Cervical Cancer Diagnosis and Treatment

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13,700 new cases annually in the U.S.
4,900 deaths annually in the U.S.
These rates have steadily decreased
400,000 cases annually worldwide
A big problem in developing nations
Number one cancer killer of women worldwide

What Is the Cervix?

- Opening of the uterus (womb) into the vagina
- Two cell types present (squamous and glandular)
- Cervical cancers tend to occur where the two cell types meet

What Is the Transformation Zone?

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Cervical Cancer Detection: Dr. George Papanicolaou

Cervical Cancer: The Problem

- 13,700 new cases annually in the U.S.
- 4,900 deaths annually in the U.S.
  - These rates have steadily decreased since the 1950's due to widespread screening
- 400,000 cases annually worldwide
  - A big problem in developing nations
  - Number one cancer killer of women worldwide

Cervical Cancer: The Traditional Pap Test

- Cervical Papanicolaou screening introduced in the U.S. in the 1940's
- Cervical cancer mortality reduced by 70%
- False negative rate for a single smear is 10 - 25%
- The most cost-effective cancer screening test yet devised
Cervical Cancer: Have We Decreased U.S. Incidence?

- 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.

Cervical Cancer: The Sad Facts

- 50% of women with newly diagnosed cervical cancer in the U.S. have never had a Pap smear
- 10% have not had a smear within 5 years of diagnosis
- Mean age at diagnosis: 51
  - Many women are in their 30s

Cervical Cancer: Screening

- Many women developing Cx CA are insured and use the health care system:
  - In an HMO study, 70% of Cx CA patients had been seen once and 42% 3 or more times in the three years prior to diagnosis (Kinney 1998)
- Obviously, if women are not screened, dysplasia can progress to invasive carcinoma

Obtaining the Pap Smear: Optimize Specimen Collection

- No intercourse or douching for 24-48 hrs prior
- Do not collect during menses
- Remove heavy discharge first
- Avoid contamination with lubricant
- Collect prior to bimanual exam and cultures
- Use both the spatula and cytobrush to sample the ecto and endocervix

Cervical Cancer: Pap Smear Technique

- For post hysterectomy patients, the top of the vagina is sampled
- Any visible cervical lesion requires a biopsy regardless of the Pap results.
  - False negative rate is up to 50% in the presence of an invasive cancer!!!
Cervical Cancer: When To Start Pap Smear Screening
- Three years after first coitus if sexually active teen
- Otherwise at age 21
- Immunocompromised
- DES Exposed

Who Is Not Getting a Pap Smear?
- Uninsured
- Elderly
- Ethnic minorities, especially Hispanic and African-American women
- Poor women, especially in rural areas
- Developing nations
- Reasons for lack of screening
  - Attitudes and concerns
  - Logistical problems

Pap Smear Screening: The Bethesda Reporting System
- Adequacy of the specimen
  - Satisfactory, limited by, unsatisfactory
- General Categorization
  - WNL, B9 cellular changes, epithelial cell abnl
- Descriptive Diagnosis
  - B9- infection, reactive
  - Abnl- ASCUS, LSIL, HSIL, AGUS, SCCA, ACA

Abnormal Pap Test: How Common Is it?
- A significant percentage spontaneously regress
  - CIN I: 65%
  - CIN II: 35-55%
  - CIN III: 20%
- CIN III is more likely to progress to invasive disease if left untreated
- Involvement of the endocervical canal impacts treatment decisions
  - Hence importance of sampling separately
- Risk and rate of progression is different in the immunocompromised

Natural History of Precancerous Changes
Cervical Cancer: Colposcopy

- Colposcopy: Use of a magnifying instrument
- Application of a vinegar-like solution onto the cervix
- See abnormalities that can't be seen with the naked eye
- Feels like getting a Pap test, but lasts longer

Source: This is a copyrighted image of the California Family Health Council, Inc. and may not be reproduced in any way without the expressed written permission of the California Family Health Council & California Department of Health Services. "What you should know if your Pap test is abnormal." Your Cervical cancer exam. Donna Bell Sanders (Education Programs Associates 1995; Campbell, CA).

What Is A Colposcopy?

What Is A Cervical Conization?

Conization:
- Removes a cone-shaped piece of tissue
- Often allows for diagnosis and treatment
- Performed with local anesthesia in the office or under general anesthesia in the operating room

Source: U.S. Pharmacopoeia, "Female Reproductive System.

Cervical Cancer: Etiology

- Cervical cancer is a sexually transmitted disease.
- HPV DNA is present in virtually all cases of cervical cancer and precursors.
- Some strains of HPV have a predilection to the genital tract and transmission is usually through sexual contact.
- Little understanding of why small subset of women are affected by HPV.
- HPV may be latent for many years before inducing cervical neoplasia.

HPV

- Most men and women who have had sex have been exposed to HPV
- More than 75% of sexually active women tested have been exposed to HPV by age 18-22
- There are many different types of HPV
  - Low risk types are associated with warts
  - Intermediate risk types
  - High risk types are associated with cancers

Cervical Cancer: Risk Factors

- Early age of intercourse
- Number of sexual partners
- Smoking
- Lower socioeconomic status
- High-risk male partner
- Other sexually transmitted diseases
- HPV infection, but up to 50-90% of the U.S. population is infected with HPV
Cervical Cancer: Risk Factors
- Women who have ever had sex
- Women with immune problems
  - Steroid medications
  - Transplanted organs
  - Chemotherapy
  - HIV
- Women who smoke

Cervical Cancer: Presentation
- Post-coital spotting
- Abnormal uterine bleeding
- Abnormal vaginal discharge
- Pain
- Bowel/bladder symptoms (hematuria, rectal bleeding)
- Constitutional symptoms (weight loss, fatigue)

Cervical Cancer: Presentation
- Systemic symptoms (pain, weight loss) are much more concerning for advanced stage disease.
- Hematuria or rectal bleeding are indicative of advanced stage disease until proven otherwise

Cervical Cancer: Staging
- Based on clinical criteria, not surgical
- Stage I: confined to the cervix
- Stage II: spread into the proximal vagina or parametria
- Stage III: spread to lower vagina, pelvic sidewall, or ureteral obstruction
- Stage IV: distant dz or mucosal involvement

Cervical Cancer: Staging
- Stage IA: Microscopic
- Stage IB: Macroscopic
  - IB1 \(\leq 4\) cm, IB2 \(> 4\) cm
- Stage IIA: Proximal vaginal extension
- Stage IIB: Proximal parametrial extension

Cervical Cancer: Staging

- Stage IIIA: Extension to distal 1/3 vagina
- Stage IIIB: Pelvic sidewall extension or hydronephrosis
- Stage IVA: Bladder or rectal mucosa
- Stage IVB: Distant disease
Cervical Cancer: Initial Office Evaluation

- History
- Physical
  - Inguinal or supraclavicular adenopathy?
  - Ascites, omental cake?
  - Parametrial or vaginal extension of tumor?
  - Biopsy for diagnosis if not already done
Cervical Cancer: Diagnostic Evaluation
- Labs: CBC, Cr, LFTs, UA
- CXR
- IVP/BE vs. CT vs. MRI vs. PET
  - CT scan is 97% specific, 25% sensitive
  - MRI has improved delineation of soft tissue planes in the pelvis and PA nodes
  - PET: small series confirms supraclavicular involvement

Cervical Cancer: Diagnostic Evaluation
- Abdominal imaging can assess for nodal disease
  - Cannot be used to assign stage
- History, physical or laboratory findings concerning for advanced stage disease should be confirmed
  - Bone scan if increased Ca++
  - Liver scan (MRI) if increased LFTs

Cervical Cancer: Diagnostic Evaluation
- EUA, Cystoscopy, Proctoscopy
  - On all patients
  - On patients with large tumors
  - On patients with vaginal extension
  - On patients with a history of hematuria or hematochezia

Cervical Cancer: Sites of Spread
- Lymph nodes are the most common site
  - Halstedian
- Bony metastasis are rare at diagnosis
  - 1.8% within 8 months of diagnosis
- Sites involved by distant metastasis in untreated patients:
  - lung: 13.9%, liver: 24.5%, vertebra: 8.1%, skull: 1.6%
- Bony mets can be seen in 25% of patients with recurrent disease

Cervical Cancer: Survival After Treatment
<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>81-96%</td>
</tr>
<tr>
<td>Stage II</td>
<td>65-87%</td>
</tr>
<tr>
<td>Stage III</td>
<td>35-50%</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>15-20%</td>
</tr>
</tbody>
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Cervical Cancer: Epidemiologic Prognostic Factors
- Younger age
- African American race
- Low socioeconomic status
- Anemia
- HIV +
Cervical Cancer: Pathologic Prognastic Factors

- Tumor size
- Depth of stromal invasion
- Capillary space involvement
- Endometrial extension
- Lymph node involvement
- Parametrial or vaginal involvement

Controversy exists as to prognosis with adenocarcinoma versus squamous carcinoma
- Neuroendocrine/Small cell clearly worse
Based on stage:

- Stage I and IIa: surgery or chemoradiation
- Stage IIb-IVa: chemoradiation
- Stage IVb: chemoradiation or clinical trials or palliative care
- Neuroendocrine tumors: neoadjuvant cisplatin/etoposide followed by local therapy

Cervical Cancer: Surgery

- Cone Biopsy: preservation of fertility
- Simple hysterectomy: transect cervix at vagina (no tissue margins around cervix)
- Modified radical hyst: remove medial half of cardinal and uterosacral ligaments
- Radical hyst: cardinal ligaments taken at pelvic sidewall
Cervical Cancer: Surgery
- Patients with early stage tumors may still have positive nodes
  - unclear what to do when discovered during radical hysterectomy
- Patients with early stage disease treated surgically but found to have a combination of intermediate risk pathologic factors benefit from adjuvant postoperative radiation
  - Deep stromal invasion, capillary space involvement, large tumor size
  - But, prevailing philosophy is that combined modality therapy increases toxicities.

Cervical Cancer: Radiation
- Radiation consists of combined external beam and intracavitary therapy
- The goal is to deliver 75-80 Gy to the tumor in order to effect a cure
- Tumor response is directly related to tumor size and dose given
  - 45Gy sterilizes microscopic disease
  - Need 80-90 Gy to sterilize macroscopic disease

Radiation - Brachytherapy
- Relies on inverse square law for dose; allows for significantly increased dose to the tumor bed while minimizing dose to normal tissues
- Given as either low dose rate (LDR) (conventional) as an inpatient over 2-3 days or high dose rate as an outpatient for approximately 15 minutes
- LDR requires fewer total treatments

Cervical Cancer: Radiation
- Toxicity to normal organs is also directly related to dose
  - Ovaries sterilized at 20 Gy
  - Solid organ toxicity at 30 Gy
  - Hollow organ toxicity at 45-55 Gy
- External beam radiation is given 1.8-2.0 Gy/fx/d for 20-25 treatments for a total dose of 40-50 Gy

Radiation - Brachytherapy
- Two systems exist
  - Tandem and ovoids
  - Interstitial needles (aka, Syed template)
- The decision between the two is based on
  - Tumor geometry
  - Institutional preference
Cervical Cancer Radiation: Prognostic Factors During Treatment
- Anemia has a significant negative impact on response and survival
  - Maintain hemoglobin $\geq 10.0$ throughout treatment
  - If treatment duration is prolonged more than 8 weeks this has a significant negative impact on response and survival
  - Avoid treatment breaks whenever possible

Cervical Cancer Radiation: Treatment Complications
- Radiation cystitis/proctitis
- Radiation enteritis
- Malabsorption, malnutrition
- Partial/complete small bowel obstruction
- Incidence overall is 5-15%

Cervical Cancer Radiation: Treatment Complications
- Complication rate is increased with
  - Thin body habitus
  - Multiple abdominal surgeries
  - Connective tissue disease
- Late complication of secondary malignancy rare
- “The gift that keeps on giving”

Cervical Cancer Treatment: Chemotherapy With Radiation
- Chemotherapy in low doses enhances the radiation effect and may compensate for the hypoxic tumor microenvironment
  - Also has an effect on distant disease
- Chemotherapy along with radiation dramatically improves
  - Response rates
  - Disease free survival
  - Overall survival

Cervical Cancer Treatment: Chemotherapy With Radiation
- Several large, multicenter, phase III randomized trials demonstrated a benefit,
- NIH consensus document urging the use of chemosensitization
- Generally, we use cisplatinum (CDDP)
  - Overall risk reduction of death is 25-50% with CDDP
  - Can use 5-FU in renal insufficiency

Cervical Cancer
- “The standard of care for Stages IB to IVA disease is concurrent chemoradiation on the basis of the overwhelming evidence cited above.
- Of the regimens employed, weekly cisplatin achieves results similar to the other regimens with less toxicity and is the current regimen of choice.”
  - Hoskins et al, Principles and Practice of Gyn Onc. 2000
Cervical Cancer Treatment: Chemotherapy Complications
- Generally well tolerated
- No alopecia (hair loss)
- Minimal to moderate nausea
  - Effectively managed with anti-emetics
- Mild bone marrow suppression
  - May require blood or erythropoeitin support

Cervical Cancer Treatment: Summary
- Stage IB1: Patient choice depending on comorbidities
- Stage IB2: Strongly consider chemo-RT
- Stage IIA: Patient choice if small tumor, else chemo-RT
- Stage IIB-IVA: chemo-RT

Cervical Cancer Treatment: Stage IVB Disease
- “Rarely suited for comprehensive radiation therapy” (Morrow and Curtin Synopsis of Gynecologic Oncology)
- Local control of bleeding with single-pulse or rapid course RT or brachytherapy
- Systemic Chemotherapy: single versus multi-agent

Cervical Cancer Treatment: Stage IVB Disease
- Patients who are young and have an excellent performance status: treat with curative intent
  - Chemo RT followed by further systemic chemo if good pelvic control
  - Neoadjuvant chemo followed by combined modality therapy if there is a good response
- Consider clinical trial participation

Cervical Cancer Recurrence: Sites of Spread
- Most common metastatic sites are
  - Lungs (36%)
  - Mediastinal and supraclavicular lymph nodes (30-68%)
  - Bones (16-28%)
  - Liver (7-20%)
Cervical Cancer Recurrence: Treatment

- Emerging GOG data now favors combination chemotherapy
- Response rates to CDDP alone in patients previously treated with CDDP during chemo RT with recurrence in the radiated field are extremely low (<10%)

Cervical Cancer Recurrence: Treatment

- Single agent CDDP response rates of 20-25%
- Active combinations include Taxol/CDDP and Topotecan/CDDP
- Current GOG study compares topo/CDDP, Gemcitabine/CDDP, Taxol/CDDP, and Nalvelbine/CDDP

Cervical Cancer Special Considerations: Pregnancy

- MRI is safe for tumor assessment
- Treat as if not pregnant if diagnosed before 20 weeks gestation
- If 20-30 weeks, individualized discussion
  - Consider neoadjuvant chemotherapy
- If over 30 weeks, delay delivery to fetal maturity
- Generally, deliver by cesarean section

Cervical Cancer Special Considerations: Pain Management

- Women with advanced cervical cancer can have a considerable amount of pain
- Pain will generally decrease with radiation and regression of the tumor
- Pain that does not decrease or increases is an ominous sign
- Pain should be aggressively treated with potent narcotics

Cervical Cancer Special Considerations: Pain Management

- MS Contin preferred over oxycontin and fentanyl patches secondary to cost
- Could also consider Methadone
- Start at 15 mg bid with MSIR 15 mg q 1 hr prn and increase MS Contin dose based on MSIR usage
- Pain medication requirements will decrease with response and allow tapering off

Cervical Cancer: Summary

- Pap smear screening is effective
- Staging is clinical
- Patients should undergo careful assessment for advanced stage dz
- Radical hysterectomy is still alive and well in early stage disease
- All patients treated with radiation should receive chemosensitization
Patients with advanced stage cervical cancer can be cured and the goal should be just that.

Patients that are not treatable with curative intent according to currently available data should be encouraged to participate in clinical trials.