CERVICAL CANCER UPDATES

Disclosure

- I have no financial disclosures.

Focus of this presentation

- Background
  - Etiology/History/Prevalence HPV
- Screening:
  - History of cervical cancer screening
  - Evolution of cervical screening
- Prevention:
  - HPV Vaccine
- Treatment:
  - Based on NCCN Guidelines

Cervical Cancer Statistics

- 13,240 will be diagnosed with cervical cancer.
- 4,170 deaths from the disease will occur.

Cervical Cancer Statistics

- 5-year survival rate for women with cervical cancer is 67.4%
- 10-year survival rate is 64%
- Broken down by stage
  - early stage - 92%
  - Regional spread - 57%
  - Distant spread – 17%

Cervical Cancer Statistics

- Percent of cases by stage
- 5-Year Relative Survival
Cervical Cancer Statistics

Etiology

- Human Papillomavirus (HPV)
- Small, non-enveloped, DS DNA
- E6 and E7 proteins cause oncogenic transformation
  - Estimated US incidence ~ 5.5 million/yr
  - Average age 15-24 yo

HPV

- Over 100 HPV types
  - 40 genotypes known to infect the anogenital area
  - “High risk” - 16, 18, 31, 33, 45, 52, 58
  - “Low risk” – 6 and 11

Risk Factors

- First age at intercourse
- Number of sexual partners
- Likelihood the partner has HPV
Prevalence – Dunne et al.
- National Health and Nutrition Examination Survey
- N=1921, cervicovaginal swabs for HPV DNA
- Overall HPV prevalence was 26.8%
  - 14 to 19 years – 24.5%
  - 20 to 24 years – 44.8%
  - 25 to 29 years – 27.4%
  - 30 to 39 years – 27.5%
  - 40 to 49 years – 25.2%
  - 50 to 59 years – 19.6%
- Significant trend of increasing prevalence each year from 14-24, then trend toward significant decrease to age 59

Prevalence
- Problem?
- Defn - the percentage of a population that is affected with a particular disease at a given time
- HPV dormancy
  - Keratinocyte stem cells in the epithelial basement layer
  - Can lay dormant for years
  - Will have a negative HPV swab

Progression to cancer
- Infection with HR-HPV
- Persistence of the HPV infection
- Progression of a clone of epithelial cells from persistent viral infection to pre-cancer
- Development of carcinoma and invasion through the basement membrane

Risk of HPV persistence and progression

Cervical Cancer

PAP Smear
- 50% of women diagnosed with cervical cancer have never had cervical cytology
- Another 10% have not been screened for > 5 years
**HPV Testing**
- More sensitive than cervical cytology alone in detecting high or low grade cervical histopathology
- Poor specificity and poor positive predictive value
- Leads to a higher number of colposcopies and cervical biopsies

**ALTS Trial**
- Reflex HPV testing as triage
- Women with ASCUS interpretation
  - Directed to colposcopy, HPV testing, or repeat cytology with colposcopy as needed
- Conclusions
  - Reflex HPV as sensitive for detecting CIN as colposcopy
  - Should be the preferred approach for patients with ASCUS
  - Majority of LSIL (83%) had HR-HPV
  - Reflex HPV not cost-effective in this group

**HPV Testing**
- Canadian Cervical Cancer Screening Trial, 2007 (n=10,154)
  - HPV vs conventional PAP smears to detect CIN 2+
  - Sensitivity - 94.6 vs 55.4% *
  - Specificity - 94.1 vs 96.8% *
- Population Based Screening Study Amsterdam, 2007 (n=17,000)
  - Conventional PAP + HPV vs PAP alone
  - Detected 70% more lesions at first screening
  - No difference in overall CIN3 detection after second screening

**ATHENA Trial**
- Addressing the Need for Advanced HPV Diagnostics study (2008-2009)
  - N= 47,208
  - Two phases
    - Initial baseline results
    - 3 year follow-up

**Comparison of cervical screening strategies**

**FIGURE 1: Cytology primary screening options**

**Strategy 1:** Cytology with reflex HPV (ASC-US triage)
- Pap Test
- ASC-US → Colposcopy
- ASC-US → HPV Test
- Pos → Routine follow-up
- Neg → Routine follow-up

**Strategy 2:** Cytology Alone
- Pap Test
- ASC-US → Colposcopy

*Note: * indicates statistical significance compared to conventional PAP smears.
HPV-vaccine era
FDA approval of HPV vaccine

- June 2006 – approved for girls and women aged 9-26
- October 2009 – approved for boys and men aged 9-26
- December 2014/2015 – approved Gardasil-9 for use in boys and girls ages 9-26
- October 5, 2018 – FDA approval for Gardasil-9 for men and women 27-45

Biomarkers

- May be more important in post-vaccination era
  - earlier detection of cervical cancer
  - improved reproducibility
  - surveillance of high-risk patients
  - post-treatment monitoring for recurrence

Biomarkers

- p16INK4a
  - Cyclin-dependant kinase inhibitor
  - Almost all carcinomas and CIN 3 stain
  - Majority of CIN 2 but few CIN 1
  - P16 negative lesions may be lower-risk for progression
  - High p16 on TMA associated with LN metastasis and poorer survival outcomes
- Ki-67
  - Expressed during cell proliferation
  - Not specific to cervical cancer
  - When used with p16 shows 94% sensitivity and 90% specificity in detecting CIN 2 or greater
- C-myc
  - Increased copy number is prognostic indicator of poor likelihood of regression

Treatment for Cervical Cancer

- Depends on the clinical stage
Clinically staged

- Pelvic examination
  - Speculum, bimanual, and rectovaginal examination for palpation and inspection of the primary tumor, uterus, vagina, and parametria
  - Examination for distant metastases
  - Palpation of groin and supraclavicular lymph nodes
Pelvic examination
- Speculum, bimanual, and rectovaginal examination for palpation and inspection of the primary tumor, uterus, vagina, and parametria
- Examination for distant metastases
  - Palpation of groin and supraclavicular lymph nodes
Cervical biopsy
- Colposcopy with directed cervical biopsy or cervical biopsy without colposcopy if visible lesion
- Conization/Endocervical curettage
Endoscopy
- Hysteroscopy, cystoscopy or proctoscopy
Imaging studies
- Intravenous pyelogram (IVP) – Evaluation for urinary tract obstruction
- Imaging with a plain chest radiograph and radiograph of the skeleton

## Treatment

- Stage
- Desire for fertility
- Tumor Volume
- Medical co-morbidities
- Known lymphatic spread
- Age
- Body habitus

## Treatment based on stage

- IA1 No LVSI – Cone vs extrafascial hysterectomy
- IA1 w LVSI, IB1, IB2, IIA – Radical hysterectomy, pelvic lymphadenectomy
- IB2, IIA, IIB, IIIA, IIIB, IVA – Concurrent chemoradiation (consideration for adjuvant chemotherapy)
- IVB – Palliative chemotherapy, clinical trial or best supportive care

## Extrafascial vs Radical hysterectomy

Candidates for fertility preservation

Cervical Cancer

Options
- Surgical
  - Radical trachelectomy, lymphadenectomy
  - Vaginal
  - Laparoscopic or robotic

The intent of the radical abdominal trachelectomy is to resect the cervix, upper 1–2 cm of the vagina, parametria, and paracolpos in a similar manner to a type III radical abdominal hysterectomy but sparing the uterine corpus

The uterine fundus is reattached to the vaginal apex

The reconstructed fundus with remaining blood supply from the intact utero-ovarian ligaments – uterine serosa without evidence of fundal ischemia

Candidates for fertility preservation

Cervical Cancer

Radical abdominal trachelectomy – the cervical tissue and parametria are separated from the uterus

The reconstructed fundus with remaining blood supply from the intact utero-ovarian ligaments – uterine serosa without evidence of fundal ischemia

Reconstruction of the uterine corpus to upper vagina after the cerclage is placed

Candidates for fertility preservation

Cervical Cancer

- Obstetric outcomes
  - >250 live births have been reported

- Survival outcomes
  - Recurrence
  - Mortality

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<tr>
<th></th>
<th>Plante 2008</th>
<th>Plante 2011</th>
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<tbody>
<tr>
<td>1st trimester loss</td>
<td>18%</td>
<td>20%</td>
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<tr>
<td>2nd trimester loss</td>
<td>8.6%</td>
<td>5%</td>
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<tr>
<td>3rd trimester delivery</td>
<td>62%</td>
<td>73%</td>
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<tr>
<td>Preterm delivery &lt;37 weeks</td>
<td>28%</td>
<td>18%</td>
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<td>&lt;32 weeks</td>
<td>12%</td>
<td>4%</td>
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<tr>
<td>Term delivery</td>
<td>40%</td>
<td>55%</td>
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- Oncologic outcomes

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<tr>
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<th>Plante 2008</th>
<th>Plante 2011</th>
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<tr>
<td>Recurrence rate</td>
<td>27 (4.5%)</td>
<td>6 (4.8%)</td>
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<tr>
<td>Death from disease (%)</td>
<td>15 (2.5%)</td>
<td>2 (1.6%)</td>
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<td>Abandoned VRT</td>
<td>10-12%</td>
<td>4 (11%)</td>
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<td>5 year PFS</td>
<td>96%</td>
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- Risk Factors: 2008
  - Lesions larger than 2 cm (29 vs 1%) 
  - Presence of LVSI (12 vs 2%)

- Risk Factors: 2011
  - Lesions larger than 2 cm

Case #1

- 33 yo G3P3
- Post-coital bleeding
- Exam showed 3cm friable cervical mass with no parametrial or vaginal induration
- Cervical biopsy – Grade 3 squamous cell carcinoma
- PET/CT Negative

Treatment

- Robotic-assisted radical hysterectomy with bilateral salpingectomy and pelvic lymph node dissection

Pathology

- 3.2 cm squamous cell carcinoma
- No LVSI
- Middle 1/3 invasion

Sedlis Criteria

**Post surgery recurrence risk:**

**Intermediate risk: Sedlis: 30%**
1. LVSI, outer 1/3, TS any
2. LVSI, middle 1/3, TS >2cm
3. LVSI, Super 1/3, TS.5
4. No LVSI/deep/middle 1/3, TS >4

**High Risk: 40%**
Positive margins, nodes, parametrium
Case #2
- 37 yo G2P2
- Abnormal pap tests off and on since 20 yo
- Cryotherapy 7 years ago
- ASCUS pap 2013
- Presented with abnormal bleeding and discharge
- Cervical mass seen on exam – Biopsy proven squamous cell carcinoma

Treatment
- Robotic assisted laparoscopic pelvic lymph node debulking with para-aortic sampling
- Concurrent cisplatin and external beam radiation therapy
- High dose vaginal brachytherapy
- Consideration for adjuvant chemotherapy

Case #3
- 56 yo
- Presented with abnormal bleeding
- Last pap 1994
- Clinical stage IIB with negative PET
- Concurrent chemoradiation
- Syed implant for brachytherapy (2/19/2015)
- 4/2015 No obvious parametrial induration

Case #3
- Fell and hit abdomen 5/2015
- Biopsied 6/2015
  - Consistent with metastatic squamous cancer
Treatment for Recurrent Cervical Cancer

- GOG 240
  - Paclitaxel/cisplatin + bevacizumab
  - Paclitaxel/topotecan + bevacizumab

Results
- Paclitaxel/topotecan not superior or inferior to paclitaxel/cisplatin
- Addition of bevacizumab shows improved PFS (8.2 months vs 5.9 months) and OS (17 months vs 13.3 months)

- Lead to FDA approval of bevacizumab on August 14, 2014

Pembrolizumab (Keytruda)

- June 12, 2018 - FDA approved pembrolizumab (Keytruda, Merck and Co. Inc.) for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1

Keynote 158

- Single cohort 98 patients recurrent, progressive cervical cancer
- 80% expressed PD-L1
- ORR – 14.3% (CR – 2.6%/PR - 11.7%)
- Median response duration not reached
- 91% had response ≥ 6 months
- No responders in group without PD-L1 expression

On the Horizon

- Advaxis
  - Engineered Listeria presenting HPV DNA as foreign agent to stimulate immune system
- PARP inhibitors
- Cediranib
- potent inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases

Questions?

References

- Pembrolizumab for recurrent or metastatic cervical cancer. JAMA. 2018;320(23):2405-2414.
References


