Cervical Cancer

Ritu Salani, M.D., M.B.A.
Assistant Professor, Dept. of Obstetrics & Gynecology
Division of Gynecologic Oncology
The Ohio State University

Estimated gynecologic cancer cases
United States 2010

Jemal, A. et al. CA Cancer J Clin 2010; 60:277-300
Estimated gynecologic cancer deaths
United States 2010

Jemal, A. et al. CA Cancer J Clin 2010; 60:277-300

Decreasing Trends of Cervical Cancer Incidence in the U.S.

- With the advent of the Pap smear, the incidence of cervical cancer has dramatically declined.
- The curve has been stable for the past decade because we are not reaching the unscreened population.

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Cancer incidence worldwide

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>New cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>12,200</td>
<td>4,210</td>
</tr>
<tr>
<td>Developing nations</td>
<td>530,000</td>
<td>275,000</td>
</tr>
</tbody>
</table>

- 85% of cases occur in developing nations

¹Jemal, CA Cancer J Clin 2010
GLOBOCAN 2008
Cervical Cancer

- Histology
  - Squamous cell carcinoma (80%)
  - Adenocarcinoma (15%)
  - Adenosquamous carcinoma (3 to 5%)
  - Neuroendocrine or small cell carcinoma (rare)

Human Papillomavirus (HPV)

- Etiologic agent of cervical cancer
- HPV DNA sequences detected is more than 99% of invasive cervical carcinomas
- High risk types: 16, 18, 45, and 56
- Intermediate types: 31, 33, 35, 39, 51, 52, 55, 58, 59, 66, 68

HPV 16 accounts for ~80% of cases
HPV 18 accounts for 25% of cases

Risk factors

- Early age of sexual activity
- Cigarette smoking
- Infection by other microbial agents
- Immunosuppression
  - Transplant medications
  - HIV infection
- Oral contraceptive use
- Dietary factors
  - Deficiencies in vitamin A and beta carotene
Multi-Stage Cervical Carcinogenesis


Presentation

- Asymptomatic
- Vaginal bleeding
  - Post coital bleeding
- Vaginal discharge
- Pelvic pain, pressure
- Vaginal passage of urine or feces
# Cervical Cancer

**Eric L. Eisenhauer, MD**  
Assistant Professor, Dept. of Obstetrics & Gynecology  
Division of Gynecologic Oncology  
The Ohio State University

## Screening

<table>
<thead>
<tr>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detect high risk lesions (CIN 2,3+) that could progress to invasive cancer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap smear has broad range of sensitivity (30-87%)&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Improved with repeated testing</td>
</tr>
<tr>
<td>Improved with HR HPV testing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Triage&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-H, LSIL, HSIL, AGC, repeat ASC-US</td>
</tr>
<tr>
<td>Refer for colposcopy and biopsy</td>
</tr>
</tbody>
</table>

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Diagnosis

• Most women with invasive cancer have a visible lesion
  – However, broad range of clinical appearances
• Grossly visible lesions should be biopsied
  – Pap alone is inadequate for visible lesions
• Firm, expanded cervix should undergo biopsy and endocervical curretage
• Women with symptoms or abnormal cytology without a visible lesion should undergo colposcopy and directed biopsy

Diagnosis

• Adequate colposcopy
  – Squamocolumnar junction and all lesions completely visualized
  – Biopsy results explain the abnormal cytology
  – Cone biopsy if colposcopy is inadequate
• Limitations of colposcopy
  – Less sensitive than presumed\(^1\)
  – Poor correlation between colposcopic impression and biopsy grade\(^2\)
  – Sensitivity improved with \(\geq 2\) biopsies\(^3\)

**Diagnosis**

- **Conclusion**
  - Multiple biopsies
  - Repeat colposcopy if abnormalities persist
  - Cone if inadequate colposcopy

---

### Histopathology

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Incidence $^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>67%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>25%</td>
</tr>
<tr>
<td>Adenosquamous carcinoma</td>
<td>5%</td>
</tr>
<tr>
<td>Rare histologies:</td>
<td>3%</td>
</tr>
</tbody>
</table>
  - Neuroendocrine carcinoma        |
  - Adenoid cystic carcinoma        |
  - Undifferentiated carcinoma      |
  - Sarcoma or lymphoma             |

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Staging

• Cervical cancer can spread by:
  – Direct extension to uterine corpus, vagina, parametria, peritoneum, bladder or rectum
  – Lymphatic spread to pelvic or aortic lymph nodes
  – Hematogenous dissemination

• Staging is a clinical evaluation to assess the extent to which the cancer has spread

Staging

• Accurate pretreatment staging of cervical cancer determines the therapeutic approach
• International Federation of Gynecology and Obstetrics (FIGO) system¹
  - Physical exam - Biopsy
  - Hysteroscopy - Cystoscopy
  - Intravenous pyelogram - Proctoscopy
  - Xray evaluation of lungs and skeleton
• Optional testing modalities such as CT and PET scan are widely used in US, and results used to plan treatment²
• Most US gyn oncologists still report FIGO stage

FIGO Staging of Cervical Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Cervical carcinoma confined to uterus</td>
</tr>
<tr>
<td>IA</td>
<td>Invasive carcinoma diagnosed only by microscopy (microinvasive)</td>
</tr>
<tr>
<td></td>
<td>- Clinically visible lesions</td>
</tr>
<tr>
<td>IB</td>
<td>Cervical carcinoma invades beyond uterus but not to pelvic wall or lower third of vagina</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extends to pelvic wall and/or</td>
</tr>
<tr>
<td></td>
<td>- Involves lower third of vagina</td>
</tr>
<tr>
<td></td>
<td>- Causes hydronephrosis or nonfunctioning kidney</td>
</tr>
<tr>
<td>III</td>
<td>Tumor spreads to other parts of the body, such as the mucosa of the bladder or rectum and/or distant metastasis</td>
</tr>
</tbody>
</table>

Prognosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Distribution</th>
<th>5 Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>9%</td>
<td>97%</td>
</tr>
<tr>
<td>IB</td>
<td>35%</td>
<td>85%</td>
</tr>
<tr>
<td>II</td>
<td>30%</td>
<td>68%</td>
</tr>
<tr>
<td>III</td>
<td>19%</td>
<td>41%</td>
</tr>
<tr>
<td>IV</td>
<td>6%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Prognosis

- Stage is the most important prognostic factor
- Lymph node metastasis is the second
  - 5 year survival with stage IB/IIA disease\textsuperscript{1,2}
    - Negative LN – 88-96%
    - Positive LN – 64-74%
  - Number of involved nodes may be important
- HPV subtype 18 may have a worse prognosis
- Smoking may increase the risk for treatment-related complications

\textsuperscript{1}\textsuperscript{Delgado G et al. Gynecol Oncol 1990.}
\textsuperscript{2}\textsuperscript{Averette HE et al. Cancer 1993.}

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Treatment

• Based on stage of disease
• Categories
  – Early stage
  – Locally advanced
  – Advanced/Metastatic disease

Treatment-Early stage
FIGO IA, IB1

• Non-radical surgery
  – Microinvasive disease
    • Conization
    • Simple hysterectomy
  – Fertility-preserving surgery
    • Discussed later
### Treatment-Early stage
**FIGO IA, IB1, nonbulky IIA1**

- **Surgery versus chemoradiation**
  - Outcomes comparable
  - Decision based on
    - Childbearing plans/preservation of ovarian function
    - Comorbidities
    - Physician and patient preference
    - Quality of life (QOL) issues (higher in surgery)

### Treatment-Early stage
**FIGO IA, IB1, nonbulky IIA1**

- **Radical hysterectomy**
  - Radical hysterectomy refers to the excision of the uterus en bloc with the parametrium (ie, round, broad, cardinal, and uterosacral ligaments) and the upper one-third to one-half of the vagina, with the ovaries left intact.
  - Open, vaginal, laparoscopic, or robotic approach
Lymphadenectomy

- Pelvic and para-aortic lymph node dissection
  - Resection of bulky pelvic lymph nodes
  - Assessment of lymphatic spread
  - Indication for post-operative chemoradiation
- Not performed for stage IA1 SCC
  - Less than 1% risk of nodal metastases
- Stage IA2, IB1, IB2, and IIA disease
  - Lymphadenectomy indicated
Adjuvant therapy

- **Intermediate risk factors**
  - Deep stromal involvement (to the middle or deep one-third)
  - Lymph vascular space invasion
  - Tumor size >4 cm

- **High risk factors**
  - Positive or close resection margins
  - Positive lymph nodes
  - Microscopic parametrial involvement

Treatment-Early stage

**FIGO IA, IB1, nonbulky IIA1**

- **Primary chemoradiation therapy**
  - RT consists of external beam radiation therapy +/- brachytherapy
  - Treatment field includes the whole pelvis
    - Extended field if known or suspected para-aortic metastases
  - The addition of weekly cisplatin to radiation resulted in superior results than RT alone
### Complications of treatment

<table>
<thead>
<tr>
<th>Radical hysterectomy</th>
<th>Chemoradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mortality: &lt;2%</td>
<td>• Major complications 3-15%</td>
</tr>
<tr>
<td>• Fistula:</td>
<td>• GI toxicity</td>
</tr>
<tr>
<td>– Higher with prior RT</td>
<td>– Diarrhea</td>
</tr>
<tr>
<td>– 1/3 to ½ heal spontaneously</td>
<td>– Enteritis</td>
</tr>
<tr>
<td>• Bladder atony and delay in removal of the catheter: 4%</td>
<td>• GU toxicity</td>
</tr>
<tr>
<td>• Lymphedema</td>
<td>– Frequency</td>
</tr>
<tr>
<td></td>
<td>– Hematuria</td>
</tr>
<tr>
<td></td>
<td>• Nerve pain</td>
</tr>
<tr>
<td></td>
<td>– Lumbosacral plexus</td>
</tr>
</tbody>
</table>

### Treatment-Advanced stage FIGO IB2-IVB

- Lymphadenectomy may be performed to determine disease spread and treatment
- Primary chemoradiation followed by brachytherapy
Special circumstances

- Role of postchemoradiotherapy hysterectomy
  - Little to no benefit
- Management of incidentally diagnosed cervical cancer after simple hysterectomy
  - Radical parametrectomy and upper vaginectomy, lymph node dissection
  - Radiation therapy

Special circumstances

- Cancer in a cervical stump
  - Post supra-cervical hysterectomy
- Cervical cancer in pregnancy
  - Factors considered
    - Stage of disease
    - Gestational age
    - Patient preference
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Ovarian Transposition

- Standard pelvic radiation doses cause ovarian ablation
- “Transposition”, or “oophoropexy”, can preserve ovarian function by surgically relocating ovaries out of the radiation field¹
- Minimally invasive
- Up to 50% success rate
- Predictive factors²:
  - Reproductive age
  - Radiation doses and fields

Fertility-sparing surgery

- **Eligibility**
  - Early cervical cancer < 4 cm
  - No evidence of metastasis
  - Desire for future child-bearing

- **Options**
  - Cervical conization for non-visible lesions
  - Radical trachelectomy and pelvic lymphadenectomy

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Fertility-sparing surgery

- **Radical trachelectomy**
  - Removal of cervix, upper vagina and parametrium, but not uterus
  - Abdominal or vaginal
  - Frozen section
  - Cervical cerclage
  - Lower uterine segment reattached to upper vagina
Fertility-sparing surgery

• Fertility outcomes after radical trachelectomy¹
  – As many as 50% of well-selected patients are able to achieve successful pregnancy
  – Rates of 1st and 2nd trimester loss are comparable to general population
  – May have increased incidence of preterm delivery


Prevention

• HPV Subtypes
  – HPV types 16 and 18 cause 70% cervical cancers
  – HPV types 6 and 11 cause 90% of genital warts

Prevention

• HPV Vaccines
  – Quadrivalent Vaccine (HPV 16/18 + 6/11)
    • In HPV naïve women, 98% effective to prevent CIN2+¹
    • 95% effective even if all 3 doses were not received
  – Bivalent Vaccine (HPV 16/18)
    • In HPV naïve women, 93% effective to prevent CIN2+²
  – Both are FDA approved
  – Neither contain live virus and are pregnancy category B


Prevention

• Recommendations for HPV Vaccination
  – Girls and young women ages 9-26
  – Maximum benefit before onset of sexual activity
  – Age-specific recommendations regardless of sexual activity
  – Given as 3 doses at 0, 1-2 and 6 months follow-up
  – Reasonable efficacy even if not all doses administered
Prevention

• Conclusions
  – Demonstrated efficacy to prevent CIN 2/3, AIS and cervical cancers, as well as anogenital dysplasia and neoplasia
  – No evidence of vaccine effect on pre-existing infections

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Surveillance

- Clinical evaluation every 3-6 months
- Review of symptoms
- Thorough examination
  - Lymph nodes assessment
  - Speculum examination
  - Rectovaginal
  - Abdominal
- Cytology
  - Low yield

Post treatment considerations

- Menopausal symptoms
  - Hormonal therapy
- Acute postradiation vaginal mucositis
- Sexual dysfunction
  - Vaginal shortening
  - Decreased vaginal lubrication
Healthy lifestyle

• Routine cancer screening
  – Increased risk of developing a second cancer
  – Continued surveillance for development of new lower genital tract disease
• Exercise
• Maintenance of a healthy weight

Healthy lifestyle

• Smoking cessation
  – Over 35% of patients continue to smoke after cervical cancer treatment
• Bone density monitoring
  – Assess menopausal status