Cervical Cancer

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Disclosures

NONE

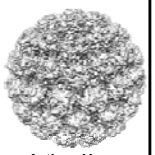
Objectives

- 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)



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- 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

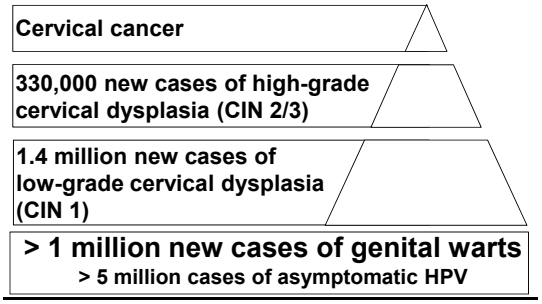
Frequency of Screening

- 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



American Cancer Society. *Cancer Facts and Figures 2013*
Schiffman M, *Arch Pathol Lab Med.* 127:946, 2003
Fleischer AB, *Sex Transm Dis.* 28:643–647, 2001

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
  - Second most common cause of cancer related deaths in women

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

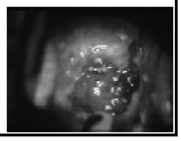
Early Stage Disease

Stage	Description
IA1	Microscopic disease, stromal invasion less than 3 mm
IA2	Microscopic disease, stromal invasion 3-5 mm, less than 7 mm horizontal spread
IB1	Lesions greater than 7 mm in horizontal spread, < 4 cm

- 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

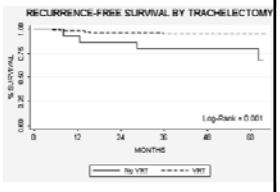
- In women who underwent radical hysterectomy and lymph node dissection
  - Confined to the cervix
  - No risk factors
- No further therapy required
  - Low risk of recurrence
  - Survival rates excellent

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



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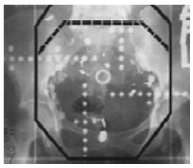
Cervical Cancer Treatment

- 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)

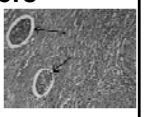
Radiation Therapy

- 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)



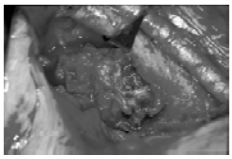
LVSI	Tumor size	Depth of invasion
+	Any	Deep third
+	≥2 cm	Middle third
+	≥5 cm	Superficial third
-	≥4 cm	Deep/middle third

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

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



Early stage: High risk

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

	Radiation	Chemoradiation
Progression free survival (4 years)	63%	80%
Overall survival	71%	81%
Toxicity	4%	22%

Locally Advanced Disease

Stage	Description
Any	With positive nodes
IB2	Lesions > 4 cm
IIA	Involvement of upper 2/3 of the vagina
IIB	Lateral extension into the parametrial tissue
IIIA	Involvement of lower 1/3 of the vagina
IIIB	Involvement of the parametrial tissue to the sidewall or hydronephrosis
IVA	Invasion into the bladder or rectal mucosa

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

Results of 5 Randomized Clinical Trials

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

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

Locally Advanced Disease

Stage	5 year survival
IB2	80%
IIA	63%
IIB	58%
III	30%
IVA	16%

Surveillance

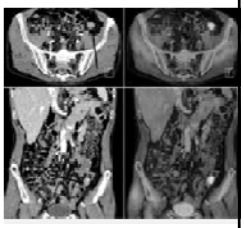
- Surveillance visits
  - Varies based on stage of disease
  - Every 3 to 6 months for 2 years
  - Then every 6 to 12 months for years 3 to 5
- Symptom review
- Physical examination
- +/- Cytology
- Imaging if recurrence suspected

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

Year	Regimen	Survival
1991	Cisplatin	6-7 months
2004	Cisplatin + Paclitaxel	9.7 months
2013	Cisplatin + Topotecan	12.5 months

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**

	Chemotherapy	Chemotherapy + Bevacizumab
Progression free survival	5.9	8.2
Overall survival	13.3	17.0

Systemic Chemotherapy

Year	Regimen	Survival
1991	Cisplatin	6-7 months
2005	Cisplatin + Topotecan	9.4 months
2009	Cisplatin + Vinorelbine/Gemcitabine	10-10.3 months
2009	Cisplatin + Paclitaxel	12.9 months
2013	Topotecan + Paclitaxel	12.5 months
2013	Chemotherapy+ bevacizumab	17 months

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**

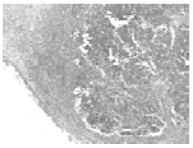
Incidental Finding of Cervical Cancer

- 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

HPV Vaccine

- Approved for females and males
- Ages 9 to 26
- Total of 3 doses
  - First: time of patient choosing
  - Second: 2 months after first
  - Third: 6 months after first
    - Must be 12 weeks after second
    - Must be 24 weeks after first
- Interruptions ≠restart regimen

HPV Vaccine

- Well tolerated
  - Minor side effects: pain, redness, swelling at injection site, fever
  - Major side effects (rare): bronchospams/hypersensitivity
  - 0.2% discontinued vaccine due to side effects
- ~$120 per dose or $360 per regimen
  - Covered by most large insurance plans
  - Federal assistance programs

HPV Vaccine

- Efficacy rates excellent: 93-100%
  - Continue with the same cervical cancer screening guidelines
- In the US, utilization of vaccine
  - 44% of children were vaccinated
  - Less than 25% completed the series

HPV Vaccine

- 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
  - Benefit may require many years after the implementation of vaccination programs
  - E.G. Australia has achieved a vaccination rates >70 percent and ~38% reduction in high grade dysplasia
    - As a necessary precursor for cervical cancer, this decreased should translate into decreased incidence of cervical cancer over the next decade.

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**