

# **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**

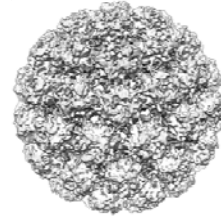
## Cervical Cancer Screening



- **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**



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## 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

Cervical cancer

330,000 new cases of high-grade cervical dysplasia (CIN 2/3)

1.4 million new cases of low-grade cervical dysplasia (CIN 1)

> 1 million new cases of genital warts  
> 5 million cases of asymptomatic HPV

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

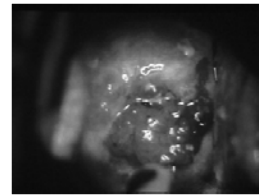
# Early Stage Disease

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**

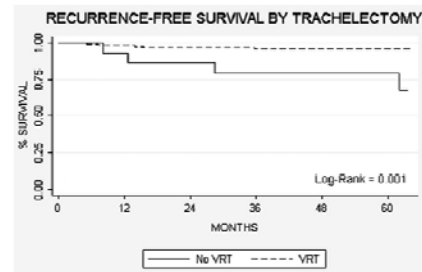
- **In women who underwent radical hysterectomy and lymph node dissection**
  - **Confined to the cervix**
  - **No risk factors**
- **No further therapy required**
  - **Low risk of recurrence**
  - **Survival rates excellent**

## **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



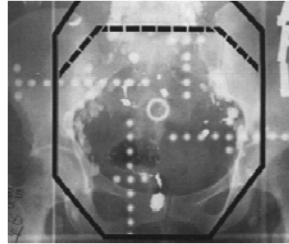
Plante M, Gynecologic Oncology, 2011. 121(2): p. 290-7

## Cervical Cancer Treatment

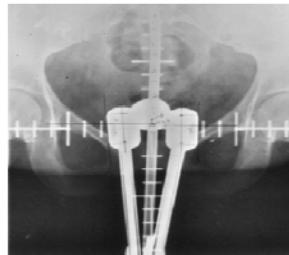
- In women with higher risk of recurrence (adjunct to surgery) or in advanced disease (primary therapy)
  - Radiation +/-chemotherapy is used
- For all women undergoing radiation therapy
  - Therapy should be completed in a timely fashion (within 8 weeks)

# Radiation Therapy

- **Teletherapy/external beam**
  - 45-50.4 Gy in 28 fractions
  - +/- Extended field

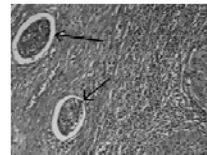


- **Brachytherapy**
  - Colpostat and tandem
  - Interstitial therapy
  - Total point A dose 80-90 Gy



## Early stage: Intermediate risk

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



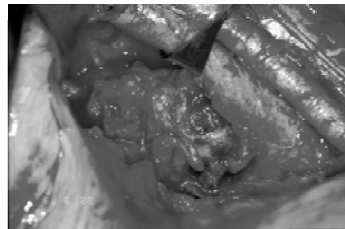
LVSI	Tumor size	Depth of invasion
+	Any	Deep third
+	≥2 cm	Middle third
+	≥5 cm	Superficial third
-	≥4 cm	Deep/middle third

## **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=Hydroxyurea; 5-FU=5-Fluorouracil; Cis=Weekly Cisplatin

## **Locally Advanced Disease**

<b>Stage</b>	<b>5 year survival</b>
IB2	80%
IIA	63%
IIB	58%
III	30%
IVA	16%

## **Surveillance**

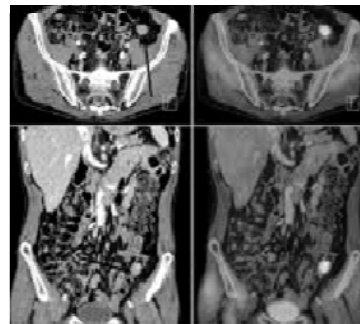
- **Surveillance visits**
  - **Varies based on stage of disease**
  - **Every 3 to 6 months for 2 years**
  - **Then every 6 to 12 months for years 3 to 5**
- **Symptom review**
- **Physical examination**
- **+/- Cytology**
- **Imaging if recurrence suspected**

# 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**

<b>Year</b>	<b>Regimen</b>	<b>Survival</b>
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**

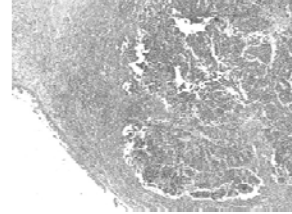
- **Final pathology with occult cervical cancer**
  - **Greater than Stage IA1**
- **Imaging to evaluate for metastatic disease**
- **Associated with poorer outcomes**
  - **Important to perform pre-operative cervical cancer screening/evaluation**

## **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**