Cervical Cancer

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Disclosures

NONE

Objectives

• Discuss cervical cancer screening recommendations
• Recognize symptoms and risk factors
• Review treatment options for women with cervical cancer
• Describe opportunities regarding cervical cancer prevention

Cervical Cancer Screening

• Pap smear/test
• Introduced 1941
• Allows for sampling of the ectocervix, endocervix and transformation zone
  – False negative rate of ~20%
• Implementation of screening has significantly reduced incidence and mortality of cervical cancer
### Human Papillomavirus (HPV)

- Discovered in 1956
- Cancer link in 1984
  - HPV detected in 99.7% of cervical cancers
- HPV testing
  - Approved by FDA in 2003

### HPV Infections

- Spread via skin-to-skin contact
- Over 200 types
  - 40 are considered sexually transmitted
  - Low risk (e.g. HPV 6/11): Condyloma acuminata
  - High risk (15 types): Premalignant and malignant disease

### HPV Infections

- Most HPV infections are transient
  - Median duration of infection: ~8 months
  - Clearance rates
    - 80% in women ages 15-25 years
    - 70% in the first year
    - > 90% within 2 years
  - HPV 16 and 18 are more likely to persist

### HPV Testing

- Indications
  - Reflex testing of atypical cells (ASCUS)
  - Adjunct to cervical cytology in women age 30-65 years
  - Use of HPV testing alone
- HPV testing not recommended
  - Women younger than age 30
  - ‘Low risk’ subtype
**HPV Infections**

- HPV → Carcinogenesis:
- Oncogenic (high risk) HPV infection
  - HPV 16 and 18 account for 70% of cases
- Persistence of HPV infection
- Progression to precancerous changes
- Development of invasion
  - Takes an average of 15 years

**Cervical Cancer Screening**

- ~65 million Pap tests/year
- 3.5 million abnormal Pap tests
- Cytology combined with HPV testing in women >30 years
  - Higher sensitivity for high grade dysplasia and cervical cancer
  - Reduced rate of colposcopy/cervical procedures

**Frequency of Screening**

- Women < 21 years
  - Screening not indicated
- Women 21-30 years
  - Every 3 year screening
- Women aged 30-65
  - Co-testing with cervical cytology and HPV testing every 5 years

**Discontinuation of Screening**

- After age 65 if
  - No history of severe dysplasia
  - Adequate prior screening
- Following hysterectomy
  - No cases of vaginal cancer
  - Not applicable if supracervical hysterectomy
- Exceptions
  - History of cervical cancer or dysplasia
  - HIV positive women
Cervical dysplasia/cancer

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical cancer</td>
<td>~12,000 cases and ~4000 deaths/year</td>
</tr>
<tr>
<td>330,000 new cases of high-grade cervical dysplasia (CIN 2/3)</td>
<td>86% of cases occur in developing countries</td>
</tr>
<tr>
<td>1.4 million new cases of low-grade cervical dysplasia (CIN 1)</td>
<td>Second most common cause of cancer related deaths in women</td>
</tr>
<tr>
<td>&gt; 1 million new cases of genital warts</td>
<td>In the world: 530,000 cases and 275,000 deaths/year</td>
</tr>
<tr>
<td>&gt; 5 million cases of asymptomatic HPV</td>
<td>Second most common cause of cancer related deaths in women</td>
</tr>
</tbody>
</table>

Cervical Cancer

- ~12,000 cases and ~4000 deaths/year
  - Lifetime risk of developing cervical cancer in the United States is 0.76%
- In the world:
  - 530,000 cases and 275,000 deaths/year
  - 86% of cases occur in developing countries

Cervical Cancer

- Most women have not been screened in 5 years
  - High rates in communities that do not have access to screening/prevention programs
  - High risk in indigent populations
- Mean age of diagnosis is ~50 years
  - ~15% occur in women >65 years

Types of Cervical Cancer

- Squamous cell carcinoma (~70%)
  - Squamous epithelium on outer surface of cervix
  - HPV 16 association
- Adenocarcinoma (25%)
  - Adenomatous glands in the endocervical canal
    - Higher risk of delayed diagnosis
  - HPV 18 association
## Clinical Presentation
- Incidental finding on screening evaluation/pelvic examination
- Irregular/heavy vaginal bleeding
- Post-coital bleeding
- Vaginal discharge
- Lower back/pelvic pain
- Bowel or urinary symptoms

## Risk Factors
- Early onset of sexual activity
- Multiple sexual partners
  - Compared to one partner, the risk is threefold with six or more partners
- High risk sexual partners
- History of sexually transmitted infections

## Risk Factors
- Immunosuppression
  - HIV
  - Transplant medications
- Early age at first birth
- Low socioeconomic status
- Cigarette smoking

## Diagnosis
- No visible lesion (diagnosed on Pap test)
  - Colposcopy and biopsies
  - Conization
- Visible lesion
  - Histologic evaluation of a cervical biopsy
  - Pap test not indicated in this case
Cervical Cancer Staging

- Clinical staging
  - Chest radiograph
  - Evaluation for hydronephrosis
  - Cystoscopy/Proctoscopy
- Lymph node assessment
  - Does not change stage but guides treatment plan
- Prognostic factors
  - Stage and nodal status

Routes of spread

- Direct extension
  - Uterus/Vagina
  - Parametria
  - Bladder/Rectum
- Lymphatic spread
  - Pelvic/Para-aortic/Inguinal
- Hematogenous spread
  - Lung, liver, bones
  - Spleen, brain

Early Stage Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1</td>
<td>Microscopic disease, stromal invasion less than 3 mm</td>
</tr>
<tr>
<td>IA2</td>
<td>Microscopic disease, stromal invasion 3-5 mm, less than 7 mm horizontal spread</td>
</tr>
<tr>
<td>IB1</td>
<td>Lesions greater than 7 mm in horizontal spread, &lt; 4 cm</td>
</tr>
</tbody>
</table>

- Treatment options
  - Based on stage
  - Patient preference
  - Tolerance to treatment

Early Stage Disease

- For Stage IA1: with negative lymphovascular space invasion
  - Conization (Fertility sparing)
  - Hysterectomy
- Stage IA2-IB1
  - Radical hysterectomy and lymph node dissection
    - Removal of the uterus, cervix, upper vagina and parametria
    - Ovaries may be preserved
      - <1% in squamous cell cancer
      - <5% in adenocarcinoma
    - Chemoradiation therapy
Early Stage: Low risk
- In women who underwent radical hysterectomy and lymph node dissection
  - Confined to the cervix
  - No risk factors
- No further therapy required
  - Low risk of recurrence
  - Survival rates excellent

Fertility sparing options
- Reproductive aged women
  - Account for 10-15% of cervical cancers
- Candidates
  - Desire for fertility preservation
  - Small tumor (<2 cm)
  - Negative LVSI
  - No lymph node metastasis/upper endocervical involvement (ECC)

Radical Trachelectomy
- Removal of cervix, parametria, and lymph node dissection
- Oncologic outcomes
  - Comparable recurrence and survival rates
- Fertility outcomes
  - ~70% Pregnancy rate
  - 30% Miscarriage rates
  - 20 Preterm delivery
  - 50% Full term delivery

Cervical Cancer Treatment
- In women with higher risk of recurrence (adjunct to surgery) or in advanced disease (primary therapy)
  - Radiation +/- chemotherapy is used
- For all women undergoing radiation therapy
  - Therapy should be completed in a timely fashion (within 8 weeks)
Radiation Therapy

- Teletherapy/external beam
  - 45-50.4 Gy in 28 fractions
  - +/- Extended field
- Brachytherapy
  - Colpostat and tandem
  - Interstitial therapy
  - Total point A dose 80-90 Gy

Early stage: Intermediate risk

- After hysterectomy, prognostic factors
  - Large tumor size
  - Depth of stromal invasion
  - Lymphovascular space invasion (LVSI)

<table>
<thead>
<tr>
<th>LVSI</th>
<th>Tumor size</th>
<th>Depth of invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>Any</td>
<td>Deep third</td>
</tr>
<tr>
<td>+</td>
<td>≥2 cm</td>
<td>Middle third</td>
</tr>
<tr>
<td>+</td>
<td>≥5 cm</td>
<td>Superficial third</td>
</tr>
<tr>
<td>-</td>
<td>≥4 cm</td>
<td>Deep/middle third</td>
</tr>
</tbody>
</table>

Early stage: High risk

- After hysterectomy, high risk factors
  - Positive margins
  - Positive parametria
  - Positive lymph nodes

Early stage: Intermediate risk

- Pelvic radiotherapy
  - Study comparing radiation to observation
    - Radiation therapy improved local control and progression free survival
    - Overall survival similar
- +/- Concurrent chemotherapy
  - Role is not clear
Early stage: High risk

- With surgery alone
  - Risk of recurrence is 40%
  - Risk of death is 50%
- Radiation versus chemoradiation therapy
  - Cisplatin +/- 5-Fluorouracil

<table>
<thead>
<tr>
<th>Progression free survival (4 years)</th>
<th>Radiation</th>
<th>Chemoradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>63%</td>
<td>80%</td>
</tr>
<tr>
<td>Overall survival</td>
<td>71%</td>
<td>81%</td>
</tr>
<tr>
<td>Toxicity</td>
<td>4%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Locally Advanced Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>With positive nodes</td>
</tr>
<tr>
<td>IB2</td>
<td>Lesions &gt; 4 cm</td>
</tr>
<tr>
<td>IIA</td>
<td>Involvement of upper 2/3 of the vagina</td>
</tr>
<tr>
<td>IIB</td>
<td>Lateral extension into the parametrial tissue</td>
</tr>
<tr>
<td>IIIA</td>
<td>Involvement of lower 1/3 of the vagina</td>
</tr>
<tr>
<td>IIIB</td>
<td>Involvement of the parametrial tissue to the sidewall or hydrenephrosis</td>
</tr>
<tr>
<td>IVA</td>
<td>Invasion into the bladder or rectal mucosa</td>
</tr>
</tbody>
</table>

Locally Advanced Disease

- After diagnosis
  - Imaging to rule out widely metastatic disease
  - Consider lymph node debulking
- Primary treatment is with chemoradiation
  - Reduced risk of recurrence
  - Primary surgery is not curative
  - Complications higher

Concurrent Chemotherapy and Radiotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>FIGO Stage</th>
<th>Control Group</th>
<th>Study Group</th>
<th>RR of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keys</td>
<td>IB2</td>
<td>RT</td>
<td>RT plus cis</td>
<td>0.54</td>
</tr>
<tr>
<td>Rose</td>
<td>IIB-IVA</td>
<td>RT plus HU</td>
<td>RT plus cis</td>
<td>0.61</td>
</tr>
<tr>
<td>Morris</td>
<td>IB2-IVA</td>
<td>RT</td>
<td>RT plus cis, 5-FU and HU</td>
<td>0.52</td>
</tr>
<tr>
<td>Whitney</td>
<td>IB2-IVA</td>
<td>RT plus HU</td>
<td>RT plus cis and 5-FU</td>
<td>0.72</td>
</tr>
<tr>
<td>Peters</td>
<td>IB-IIA (post-operative)</td>
<td>RT</td>
<td>RT plus cis and 5-FU</td>
<td>0.50</td>
</tr>
</tbody>
</table>

RR=Relative Risk; RT=Radiotherapy; HU=Hydroxyruea; 5-FU=5-Flurouracil; Cis=Weekly Cisplatin
**Locally Advanced Disease**

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB2</td>
<td>80%</td>
</tr>
<tr>
<td>IIA</td>
<td>63%</td>
</tr>
<tr>
<td>IIB</td>
<td>58%</td>
</tr>
<tr>
<td>III</td>
<td>30%</td>
</tr>
<tr>
<td>IVA</td>
<td>16%</td>
</tr>
</tbody>
</table>

**Surveillance**

- Surveillance visits
  - Varies based on stage of disease
  - Every 3 to 6 months for 2 years
  - Then every 6 to 12 months for years 3 to 5
- Symptom review
- Physical examination
- +/- Cytology
- Imaging if recurrence suspected

**Cervical Cancer Recurrence**

- Recurrent disease occurs in 15-61% women with cervical cancer
  - Majority occur within first two years
- Locally recurrence
  - Vaginal symptoms
  - Pelvic exam findings
- Distant disease
  - Fatigue/Weight loss
  - Nausea
  - Bone pain

**Cervical Cancer Recurrent Disease**

- Imaging to assess extent
- Prevalence:
  - Pelvic recurrence (30-70%)
  - Lymph nodes (66%)
  - Lung/liver (33%)
  - Peritoneum (5-27%)
  - Other (20%)
Local Recurrence

- Management depends on prior treatment and patient choice
- Hysterectomy
  - Cervical recurrence
- Pelvic exenteration +/- radiation therapy
  - Central recurrence
- Radiation therapy
- Limited metastatic disease
  - Isolated lung lesion

Cervical Cancer
Advanced, Persistent, Recurrent Disease

- Recurrent disease
- Widely metastatic disease (Stage IVB)
- Persistent disease

Systemic Chemotherapy

- Cisplatin 20-30% response rates
- Platinum doublets
  - Median survival ~12 months

<table>
<thead>
<tr>
<th>Year</th>
<th>Regimen</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>Cisplatin</td>
<td>6-7 months</td>
</tr>
<tr>
<td>2004</td>
<td>Cisplatin + Paclitaxel</td>
<td>9.7 months</td>
</tr>
<tr>
<td>2013</td>
<td>Cisplatin + Topotecan</td>
<td>12.5 months</td>
</tr>
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</table>

Cervical Cancer
Advanced, Persistent, Recurrent Disease

- Cisplatin doublets are first line
- Prior cisplatin with radiation therapy
  - Carboplatin and paclitaxel is an alternative
    - Favorable toxicity profile
    - Cisplatin should be used if not previously used
- Nonplatinum doublets may also be used
  - Prior toxicities/treatments
  - Topotecan and paclitaxel
Cervical Cancer
Advanced, Persistent, Recurrent Disease

- Chemotherapy +/- anti-vascular endothelial growth factor bevacizumab
- Increased toxicity in bevacizumab arm
- Hypertension, VTE, GI complications
- 30% reduction in risk of death

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Chemotherapy + Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression free survival</td>
<td>5.9</td>
<td>8.2</td>
</tr>
<tr>
<td>Overall survival</td>
<td>13.3</td>
<td>17.0</td>
</tr>
</tbody>
</table>

Systemic Chemotherapy

<table>
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<tr>
<th>Year</th>
<th>Regimen</th>
<th>Survival</th>
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<tr>
<td>1991</td>
<td>Cisplatin</td>
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</tr>
<tr>
<td>2005</td>
<td>Cisplatin + Topotecan</td>
<td>9.4 months</td>
</tr>
<tr>
<td>2009</td>
<td>Cisplatin + Vinorelbine/Gemcitabine</td>
<td>10-10.3 months</td>
</tr>
<tr>
<td>2009</td>
<td>Cisplatin + Paclitaxel</td>
<td>12.9 months</td>
</tr>
<tr>
<td>2013</td>
<td>Topotecan + Paclitaxel</td>
<td>12.5 months</td>
</tr>
<tr>
<td>2013</td>
<td>Chemotherapy + bevacizumab</td>
<td>17 months</td>
</tr>
</tbody>
</table>

Second Line Therapy

- Platinum agents (15%)
- Taxanes (20-25%)
- Ifosfamide (22%)
- Topotecan (19%)
- Vinorelbine (15%)
- Pemetrexed (15%)
- Gemcitabine
- Bevacizumab

Miscellaneous topics

- Cervical cancer found incidentally at the time of simple hysterectomy
- Neuroendocrine cancers
- Neoadjuvant chemotherapy
- Cervical cancer in pregnancy
- HPV vaccine
### Incidental Finding of Cervical Cancer

- Final pathology with occult cervical cancer
  - Greater than Stage IA1
- Imaging to evaluate for metastatic disease
- Associated with poorer outcomes
  - Important to perform pre-operative cervical cancer screening/evaluation

### Incidental Finding of Cervical Cancer

- Early stage
  - Radical parametrectomy/lymph node dissection
  - Radiation therapy
- Advanced stage
  - Chemoradiation
  - Chemotherapy

### Neuroendocrine tumors

- ~2% of all cervical cancers
- Histologic variants
  - Small cell
  - Large cell
  - Typical/atypical carcinoid
- Worse prognosis than squamous or adenocarcinoma
- Treated with multimodality therapy
  - Surgery, radiation and chemotherapy

### Neoadjuvant chemotherapy

- Use of chemotherapy prior to surgery or chemoradiation
  - Decrease extent of disease
  - Fertility preservation
  - Cervical cancer in pregnancy
Neoadjuvant chemotherapy

- Limited role
  - May reduce the need for post-operative radiation therapy
- Meta-analysis demonstrated
  - Significantly improved progression free survival
  - No difference in overall survival
  - Similar results regardless of stage
  - Ongoing studies

Cervical Cancer and Pregnancy

- 1-2 cervical cancers/2,000-10,000 pregnancies
  - Cervical dysplasia noted in up to 5% of all pregnancies
- Options depend on stage and trimester
  - Delay of treatment
  - Undergo immediate treatment

Cervical Cancer and Pregnancy

- Early stage
  - Conization
  - Radical hysterectomy and node dissection at the time of C-section
- Advanced stage
  - Primary chemoradiation with termination of pregnancy
  - Emerging role of neoadjuvant chemotherapy

HPV Vaccine

- Non-infectious and contains no viral DNA
- Consist of viral capsid protein (L1) that assembles into a virus like particle (VLP)
  - Elicits type specific antibody response from patient for future protection
- Quadrivalent vaccine
  - HPV 6, 11, 16 and 18
- Bivalent vaccine
  - HPV 16 and 18
<table>
<thead>
<tr>
<th>HPV Vaccine</th>
<th>HPV Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Approved for females and males</td>
<td>• Well tolerated</td>
</tr>
<tr>
<td>• Ages 9 to 26</td>
<td>– Minor side effects: pain, redness, swelling at injection site, fever</td>
</tr>
<tr>
<td>• Total of 3 doses</td>
<td>– Major side effects (rare): bronchospams/hypersensitivity</td>
</tr>
<tr>
<td>– First: time of patient choosing</td>
<td>– 0.2% discontinued vaccine due to side effects</td>
</tr>
<tr>
<td>– Second: 2 months after first</td>
<td>• ~$120 per dose or $360 per regimen</td>
</tr>
<tr>
<td>– Third: 6 months after first</td>
<td>– Covered by most large insurance plans</td>
</tr>
<tr>
<td>• Must be 12 weeks after second</td>
<td>– Federal assistance programs</td>
</tr>
<tr>
<td>• Must be 24 weeks after first</td>
<td></td>
</tr>
<tr>
<td>• Interruptions ≠ restart regimen</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HPV Vaccine</th>
<th>HPV Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Efficacy rates excellent: 93-100%</td>
<td>• Estimated that vaccination rates of 70% would result in a decrease in 344,520 new cases of cervical cancer annually and avoid 178,182 cervical cancer-related deaths</td>
</tr>
<tr>
<td>– Continue with the same cervical cancer screening guidelines</td>
<td>– Benefit may require many years after the implementation of vaccination programs</td>
</tr>
<tr>
<td>• In the US, utilization of vaccine</td>
<td>– E.G. Australia has achieved a vaccination rates &gt;70 percent and ~38% reduction in high grade dysplasia</td>
</tr>
<tr>
<td>• 44% of children were vaccinated</td>
<td>• As a necessary precursor for cervical cancer, this decreased should translate into decreased incidence of cervical cancer over the next decade.</td>
</tr>
<tr>
<td>• Less than 25% completed the series</td>
<td></td>
</tr>
</tbody>
</table>
Opportunities

- Public health awareness/Health care access
  - Of cervical cancer patients:
    - 50% of women have never had cervical screening
    - 10% not screened in past 5 years
- HPV vaccination education
- Counsel women on high risk sexual behavior
  - Condom use/HIV testing
- Encourage smoking cessation
  - Increases risk of by 4 fold