that would increase her risk of cervical neoplasia include SLE, and history of organ transplantation immunosuppressive therapies.

Q4: What is meant by the term "high-grade squamous intraepithelial lesion (HGSIL)"?

It indicates moderate or severe cervical intraepithelial neoplasia or carcinoma in situ (CIN2 and CIN3). Of all women with HGSIL results, 2% or less have invasive cervical cancer at that time, however about 20% would progress to having invasive cervical cancer without treatment.

- Cells were identified on cytology (Pap test) suggesting abnormal cellular maturation between 1/3 and full thickness of the squamous epithelial layer of the cervix.
- Each Pap test report should have a statement of specimen adequacy (satisfactory, unsatisfactory), general categorization (negative for intraepithelial lesion or malignancy, epithelial cell abnormality, other), and interpretation/result (negative for intraepithelial lesion or malignancy, epithelial cell abnormalities). Possible Pap test results include: ASCUS, ASC-H, LGSIL, HGSIL, AGC, AIS, and squamous cell carcinoma.

*This is called Bethesda system, it's for reporting cervical or vaginal cytologic diagnoses.

ASC-US	Atypical squamous cells of undetermined significance
ASC-H	Atypical squamous cells – cannot exclude HGSIL
LGSIL	Low grade squamous intraepithelial lesion
HGSIL	High grade squamous intraepithelial lesion
AGC	Atypical Glandular Cells, suspicious for AIS or cancer.
AIS	Adenocarcinoma in situ

➔ Each category of abnormal cytologic reading encompasses a spectrum of possible correlating pathologic (histologic) diagnosis that should be further explored and identified.

Teaching case

Q5: What would you recommend as the next step in the evaluation of this patient's abnormal Pap test?

- Abnormal Pap test results require further work-up, typically to establish a diagnosis.
- This patient will require colposcopy and directed biopsies, including an endocervical curettage (ECC). Once a diagnosis is made based on these findings, appropriate treatment can then be recommended.
- Available algorithms for abnormal cytologic and pathologic cervical neoplasia are detailed from ASCCP (American Society for Colposcopy and Cervical Pathology).
- Patient should also be counseled about STI testing (including HIV), smoking cessation, and use of barrier contraception.

Q6: Would typing for the human papillomavirus (HPV) aid in the management of this patient?

- This patient requires colposcopic examination. In this patient with HGSIL, there is no role for HPV testing, as the result is expected to be positive.
- For LGSIL, HPV can be expected to be positive in 77% of cases, making this test impractical in deciding totriage to colposcopy.
- Low risk HPV types include 6 and 11, are associated with cervical warts. High risk HPV types include 16 and 18, are associated with high grade cervical dysplasia and cervical cancer.

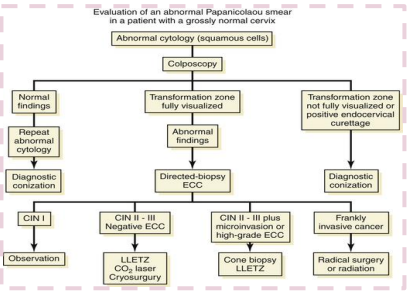
437 note: indications for HPV testing :
1. Screening at age of 25.

2. We can use it as a triage (when we have low grade cytology) (atypical squamous cells of undetermined significance ASCUS) if HPV is negative then patient is normal, if HPV is positive then ASCUS means there is something serious then we refer the patient to colposcopy.

3. Co testing (women above 30 we can combine it with cytology) we do it every 5 years.

4. Monitor response for treatment

Summary



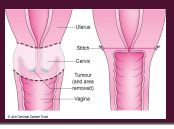
When you do Pap smear, look for cervix

- abnormal cervix
  - Punch biopsy
- Normal cervix
  - -ve result
  - +ve result
    - Low grade
      - ASC-US
        - HPV test Or Repeat pap after 6-12 m
          - -ve HPV
          - +ve HPV
      - LSIL
    - High grade
      - ASC-H
      - HSIL
        - Colposcopy + biopsy

A diagnostic excisional procedure can be done.

- No CIN
- CIN 1
  - **FOLLOW UP :** HPV test AND / OR Repeat pap in 12 m
    - -ve result
    - +ve result
      - If CIN1 persists for more than 2 years
        - A diagnostic excisional procedure can be done.
- CIN 2 or CIN 3
  - Ablation or Excisional methods
- Carcinoma in situ " stage 0"
  - Excisional methods
- Invasive cervical cancer
  - stage 1
    - I A
    - I B
  - stage 2
    - II A
    - II B
  - stage 3
  - stage 4
    - IV A
    - IV B

- Excisional methods
- Trachelectomy



- Hysterectomy
- Radiotherapy
- chemotherapy
- chemoradiation
- Palliative

Online meded

1. HPV (16,18,30s) are the main causes of cervical cancer.
2. Cervical cancer occurs in the 30s and the 60s of age.
3. In the reproductive years the patient will present with postcoital bleeding or asymptomatic screening.
4. In the postmenopausal period the patient will present with bleeding
5. The risk factors of cervical cancer include anythings gives you HPV such as sex and STD, also smocking is a factor.
6. To screen for cervical cancer you have to use pap smear.
7. All women should have an asymptomatic screening by the age of 21, and repeat it every 3 years except HIV patient every year, and patients over 30 every 5 years.
8. In general we should stop screening at the age of 65, except patients who have positive screening.

<table>
<tr><th colspan="4">Pap smear</th></tr>
<tr><th colspan="2">Positive = Abnormal result</th><th colspan="2">Atypical squamous cells of undetermined significance (ASCUS)</th><th>Negative (Normal)</th></tr>
<tr><th colspan="2">colposcopy</th><th>HPV DNA</th><th>Repeat the pap smear after 6 months</th><td rowspan="2">Repeat every 3 years.</td></tr>
<tr><td>-Ve Endo & +Ve Ecto :

manage with leep procedure.</td><td>+Ve Endo & -Ve Ecto

manage with cone biopsy.</td><td>1-Positive : consider the colposcopy is abnormal

2-Negative : Consider it normal</td><td>1-Positive :consider the colposcopy is abnormal

2-Negative : Consider it normal.</td></tr>
</table>

Reference

38 CHAPTER

Cervical Dysplasia and Cancer

NEVILLE F. HACKER

CLINICAL KEYS FOR THIS CHAPTER

- Cervical cancer is the major cause of death from cancer in women worldwide, but most new cases and deaths occur in developing countries where screening for cervical cancer is poorly developed.
- Cervical cancer is caused by persistent infection with a high-risk human papillomavirus (HPV), and vaccines have been developed against some of these viruses. Vaccination of girls (and boys) before they are sexually active should significantly decrease the incidence of cervical cancer in the future.
- Persistent infection with a high-risk HPV virus initially produces an intraepithelial lesion called high-grade squamous intraepithelial lesion. This entity can be detected by screening with a Papanicolaou smear, liquid-based cytology, or a primary HPV test, and successfully treated, thereby preventing the development of invasive cervical cancer.
- Invasive cancer of the cervix usually occurs between 40 and 60 years of age and most commonly presents early because of postcoital bleeding if the woman is sexually active. If she is not sexually active, the disease may remain asymptomatic until it is quite advanced.
- All patients with cervical cancer may be treated with chemoradiation, usually involving a combination of external beam therapy followed by brachytherapy. Radical hysterectomy and pelvic lymphadectomy is a less morbid and equally effective approach for patients with early stage disease.

Cervical cancer is the third most common cancer in women worldwide, after breast and colorectal cancer, but it is the major cause of death from cancer in women, killing around 275,000 women a year. About 80% of new cases occur in developing countries, where cervical screening programs are limited or nonexistent. **In developed countries, regular screening has markedly decreased the incidence of the disease,** and most cases now occur in women who have not had regular Papanicolaou smears. In the United States, cervical cancer now ranks only 13th among cancers in women, with 12,340 new cases expected in 2013, and 4030 deaths.

Studies have identified persistent infection with a high-risk human papillomavirus (HPV) as the cause of virtually all cervical cancers. Randomized clinical trials of prophylactic HPV vaccines have demonstrated dramatic efficiency in preventing HPV 16 and 18 infections, as well as precancerous cervical lesions. Although it will take several decades to demonstrate a decreased incidence of invasive cervical cancer, **with widespread use, HPV vaccination should markedly decrease the incidence of cervical cancer in future generations.**

Etiology and Epidemiology

There are 15 high-risk HPV types and types 16 and 18 are responsible for 70% of cervical cancers. Types 6 and 11 have been associated with cervical condylomas and low-grade cervical intraepithelial neoplasia (CIN).

The adolescent cervix is believed to be more susceptible to carcinogenic stimuli because of the active process of squamous metaplasia, which occurs within the transformation zone during periods of endocrine change. This squamous metaplasia is normally a physiologic process, but under the influence of the HPV, cellular alterations occur that result in an atypical transformation zone. These atypical changes initiate CIN, which is the preinvasive phase of cervical cancer.

Cervical cancer and its precursors have been associated with several epidemiologic variables (Box 38-1).

BOX 38-1

RISK FACTORS FOR CERVICAL CANCER

- Young age at first coitus (<17 yr)
- Multiple sexual partners
- Sexual partner with multiple sexual partners
- Young age at first pregnancy
- High parity
- Lower socioeconomic status
- Smoking

These risk factors basically increase the likelihood of exposure to a high-risk HPV type.

The disease is relatively rare before 25 years of age, and the mean age is about 47 years.

Primary Prevention

Two prophylactic vaccines are presently available. The **quadrivalent vaccine Gardasil,** which is manufactured by Merck and Co. and protects against HPV types 6, 11, 16, and 18, was approved by the U.S. Food and Drug Administration (FDA) in June 2006 for females aged 9 through 26 years. The **bivalent vaccine Cervarix,** which is manufactured by Glaxo Smith Kline and protects against HPV types 16 and 18, was approved by the FDA in October 2009, for use in females aged 10 through 25 years.

HPV vaccination is most effective if performed before the onset of sexual activity. Vaccination is still recommended after commencement of sexual activity, and even after prior abnormal cytology or CIN, but it is likely to be less effective after HPV exposure. In 2007, Australia was the first country in the world to introduce HPV vaccination into the National Immunization Program for all schoolgirls aged 12 years.

Screening of Asymptomatic Women

The American College of Obstetricians and Gynecologists (ACOG) has recommended that all women should undergo an annual physical examination, including a Papanicolaou (Pap) smear, within 3 years of sexual intercourse, or by age 21. The false-negative rate for conventional Pap smears for high-grade intraepithelial lesions is generally reported to be about 20%, but it is higher for glandular lesions and for invasive cancers.

New technologies have been developed to decrease the false negative rate. Thin Prep (Cytyc Corporation) and Surepath (TriPath Imaging) are automated liquid-based slide-preparation systems. With liquid-based cytology (LBC), the spatula or brush taking the smear is placed into a fixative solution, instead of smearing the cells directly onto a glass slide. Blood, mucus, and inflammatory cells are eliminated and a monolayer smear is then automatically prepared by a machine. Focal Point (Surepath) and ThinPrep Imager (Cytyc) are computerized image processors that select the most abnormal cells on a slide. They increase the sensitivity of slide reading, while decreasing the time needed by the cytotechnician to read each slide, thereby improving the cost effectiveness of screening.

The American Society for Colposcopy and Cervical Pathology (ASCCP) has recommended that screening with Liquid Based Cytology (LBC) should occur every 3 years from 21 to 30 years. Thereafter, they recommend continued screening every 3 to 5 years with LBC for HPV testing. Both the endocervical canal and the exocervix (or ectocervix) should be sampled when taking the Papanicolaou smear.

HPV deoxyribonucleic acid (DNA) testing is much more sensitive than cervical cytology, but less specific. It is presently being investigated as a primary screening test for women after the age of 25 to 30 in many developed countries. The negative predictive value of the HPV test is very high, so screening intervals could safely be extended to at least 5 years. If the HPV test is positive, reflex cervical cytology is performed to determine the need for referral for colposcopy.

Women should have regular cervical screening even if they have received the HPV vaccine, because the vaccine does not protect against all high-risk HPV viral types.

Cervical Topography

During early embryonic development, the cervix and upper vagina are covered with columnar epithelium. During intrauterine development, the columnar epithelium of the vagina is progressively replaced by squamous epithelium. At birth, the vagina is usually covered with squamous epithelium, and the columnar epithelium is limited to the endocervix and the central portion of the exocervix (or ectocervix). **In about 4% of normal female infants, the columnar epithelium extends onto the vaginal fornices.** Macroscopically, the columnar epithelium has a red appearance because it is only a single cell layer thick, allowing blood vessels in the underlying stroma to show through it.

The embryologic squamous and columnar epithelia are designated the original or native squamous and columnar epithelia, respectively. The junction between them on the exocervix (or ectocervix) is called the original squamocolumnar junction.

Throughout life, but particularly during adolescence and a woman's first pregnancy, metaplastic squamous epithelium covers the columnar epithelium so that a new squamocolumnar junction is formed more proximally. This junction moves progressively closer to the external os and then up the endocervical canal. **The transformation zone is the area of metaplastic squamous epithelium located between the original squamocolumnar junction and the new squamocolumnar junction** (Figure 38-1).

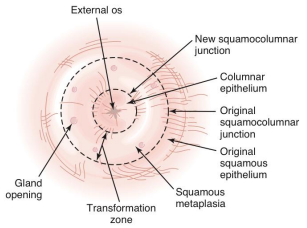


FIGURE 38-1 Schematic representation of the transformation zone.

Classification of an Abnormal Papanicolaou Smear

In 1988, a consensus meeting was convened by the Division of Cancer Control of the National Cancer Institute to review existing terminology and to recommend effective methods of cytologic reporting. As a result of this meeting, **the Bethesda system** was devised and requires **(1) a statement regarding the adequacy of the specimen** for diagnosis, **(2) a diagnostic categorization** (normal or other), and **(3) a descriptive diagnosis.** A revised Bethesda system was developed in 2001 and is shown in Box 38-2.

CERVICAL INTRAEPITHELIAL NEOPLASIA

CIN represents a spectrum of disease, ranging from LSIL, low-grade squamous intraepithelial lesion (formerly called CIN I or mild dysplasia) to HSIL, high-grade squamous intraepithelial lesion (formerly called CIN II and III, or moderate and severe dysplasia). At least 35% of patients with HSIL will develop invasive cancer within 10 years, whereas LSIL often spontaneously regresses. With CIN, there is abnormal epithelial proliferation and maturation above the basement membrane. Involvement of the inner one-third of the epithelium represents LSIL, while involvement of the outer two-thirds represents HSIL (Figure 38-2). The disease is asymptomatic.

COLPOSCOPY

The colposcope is a stereoscopic binocular microscope of low magnification, usually 10× to 40×. Illumination is centered, and the focal length is between 12 and 15 cm.

To perform a colposcopic examination, an appropriately sized speculum is inserted to expose the cervix, which is cleansed with a cotton pledget soaked in 3% acetic acid to remove adherent mucus and cellular debris. A green filter can be employed to accentuate the vascular changes that frequently accompany pathologic alterations of the cervix.

At colposcopy, the original or native squamous epithelium appears gray and homogeneous. The columnar epithelium appears red and grapelike. **The transformation zone can be identified by the presence of gland openings that are not covered by the squamous metaplasia and by the paler color of the metaplastic epithelium compared with the original squamous epithelium. Nabothian follicles may also be seen in the transformation zone. Normal blood vessels branch like a tree.**

BOX 38-2

THE 2001 BETHESDA CLASSIFICATION OF CYTOLOGIC ABNORMALITIES (ABRIDGED)

Specimen Adequacy

Satisfactory for evaluation (note presence/absence of endocervical/transformation zone component)
Unsatisfactory for evaluation (specify reason)
Specimen rejected/not processed (specify reason)
Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (specify reason)

General Categorization (Optional)

Negative for intraepithelial lesion or malignancy
Epithelial cell abnormality
Other

Interpretation/Result

Negative for Intraepithelial Lesion or Malignancy

Organisms (e.g., *Trichomonas vaginalis*)
Reactive cellular changes associated with inflammation (includes typical repair), radiation, intrauterine contraceptive device
Atrophy

Epithelial Cell Abnormalities

Squamous Cell

Atypical squamous cells of undetermined significance (ASCUS) cannot exclude high-grade squamous intraepithelial lesions (ASC-H)
Low-grade squamous intraepithelial lesion (LSIL) encompassing: human papillomavirus/mild dysplasia/cervical intraepithelial neoplasia (CIN I)
HSIL encompassing: moderate and severe dysplasia, carcinoma in situ; CIN 2 and CIN 3
Squamous cell carcinoma

Glandular Cell

Atypical glandular cells (AGC) (specify endocervical, endometrial, or not otherwise specified)
Atypical glandular cells, favor neoplastic (specify endocervical or not otherwise specified)
Endocervical adenocarcinoma in situ (AIS)
Adenocarcinoma

Other

For example, endometrial cells in a woman ≥40 years of age

Evaluation of a Patient with an Abnormal Papanicolaou Smear

An algorithm for the evaluation of patients with abnormal Papanicolaou smears is presented in Figure 38-3.

Any patient with a grossly abnormal cervix should have a punch biopsy performed, regardless of the results of the Papanicolaou smear.

Patients with atypical squamous cells of undetermined significance (ASCUS) found on their smear may have a repeat smear in 6 months. Alternatively, HPV testing, such as with the Hybrid Capture assay (Digene Diagnostics, Silver Spring, MD) may be used to triage such patients. About 6-10% of patients with an ASCUS smear will have high-grade CIN on colposcopy, and 90% of these can be detected by HPV testing for high-risk viral types.

The colposcopic hallmark of cervical intraepithelial neoplasia is an area of sharply delineated acetowhite epithelium—that is, epithelium that appears white after the application of acetic acid. It is thought that the acetic acid dehydrates the cells and that there is increased light reflex from areas of increased nuclear density. **Within the acetowhite areas, there may or may not be abnormal vascular patterns.**

There are two basic changes in the vascular architecture in patients with CIN: punctation and mosaicism (Figure 38-4). Punctation is caused by single-looped capillaries lying within the subepithelial papillae, seen end-on as a "dot" as they course toward the surface of the epithelium. Mosaicism is caused by a fine network of capillaries disposed parallel to the

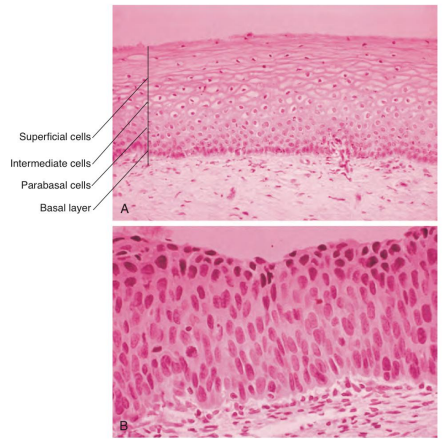


FIGURE 38-2 Histologic appearance of normal cervical squamous epithelium **(A)** and high-grade squamous intraepithelial lesion (HSIL) **(B)** of the cervix. In the normal epithelium, note the orderly maturation from the basal layer to the parabasal cells, glycogenated intermediate cells, and flattened superficial cells. In the HSIL, the entire thickness of the epithelium is replaced by immature cells that are variable in size and shape and have irregular nuclei. Mitotic figures are seen in the lower two-thirds of the epithelium.

Reference

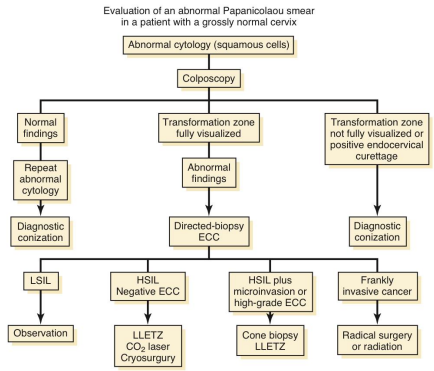


FIGURE 38-3 Algorithm for evaluation of patients with an abnormal Papanicolaou smear and a grossly normal-appearing cervix. *ECC,* Endocervical curettage; *HSIL,* high-grade squamous intraepithelial lesion; *LLETZ,* large loop excision of the transformation zone; *LSIL,* low-grade squamous intraepithelial lesion.

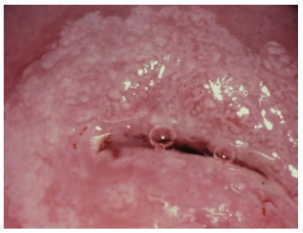


FIGURE 38-4 Colposcopic appearance of a patient with high-grade squamous intraepithelial lesion. Note the densely acetowhite epithelium with sharply demarcated borders, and the coarse mosaic vascular pattern.

surface in a mosaic pattern. Punctate and mosaic patterns may be seen together within the same area of the cervix. The more dilated and irregular the punctate and mosaic capillaries and the greater the intercapillary distance, the more atypical is the tissue on histologic examination. Similarly, the whiter the lesion, the more severe the dysplasia.

With microinvasive carcinoma, extremely irregular punctate and mosaic patterns are found, as are small atypical vessels. **The irregularity in size, shape, and arrangement of the terminal vessels becomes even more striking in frankly invasive carcinoma, with exaggerated distortions of the vascular architecture producing comma-shaped, corkscrew-shaped, and dilated, blind-ended vessels.**

BIOPSY AND ENDOCERVICAL CURETTAGE

If the colposcopic examination is satisfactory, which implies that the entire transformation zone has been visualized, a punch biopsy is taken from the worst area or areas, together with an endocervical curettage. The endocervical curettage is not performed in patients who are pregnant.

A diagnostic cone biopsy of the cervix is indicated in the following circumstances:

1. **Pap smear shows a high-grade lesion and the colposcopic examination is unsatisfactory.**
2. **Endocervical curettings show a high-grade lesion.**
3. **Pap smear shows a high-grade lesion that is not confirmed on punch biopsy.**

4. **Pap smear shows adenocarcinoma in situ.**
5. **Microinvasion is present on the punch biopsy.**

Treatment of Intraepithelial Neoplasia

It is reasonable to observe biopsy-proven LSIL without active treatment, as many cases will spontaneously regress. Active treatment is indicated for HSIL.

Superficial ablative techniques, such as large loop excision of the transformation zone (LLETZ), cryosurgery, or carbon dioxide laser are appropriate if the entire transformation zone is visible.

LARGE LOOP EXCISION OF THE TRANSFORMATION ZONE

LLETZ has gained popularity because **the equipment is relatively cheap, it can be performed on an outpatient basis under local anesthesia, and tissue is obtained for histologic evaluation.** Hence, occult invasive lesions should be more readily diagnosed. In unskilled hands, diathermy artifact may make histologic interpretation impossible.

LASER

Destruction of the transformation zone by carbon dioxide laser (light amplification by stimulated emission of radiation) ablation can be performed as an outpatient procedure, under local anesthesia. Bleeding may sometimes occur, but scarring is minimal and large lesions may be destroyed with low failure rates (in the order of 5-10%). **The equipment is expensive, so laser has lost favor in most centers.**

CRYOSURGERY

The cryosurgery technique is a relatively painless outpatient procedure that can be performed without anesthesia. There is no bleeding, and the equipment is cheap. However, **there is a high failure rate for large lesions and for lesions extending down glandular crypts.** It is mainly useful for lesions involving 1 or 2 quadrants. The major side effect is a rather copious vaginal discharge that persists for several weeks.

CERVICAL CONIZATION

Cervical conization is mainly a diagnostic technique, but it may also be therapeutic if the surgical margins are clear. **Bleeding, infection, cervical stenosis, and cervical incompetence are the major complications. Laser conization decreases the risk of cervical stenosis compared with cold knife conization.**

HYSTERECTOMY

Hysterectomy is rarely necessary for the treatment of HSIL. It may be applicable when there is concomitant uterine or adnexal disease.

Persistence and recurrence rates combined are approximately 2-3% after hysterectomy. This number should be significantly reduced by using colposcopy and Schiller staining (Lugol iodine) preoperatively to exclude intraepithelial neoplasia in the upper vagina.

Invasive Cancer

SYMPTOMS

Invasive cancer usually presents with postcoital, intermenstrual, or postmenopausal vaginal bleeding. In patients who are not sexually active, bleeding from cervical cancer usually does not occur until the disease is quite advanced (unlike patients with endometrial cancer, who almost always bleed early). **Persistent vaginal discharge, pelvic pain, leg swelling, and urinary frequency are usually seen with advanced disease.** In developing countries, it is not uncommon for patients to present with loss of urine or stool from the vagina, because of fistula formation.

PHYSICAL FINDINGS

Patients with cervical cancer usually have a normal general physical examination. Weight loss occurs late in the disease. With advanced disease, there may be enlarged inguinal or supraclavicular lymph nodes, edema of the legs, or hepatomegaly, but these are not commonly seen.

On pelvic examination the cervix may be ulcerative or exophytic (Figure 38-5). It usually bleeds on palpation and there is often an associated serous, purulent, or bloody discharge. The lesion may involve the adjacent vagina and extend toward the introitus.

A rectovaginal examination is essential to determine the extent of disease. **The diameter of the primary cancer and spread to the parametria are much more easily detected with a finger in the rectum, as is extension into the uterosacral ligaments.**

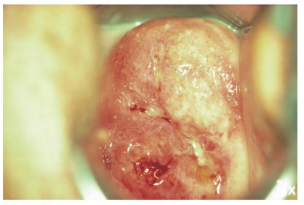


FIGURE 38-5 Invasive squamous cell carcinoma of the cervix. Note the irregular, ulcerated surface of the exocervix (or ectocervix). A biopsy of such a lesion is mandatory.

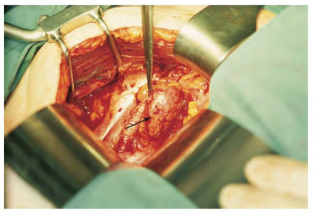


FIGURE 38-6 Grossly enlarged lymph node *(arrow)* at the bifurcation of the common iliac artery in a patient with stage IB2 carcinoma of the cervix. Large nodes such as this can cause ureteric obstruction.

PATHOLOGIC FEATURES

Most uterine cervical cancers are squamous in origin. Adenocarcinomas and adenosquamous carcinomas are increasing in incidence and account for about 20-25% of cases. Melanomas and sarcomas occur rarely.

PATTERNS OF SPREAD

Invasive cervical cancer spreads by direct invasion to involve the cervical stroma, corpus, vagina, and parametrium; lymphatic spread to pelvic and then paraaortic lymph nodes (Figure 38-6); and hematogenous spread, particularly to the lungs, liver, and bone.

PREOPERATIVE INVESTIGATIONS

The official International Federation of Gynecology and Obstetrics (FIGO) staging for cervical cancer was changed in 2009. It remains a clinical staging method based on physical examination and noninvasive testing, because most patients with cervical cancer worldwide are treated with radiation therapy (Table 38-1). **Studies allowed include biopsies, cystoscopy, sigmoidoscopy, chest and skeletal radiographs, intravenous pyelography, and liver function tests.**

An abdominal and pelvic computed tomographic (CT) scan or a magnetic resonance imaging scan (MRI) may be helpful in planning management, but the results do not influence the FIGO stage. The MRI is particularly helpful in defining the extent of the primary lesion, including any extension into the parametrium, bladder, or rectum. Neither is particularly sensitive for detecting lymph node metastases, and **positron-emission tomographic (PET) scanning is being increasingly used** for this purpose. **The incidence of paraaortic lymph node metastases is approximately 20% in patients with stage II disease and 30% in those with stage III. The status of the paraaortic nodes is the single most important prognostic factor.**

Laboratory studies may reveal abnormalities with advanced disease, the most common being anemia from blood loss, elevated blood urea nitrogen and creatinine levels from ureteric obstruction, and abnormal liver function tests if there are liver metastases. **Ureteric obstruction occurs in about 30% of patients with stage III disease and in 50% of patients with stage IV disease.** Hypercalcemia may denote bone metastases.

TREATMENT OF INVASIVE CANCER

Stage IA (Microinvasive Carcinoma)

A preoperative diagnosis of microinvasive carcinoma can be made only on the basis of a cone biopsy of the cervix with clear surgical margins, which allows multiple-step sections to be taken at 2-mm intervals. With a punch biopsy, the sampling of the cervix is too limited, and a more frankly invasive focus may be missed. The concept of microinvasive carcinoma also applies to glandular lesions, although an occasional adenocarcinoma will have a skip lesion higher in the endocervical canal.

When the depth of invasion on cone biopsy is 3 mm or less, horizontal dimension is 7 mm or less (stage IA1), and there is no lymphatic or vascular space involvement, an extra-fascial abdominal or vaginal hysterectomy is appropriate treatment. Cervical conization alone may suffice if the patient desires to maintain her fertility, as long as the cone margins are free of disease and the endocervical curettings (taken after the conization) are negative. **For stage IA2 disease, or if there is lymphatic or vascular space involvement, most gynecologic oncologists recommend modified radical hysterectomy and pelvic lymph node dissection.** If childbearing is desired, large-cone biopsy or radical trachelectomy combined with pelvic lymphadenectomy may be offered.

Stages IB1 and IB2

Stage IB disease may be treated by either primary surgery (radical hysterectomy and bilateral pelvic lymphadenectomy) or primary chemoradiation therapy. The advantages of surgery are that the ovaries may be spared in younger women, surgical staging may be carried out, and chronic radiation complications may be avoided, particularly vaginal stenosis, radiation proctitis, and radiation cystitis. Primary surgery is regarded as the treatment of choice for Stage IB1 cervical cancer.

The results of treatment by either method are similar when both the surgeon and the radiotherapist are knowledgeable and skilled. Chemoradiation is often chosen for Stage IB2 lesions, but primary surgery followed by tailored external beam therapy is a valid alternative approach. Patients with deep stromal penetration and extensive vascular space invasion but negative lymph nodes may receive a "small field" of pelvic radiation, whereas patients with positive common iliac or paraaortic nodes may receive extended field radiation, usually combined with cisplatin.

TABLE 38-1
INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS STAGING OF CARCINOMA OF THE CERVIX UTERI (2009)

Stage	
I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5.0 mm and largest extension ≤7.0 mm
IA1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm
IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm
IB	Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than stage IA*
IB1	Clinically visible lesion ≤4.0 cm in greatest dimension
IB2	Clinically visible lesion >4.0 cm in greatest dimension
II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA	Without parametrial invasion
IIA1	Clinically visible lesion ≤4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4.0 cm in greatest dimension
IIB	With obvious parametrial invasion
III	The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or nonfunctioning kidney†
IIIA	Tumor involves lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney
IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum; a bullous edema, as such, does not permit a case to be allotted to stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

From FIGO Committee on Gynecologic Oncology: Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynecol Obst* 105:103–104, 2009.
*All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be >5.00 mm taken from the base of the epithelium of the original tissue—squamous or glandular. The depth of invasion should always be reported in mm, even in those cases with "early (minimal) stromal invasion" (=1 mm). The involvement of vascular/lymphatic spaces should not change the stage allotment.
†On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or nonfunctioning kidney are included, unless they are known to be due to another cause.

RADICAL HYSTERECTOMY. In this procedure, the uterus is removed along with adjacent portions of the vagina, cardinal ligaments, uterosacral ligaments, and bladder pillars.

The most common complication of radical hysterectomy is bladder dysfunction, which occurs because of interruption to the autonomic nerves traversing the cardinal and uterosacral ligaments. Normal bladder function is usually restored within 1 to 3 weeks, but 1-2% of patients have permanent dysfunction necessitating lifelong self-catheterization. A nerve-sparing radical hysterectomy has been described and is increasingly used.

The most serious complication of radical hysterectomy is ureteric fistula or stricture, which occurs in 1-2% of cases. A less common but life-threatening complication is **deep venous thrombosis,** with or without **pulmonary embolism.** The incidence of venous thromboembolism can be reduced with the use of external pneumatic calf compressors at the time of surgery, early ambulation, and prophylactic anticoagulants. Some degree of **lymphedema** occurs in 15-20% of patients having a pelvic lymphadenectomy.

RADICAL TRACHELECTOMY. For young women with early cancer (up to 2 cm diameter), radical vaginal or abdominal trachelectomy and pelvic lymphadenectomy may allow fertility preservation, without significantly compromising survival.

RADIATION THERAPY. For patients with stage IB2 disease, most centers use primary chemoradiation, using weekly cisplatin as the radiation sensitizer. **Therapy usually begins with external radiation in an attempt to shrink the central tumor and improve the dosimetry of the subsequent intracavitary therapy (brachytherapy).**

If primary radical hysterectomy is performed, external radiation may be used postoperatively for patients with lymph node metastases or inadequate surgical margins, but brachytherapy may be avoided, thereby

Reference

decreasing the incidence of vaginal stenosis. The addition of weekly cisplatin (40 mg/m^2 intravenously) during external beam therapy has been shown to improve survival.

Stage IIA1 or IIA2

In patients with minimal involvement of the posterior vaginal fornix (up to 1 cm), radical hysterectomy, upper vaginectomy and pelvic lymphadenectomy is appropriate, particularly for patients with stage IIA1 disease. With more extensive posterior forniceal involvement, chemoradiation therapy is the treatment of choice, because surgery would leave the patient with a much shortened vagina. If there is involvement of the anterior fornix, surgical margins on the bladder would be close, and treatment should be with chemoradiation therapy. Most patients with stage IIA2 disease will be treated with chemoradiation.

Stage IIB

Most patients with stage IIB lesions are treated with a combination of external beam chemoradiation and intracavitary brachytherapy. **If positive paraaortic or high common iliac lymph nodes are detected preoperatively on imaging, extended-field radiation may be employed** to treat all of the paraaortic lymph nodes up to the diaphragm.

Stages IIIA and IIIB

Patients with stage IIIA and stage IIIB disease are treated with chemoradiation therapy, usually external beam followed by intracavitary brachytherapy. In patients with locally advanced disease, distortion of the cervix and vagina may make brachytherapy difficult to apply. Therefore, a higher dose of external therapy, up to 7000 centigray (cGy), may be necessary. Alternatively, interstitial radiation may be given to get a better dose distribution than would be possible with intracavitary therapy.

Stage IVA

Pelvic chemoradiation therapy is used in most patients with stage IVA lesions. If radiation therapy results in only partial tumor regression, a "salvage" pelvic exenteration may be performed. **Primary pelvic exenteration is performed only rarely,** usually when the patient presents with a rectovaginal or vesicovaginal fistula.

Stage IVB

These patients basically require palliative care and control of symptoms, because they are not curable. Control of symptoms will usually necessitate some pelvic radiation therapy to palliate bleeding from the vagina, bladder, or rectum. Bone metastases may require radiation, and chemotherapy may be offered for systemic metastases to prolong survival.

Recurrent or Metastatic Disease

CHEMOTHERAPY. The effectiveness of chemotherapy is limited for metastatic cervical cancer.

Several drugs have been tested and found to be active in up to 35% of cases. Most responses are partial, and the patients usually progress within 12 months. **The most active agents are cisplatin, bleomycin, mitomycin C, methotrexate, and cyclophosphamide.**

PELVIC EXENTERATION. Pelvic exenteration is generally reserved for patients who have a central recurrence following pelvic irradiation. **Total exenteration involves removal of the pelvic viscera, including the uterus, tubes, ovaries, vagina, bladder, and rectum** (Figure 38-7). Depending on the site and extent of the disease, the operation may be limited to an anterior exenteration, which spares the rectum, or a posterior exenteration, which spares the bladder.

Following the extirpative surgery, pelvic reconstruction is necessary. If the bladder is removed, the ureters must be implanted into a portion of the small or large bowel that has been isolated from the remainder of the gastrointestinal tract to form a conduit. **A continent conduit may be created,** particularly in younger patients. When the disease is confined to the upper vagina and rectovaginal septum, the lower rectum and anal canal may be preserved and reanastomosed to the sigmoid colon. A temporary colostomy is often required to protect the reanastomosis because of the prior irradiation. **Vaginal reconstruction can be performed using a split-thickness skin graft, bilateral gracilis myocutaneous grafts, a rectus abdominus myocutaneous flap, or a segment of large intestine.**

Relatively few patients with recurrent cancer of the cervix are suitable to undergo pelvic exenteration because most have metastases outside the pelvis or fixation of the tumor to structures that cannot be removed, such as the pelvic side wall. All patients should have a preoperative PET/CT scan to exclude nodal or other systemic metastases.

In selecting patients who may be suitable for pelvic exenteration, the triad of unilateral leg edema, sciatic pain, and ureteral obstruction is ominous and usually indicates unresectable disease in the pelvis.

Cervical Carcinoma in Pregnancy

Carcinoma of the cervix associated with pregnancy usually implies diagnosis during pregnancy or within 6 months postpartum. It is relatively uncommon, invasive carcinoma occurring in approximately 1 in 2200 pregnancies.

SYMPTOMS

The symptoms are similar to those in nonpregnant patients, with painless vaginal bleeding being the most common. During pregnancy, this symptom can readily be attributed to conditions such as threatened abortion or placenta previa, so there is often an unnecessary delay in diagnosis.

Diagnosis

A prenatal Pap smear leads to the diagnosis in most cases. **Pregnancy tends to exaggerate the colposcopic features of SIL so that overdiagnosis is more likely than the reverse.** Endocervical curettage should not be performed during pregnancy because of the risk of rupturing the membranes. **Cone biopsy, if required, is best performed during the second trimester to avoid the possibility of induced abortion in the first trimester and severe hemorrhage and premature labor in the third trimester.** Unfortunately, about half of the patients are not diagnosed until the postpartum period. The later the diagnosis is made, the more likely the cancer is to be in an advanced stage.

MANAGEMENT

HSIL diagnosed during pregnancy should be managed conservatively, with the pregnancy allowed to proceed to term, vaginal delivery anticipated, and appropriate therapy carried out 6 to 8 weeks postpartum.

Microinvasive carcinoma of the cervix diagnosed by conization of the cervix during pregnancy may also be managed conservatively, the pregnancy being allowed to continue to term. At term, vaginal delivery or cesarean delivery may be appropriate based on obstetrical considerations, followed by appropriate surgical management 6 to 8 weeks later. If further childbearing is not desired, appropriate surgical management may occur at the time of cesarean delivery.

Frankly invasive cancer requires relatively urgent treatment. The risks and benefits of all treatment options must be carefully discussed with the parents, particularly the mother. Some mothers are unwilling to sacrifice their fetus, even if continuing the pregnancy would significantly impair their own prognosis. Such patients are best treated with neoadjuvant chemotherapy.

For early lesions, radical hysterectomy and pelvic lymphadenectomy may be performed. Before 20 weeks' gestation, this is performed with the fetus in situ.

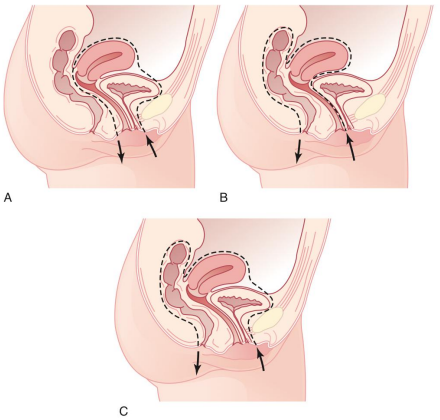


FIGURE 38-7 Organs removed in anterior exenteration **(A)**, posterior exenteration **(B)**, and total pelvic exenteration **(C)**.

TABLE 38-2

SURVIVAL BY THE INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS STAGE (*N* = 11,639)

		Overall Survival Rates (%)				
Stage	Patients	1-Year	2-Year	3-Year	4-Year	5-Year
IA1	829	99.8	99.5	98.3	97.5	97.5
IA2	275	98.5	96.9	95.2	94.8	94.8
IB1	3020	98.2	95.0	92.6	90.7	89.1
IB2	1090	95.8	88.3	81.7	78.8	75.7
IIA	1007	96.1	88.3	81.5	77.0	73.4
IIB	2510	91.7	79.8	73.0	69.3	65.8
IIIA	211	76.7	59.8	54.0	45.1	39.7
IIIB	2028	77.9	59.5	51.0	46.0	41.5
IVA	326	51.9	35.1	28.3	22.7	22.0
IVB	343	42.2	22.7	16.4	12.6	9.3

Data from the 26th Annual Report on the Results of Treatment in Gynecological Cancer: Patients treated 1999-2001. *Int J Gynecol Obstet* 95:543–5103, 2006, with permission. These data are based on the 1994 FIGO Staging in which stage IIA is not divided into IIA1 and IIA2.

Between 20 and 25 weeks, hysterotomy through a high incision in the uterine fundus is performed to remove the fetus before the radical surgery. After about 25 weeks, it is usual to await fetal viability at about 34 weeks. Classical cesarean delivery followed immediately by radical hysterectomy and bilateral pelvic lymphadenectomy is then undertaken.

For some patients with early disease and for all patients with advanced disease, the alternative to radical surgery is radiation therapy. Treatment begins with external beam therapy to shrink the tumor. Abortion usually occurs spontaneously during the course of external therapy; if it does not, uterine curettage should be performed in the first trimester or hysterotomy through a high incision in the corpus in the second trimester before brachytherapy is given.

If a decision is made to await fetal viability, it is important to be certain by ultrasonography that the fetus is apparently healthy and to obtain a mature lecithin-to-sphingomyelin ratio to ensure fetal lung maturity before delivery. Neoadjuvant chemotherapy is increasingly used to try to "contain" the disease, and about 10% of patients will have a complete response to the chemotherapy.

Because of the increased risk of hemorrhage and infection likely to be associated with delivery through a cervix containing gross cancer, classic cesarean delivery is the preferred method of delivery. **For patients in whom inadvertent vaginal delivery has occurred, there is no evidence to indicate that the prognosis is altered.**

Prognosis for Cervical Cancer

Prognosis is related directly to clinical stage (Table 38-2). With higher stage disease, the frequency of nodal metastasis escalates, and the 5-year survival rate diminishes. Adenocarcinomas and adenosquamous carcinomas have a somewhat lower 5-year survival rate than do squamous carcinomas, stage for stage.

Matched, controlled studies have demonstrated identical survivals for pregnant and nonpregnant patients.

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Good Luck!

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