CERVICAL LESIONS

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UROGYNAECOLOGY
The Papanicolaou test is a method of cervical screening used to detect potentially precancerous and cancerous processes in the cervix.

Abnormal findings are often followed up by more sensitive diagnostic procedures and if warranted, interventions that aim to prevent progression to cervical cancer.
### Risk of cervical neoplasia with abnormal cervical cytology results in women ages 30 to 64

<table>
<thead>
<tr>
<th>Cervical cytology*</th>
<th>Incidence (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CIN 2+</td>
</tr>
<tr>
<td>Negative</td>
<td>0.68</td>
</tr>
<tr>
<td>(ASC-US)</td>
<td>6.9</td>
</tr>
<tr>
<td>- HPV-positive</td>
<td>18</td>
</tr>
<tr>
<td>- HPV-negative</td>
<td>1.1</td>
</tr>
<tr>
<td>(LSIL)</td>
<td>16</td>
</tr>
<tr>
<td>- HPV-positive</td>
<td>19</td>
</tr>
<tr>
<td>- HPV-negative</td>
<td>5.1</td>
</tr>
<tr>
<td>(ASC-H)</td>
<td>35</td>
</tr>
<tr>
<td>High-grade intraepithelial lesion</td>
<td>69</td>
</tr>
<tr>
<td>Atypical glandular cells</td>
<td>13</td>
</tr>
<tr>
<td>Squamous cell cancer</td>
<td>84</td>
</tr>
</tbody>
</table>

HPV: human papillomavirus; CIN: cervical intraepithelial neoplasia.
Bethesda 2014 classification system for cervical cytology

- **Squamous cell**
  - Atypical squamous cells
    - Of undetermined significance (ASC-US)
    - Cannot exclude HSIL (ASC-H)
  - Low-grade squamous intraepithelial lesion (LSIL)
  - High-grade squamous intraepithelial lesion (HSIL)
  - Squamous cell carcinoma

- **Glandular cell**
  - Atypical Glandular cells,
    - Endocervical cells
    - Endometrial cells
    - NOS
  - Atypical Glandular cells, favor neoplastic
  - Endocervical adenocarcinoma in situ
  - Adenocarcinoma
WHAT IS ABNORMAL PAP SMEAR?

1. Abnormal due to inadequacy
2. Abnormal due to inflammation
3. Abnormal due to infection
4. Abnormal due to dysplastic changes
PAP SMEAR
UNSATISFACTORY

- UNSATISFACTORY
  - TX ANY INFECTION
  - GIVE A COURSE OF ESTROGEN IF POST MENOPAUSE WITH ATROPHY
  - REPEAT 6/12

- 2ND SMEAR UNSATISFACTORY
  - REPEAT 6/12

- 3RD SMEAR UNSATISFACTORY
  - COLPOSCOPY
Inflammatory smear

Inflammation on Pap smear results, does not indicate any particular pathology.

Therefore, does not necessitate routine treatment.
POSSIBLE CAUSES

- Infection
- Chronic cervicitis
- Atrophic cervicitis
- Chemical or mechanical irritation to cervix
  - tampon, douching
Infection

COMMON INFECTIONS:

• Trichomonas vaginalis
• Fungal ie candidiasis
• Bacterial Vaginosis
• Actinomyces
• Herpes Simplex

ORGANISM TREATMENT
Dysplasia

DYSPLASTIC CHANGES SQUAMOUS CELL

• ASCUS
  • ASC-H
  • LGSIL
  • HGSIL
  ▶ INVASIVE SQUAMOUS CELL CARCINOMA

ABNORMALITY GLANDULAR ABNORMALITY

• AGS
• AIS
• INVASIVE ADENOCARCINOMA
Squamous cell changes

ABNORMAL PAP SMEAR DUE TO DYSPLASTIC CHANGES - SQUAMOUS CELL ABNORMALITIES

1- Atypical Squamous Cells (ASC)
   - Atypical Squamous Cells-Undetermined Significance (ASC-US)
   - Atypical Squamous Cells, Cannot Exclude High Grade Lesion (ASC-H)

2- Low-grade Squamous Intraepithelial Lesion (LSIL) (Mild Dyskaryosis / HPV/CIN 1)

3- High-grade Squamous Intraepithelial Lesion (HSIL) (Mod or Severe Dyskaryosis / CIN 2,3)

4- Invasive Squamous Cell Carcinoma
1. Undetermined Significance (ASC-US)
   Cytologic changes suggestive of a low grade squamous lesion but lack criteria for definitive interpretation.

2. Cannot Exclude High Grade Lesion (ASC-H)
   Cytologic changes suggestive of a high grade squamous lesion but lack criteria for definitive interpretation.
Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology

Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology

- **Repeat Cytology**
  - @ 1 year
  - Acceptable
  - **Negative**
    - Routine Screening*
  - **≥ ASC**
    - Colposcopy
      - Endocervical sampling preferred in women with no lesions, and those with inadequate colposcopy; it is acceptable for others
      - Manage per ASCCP Guideline

- **HPV Testing**
  - Preferred
  - **HPV Positive**
    - (managed the same as women with LSIL)
  - **HPV Negative**
    - Repeat Cotesting @ 3 years

*Management options may vary if the woman is pregnant or ages 21-24. *Cytology at 3 year intervals
LOW GRADE INTRAEPITHELIAL LESSION (LGSIL) / CIN 1

CIN I being the morphologic manifestation of a self-limited sexually transmitted HPV infection

- 60% of CIN I regress spontaneously
- 30% of CIN I persists.
- 10% of CIN I lesions progress to CIN III
- 1% may ultimately progress to invasive cancer.
Management of Women with Low-grade Squamous Intraepithelial Lesions (LSIL)

Management of Women with Low-grade Squamous Intraepithelial Lesions (LSIL)*

- **LSIL with negative HPV test**
  - Preferred
  - Repeat Cotesting @ 1 year
    - Cytology Negative and HPV Negative
    - Repeat Cotesting @ 3 years
  - Acceptable

- **LSIL with no HPV test**
  - Colposcopy

- **LSIL with positive HPV test**
  - ≥ ASC or HPV positive
  - Colposcopy
The Natural History of HPV Infection

Normal ↔ CIN1 ↔ CIN2 ↔ CIN3

|------ Pre-cancerous cell changes ------|

Cervical cancer

Cervix viewed from below

HPV Infection

Persistent Infection (approx. 5 to 20 years)

Invasion
A lesion that persist after 1-2 years or any progression during follow up suggest need of treatment

If HPV testing is available, +ve HPV: indication for treatment.

Treatment- local ablative/ excision

Follow up after treatment for CIN1

- repeat smear in 6/12
- repeat smear and colposcopy in 12/12
- If normal, yearly pap smear x 2 years then back to normal routine
3. HIGH GRADE INTRAEPITHELIAL LESSION (HGSIL)/ CIN 2-3

CIN 2-3 is a cervical cancer precursor

1. CIN 2
   - 40% of CIN II regress
   - 30% of CIN II persist
   - 20% of CIN II progress to CIN III
   - 5% of CIN II progress to CIN III

2. CIN 3
   - 33% of CIN III regress
   - 18% of CIN III progress to invasive disease over a 10 years
   - 36% of CIN III progress to invasive disease over a 20 years
Management of Women Ages 21-24 yrs with Atypical Squamous Cells, Cannot Rule Out High Grade SIL (ASC-H) and High-grade Squamous Intraepithelial Lesion (HSIL)

Management of Women Ages 21-24 yrs with Atypical Squamous Cells, Cannot Rule Out High Grade SIL (ASC-H) and High-grade Squamous Intraepithelial Lesion (HSIL)

Colposcopy  
(Immediate loop electrosurgical excision is unacceptable)

- No CIN2,3
- Observation with colposcopy & cytology *  
  @ 6 month intervals for up to 2 years

- Two Consecutive Cytology Negative Results and No High-grade Colposcopic Abnormality
  - Routine Screening

- Other results
  - HSIL Persist for 24 months with no CIN2,3 identified
  - Biopsy

- High-grade colposcopic lesion or HSIL  
  Persist for 1 year

- Manage per AASCP Guideline for young women with CIN2,3

- Diagnostic Excisional Procedure
  (If no CIN2,3, continue observation)
PAP SMEAR HGSIL COLPOSCOPY AND BIOPSY

Subsequent management depends on:

- Whether lesion identified
- Whether colposcopy satisfactory
- Annual smear following treatment

MANAGEMENT APPROACH EXCISION METHOD

- LLETZ
- Cold knife cone biopsy
- Hysterectomy
ABLATIVE METHODS

- Cryocautery
- Electrodiathermy
- Cold coagulation
INVASIVE SQUAMOUS CELL CANCER

- PAP SMEAR
- COLPOSCOPY AND
- BIOPSY

Subsequent management depends on Stage of the disease
ABNORMAL PAP SMEAR DUE TO DYSPLASTIC CHANGES - GLANDULAR CELL ABNORMALITIES

1. Atypical Glandular Cells (AGS) (undetermined or favour neoplastic)
2. Adenocarcinoma in Situ (AIS)
3. Invasive Adenocarcinoma
GLANDULAR ABNORMALITIES

The most common significant lesions associated with AGC (Atypical Glandular Cells) are actually squamous

Management should include colposcopy and endocervical sampling

ATYPICAL ENDOMETRIAL CELLS

Always perform endometrial sampling If endometrial sampling is negative : colposcopy with endocervical sampling
ATROPHY SMEAR

LOCAL ESTROGEN CREAM 1G ON FOR 2 WEEKS THEN TWICE WEEKLY FOR 6 WEEKS

ATROPHY SMEAR REPEAT IN 6 MONTHS
REACTIVE CELLULAR CHANGES

REACTIVE CELLULAR CHANGES DUE TO

- RADIATION
- REPAIR
- IUCD

REACTIVE CELLULAR CHANGES REPEAT IN 1 YEAR
Management of Women with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia—Grade 1 (CIN1) Preceded by "Lesser Abnormalities"

Follow-up without Treatment

Cotesting at 12 months

- HPV(-) and Cytology Negative
  - Age appropriate retesting 3 years later
    - Cytology negative
      - HPV(-)

≥ ASC or HPV(+)

Colposcopy

No CIN

- Manage per ASCCP Guideline

CIN2,3

- If persists for at least 2 years
  - Follow-up or Treatment 

CIN1

If persists for at least 2 years

Follow-up or Treatment 

Management of Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia—Grade 2 and 3 (CIN2,3)

- **Adequate Colposcopy**
  - Either Excision\(^\d\) or Ablation of T-zone\(^*\)
  - Cotesting at 12 and 24 months
    - 2x Negative Results
    - Repeat cotesting in 3 years
  - Routine screening

- **Inadequate Colposcopy or Recurrent CIN2,3 or Endocervical sampling is CIN2,3**
  - Diagnostic Excisional Procedure\(^\d\)
  - Any test abnormal
    - Colposcopy With endocervical sampling
ABNORMAL PAP SMEAR IN PREGNANCY

Reported abnormal smear during pregnancy

- 1%- 8%
- Follow-up should be similar to non pregnant state-every trimester regardless of gestation
- Suspicious lesion should be biopsied.
- Cervical biopsy does not increase the risk of miscarriage
- If evidence of invasive cancer- require excision
Cervical cancer

Epidemiology

- Worldwide, cervical cancer is the second leading cause of cancer mortality in women.
- Among the ~500,000 new cases each year,
- ~75% occur in developing countries.
- Cervical cytologic testing has reduced the incidence of cervical cancer by 70% in countries where it is easily available.
Cervical Cancer and HPV

- Human papillomavirus (HPV) is central to cervical carcinogenesis
- Worldwide, the prevalence of HPV in cervical tumors is 99.7%
- High-risk HPV types include 16, 18, 31 and 41
- High-risk HPV infection is necessary but insufficient for cervical cancer
Spectrum of Changes in Cervical Squamous Epithelium Caused by HPV Infection

* CIN = cervical intraepithelial neoplasia

- Normal Cervix
- HPV Infection/ CIN* 1 / CIN 2 / CIN 3 /
- Cervical cancer
Natural history

- % Regress Persist Progress to CIS
- Progress to Invasion
- CIN 1 60 30 10 1
- CIN 2 40 35 20 5
- CIN 3 30 <56 - 18 (5y), 36
Additional Risk Factors for CX Cancer

- Early onset sexual activity
- Multiple sexual partners
- High-risk sexual partner
- History of a sexually transmitted infection
- Immunosuppression
- Low socio-economic status
- Previous history of vulvar, vaginal or cervical squamous dysplasia
Diagnosis of cervical cancer

- Cervical cytology (Pap smear); results may suggest invasive cancer
- Diagnosis must be confirmed by a biopsy
- When a tumor is clinically evident, a biopsy is usually sufficient
Histologic Subtypes

Squamous-Cell Carcinoma

- Keratinizing or Nonkeratinizing
- Verrucous
- Papillary transitional
- Lymphoepithelioma-like

Adenocarcinoma

- Mucinous
- Endometrioid
- Clear Cell
- Serous
- Mesonephric
- Well differentiated villoglandular
- Minimal deviation (adenoma malignum)

Other epithelial - Adenosquamous - Glassy Cell - Carcinoid Tumor - Neuroendocrine - Small-cell - Undifferentiated
Patterns of Spread

- Local Invasion
- Lymphatic
  - Risk relates to depth of invasion, Pelvic nodes before paraaortic or supraclavicular
  - Hematogenous - More likely in adenocarcinoma, neuroendocrine or small cell tumors
  - Intraperitoneal - Unknown incidence - Poor prognosis
Cervical Cancer Staging

The International Federation of Gynecology and Obstetrics (FIGO) staging system is exclusively based on clinical evaluation.

This allows staging to occur in low resource settings.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Extent of disease</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Carcinoma in situ (CIN)</td>
<td>~100%</td>
</tr>
<tr>
<td>I</td>
<td>Limited to cervix</td>
<td></td>
</tr>
<tr>
<td>Ia1</td>
<td>Microscopic disease: stromal invasion &lt;3mm, lateral spread &lt;7mm</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Ia2</td>
<td>Microscopic disease: stromal invasion &lt;3mm and &gt;5mm, lateral spread &lt;7mm</td>
<td></td>
</tr>
<tr>
<td>Ib1</td>
<td>Macroscopic lesion &lt;4cm in greatest dimension</td>
<td>~90%</td>
</tr>
<tr>
<td>Ib2</td>
<td>Macroscopic lesion &gt;4cm in greatest dimension</td>
<td>80-85%</td>
</tr>
<tr>
<td>II</td>
<td>Extension to uterus/parametria/vagina</td>
<td>~75-78%</td>
</tr>
<tr>
<td>IIa1</td>
<td>Involvement of upper two thirds of vagina without parametrial invasion, &lt;4cm greatest diameter</td>
<td></td>
</tr>
<tr>
<td>IIa2</td>
<td>Involvement of upper two thirds of vagina without parametrial invasion, &gt;4cm greatest diameter</td>
<td></td>
</tr>
<tr>
<td>IIb1</td>
<td>Involvement of upper two thirds of vagina with parametrial invasion</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Extension to pelvic side wall and/or lower third of vagina</td>
<td>~47-50%</td>
</tr>
<tr>
<td>IIIa</td>
<td>Involvement of lower third of vagina</td>
<td></td>
</tr>
<tr>
<td>IIIb</td>
<td>Extension to pelvic side wall and/or hydrenephrosis</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Extension to adjacent organs or beyond true pelvis</td>
<td>~20-30%</td>
</tr>
<tr>
<td>IVa</td>
<td>Extension to adjacent organs e.g. bladder, bowel</td>
<td></td>
</tr>
<tr>
<td>IVb</td>
<td>Distant metastases</td>
<td></td>
</tr>
<tr>
<td>Stage</td>
<td>0</td>
<td>I</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Extent of tumor</td>
<td>Carcinoma in-situ</td>
<td>Confined to cervix</td>
</tr>
<tr>
<td>5-year survival</td>
<td>100%</td>
<td>85%</td>
</tr>
<tr>
<td>Stage at presentation</td>
<td>47%</td>
<td>28%</td>
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</table>
Stages

Close up of cervix showing development of abnormal cells into cervical cancer

Early stage

Mid stage

Late stage

1 mm

2 mm

Millimeters (mm)

3 mm
What are the symptoms of cervical cancer?

Early stage disease:
- Often no symptoms!
- Vaginal discharge
- Abnormal bleeding - Post-coital bleeding - Abnormal menses - Post-menopausal bleeding
Late stage disease:

- Pelvic or lower back pain
- Sciatica
- Weight loss
- Bowel or bladder fistula
How is cervical cancer staged?

- Physical exam
  - Palpation and inspection of primary tumor
  - Palpation of groin and supraclavicular lymph nodes
  - Rectovaginal exam
  - Exam under anesthesia
- Diagnostic exam(s) - Chest X-ray - Intravenous pyelogram (IVP)
- Procedures - Conization - Cystoscopy - Proctosigmoidoscopy
Imaging Modalities Prognosis- NOT Staging

• Computed Tomography (CT scan)
• Magnetic Resonance Imaging (MRI) - May help define extent of disease in cervix and parametria
• Positron Emission Tomography (PET) - Superior for detecting metastatic disease compared to CT or MRI
• Surgical “Staging” - The “gold standard” for lymph node evaluation
Stage Determines Treatment

- Early Stage (I-IB1 [IB2-IIa])
  - Primary Surgery
  - Chemoradiation
- Locally Advanced (IB2-IVA) - Primary Chemoradiation
- Disease with Distant Metastases (IVB) - Systemic chemotherapy
Treatment of Early Stage (I-IIA)/SURGERY

- **Pros**
  1. Preserves ovarian function
  2. Opportunity for pathologic information
  3. Preferred for women at risk for irradiation complications

- **Cons**
  1. Surgical morbidity and mortality
  2. Risk of general anesthesia
  3. Risk of bleeding/transfusion
  4. Possibility of long-term bowel and bladder problems
  5. Possible need for post-op XRT
RADIATION THERAPY

- **Pros**
  1. Avoids risks of surgical morbidity
  2. Blood loss/transfusion
  3. General anesthesia
  4. Allows for outpatient treatment

- **Cons**
  1. Permanent ovarian failure
  2. Vaginal shortening and fibrosis
  3. Possibility of long-term bowel and bladder problems
  4. Risk of bladder or bowel fistula, or rectal stricture
Surgical options for early stage cervical cancer
Stage IA1 Stage IA2-IB1

Cervical Cancer Candidates for Radical Trachelectomy Criteria for eligibility:

- Confirmed cervical cancer
- Stage IA1 with LVSI, IA2-IB1
- Lesion 2cm
- Post conization 4-6 weeks
- BMI < 35kg/m2
- Desire for future fertility
- No evidence of impaired fertility
Radical Trachelectomy Obstetrical outcomes

- 62% of pregnancies reach 3rd trimester (65% term)
- 1st trimester loss: 16-20% (Equal to general population)
- 2nd trimester loss: 9% (4% in general population)

Fertility outcomes:
- 50-60% of women attempting will succeed spontaneously
Prognostic Factors

- Status of lymph nodes
- Size of primary tumor
- Depth of stromal invasion
- +/- lymph-vascular space (LVSI) invasion
- +/- parametrial extension
- Histologic cell type
- Close vaginal margines
Indications for Adjuvant Therapy

Women with one or more of the findings below are considered to be at HIGH risk

- for recurrent disease
- Positive or close resection margins
- Positive lymph nodes
- Parametrial involvement
IIB-IVA (Locally Advanced) Cervical Cancer

- Radiation therapy
- Addition of chemotherapy can reduce the risk of death by 30-50%
- Recommended Tx:
  - External beam radiation
  - Concurrent cisplatin (40mg/m2 per week)
  - Intracavitary brachytherapy
Post-treatment Follow Up

- **Clinical Evaluation**
  - Review of symptoms, physical exam with attention to supraclavicular and inguinal lymph nodes, rectovaginal exam, abdominal exam,
  - +/- cytology
  - every 3 months for one year
  - every 4 months for one year -
  - every 6 months for 3 years - annually

- Annual Chest X-Ray
- Other studies only as clinically indicated
Recurrent or Metastatic (IVB) Cervical Cancer

- Rarely, recurrent disease can be cured
- Surgery for those previously irradiated
- Radiation for those with previous surgery
- Triad of symptoms:
  1) Ureteral obstruction (hydronephrosis)
  2) Sciatica
  3) Lower extremity edema suggest sidewall involvement and surgery is NOT advised
- When curative surgery or XRT not possible, palliation is the goal
- Chemotherapy
Pelvic Exenteration

- Anterior Pelvic Exenteration:
  - Pelvic reproductive organs
  - Bladder and distal ureters
  - Entire pelvic floor
  - Preservation of the rectum
Pelvic Exenteration

Posterior Pelvic Exenteration:

- Pelvic reproductive organs
- Rectum and anus
- Entire pelvic floor
- Preservation of the bladder and the ureters
Pelvic Exenteration Reconstructive Phase:

- Urostomy
- Colostomy
- Vaginal reconstruction
80% of recurrences occur within 2 years of primary

- Depends on site of recurrence and ability to pursue potentially curative therapy
- Overall, poor prognosis if curative therapy not possible

Favorable prognostic factors

1. Localized, central pelvic recurrence
2. Disease-free interval >6 months
3. Size < 3cm
4. No sidewall fixation