Cervical Dysplasia and Invasive Cervical Cancer

Satellite Conference and Live Webcast
Friday, October 10, 2008
1:00 - 3:00 p.m.

Faculty
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Chief, Gynecologic Oncology

Produced by the Alabama Department of Public Health
Video Communications and Distance Learning Division

Objectives
• Overview of cervical cancer
• Understand Role of HPV
• Apply algorithms from www.asccp.org
• Apply methods of diagnosis of cervical cancer

Objectives
• Understand staging of cervical cancer
• Describe treatment of various stages of cervical cancer
• Understand roles of surgery, radiation therapy and chemotherapy for the management of cervical cancer
### Cervical Dysplasia
- Schauenstein (1908) first proposed that SCC of cervix evolves by a progression of a preinvasive lesion (carcinoma in situ).
- Papanicolaou described CIS and less anaplastic lesions called dysplasia.
- WHO defines dysplasia as “lesion in which part of the epithelium is replaced by cells showing varying degrees of atypia.”

### Epidemiology
- Abnormal Pap = 3.5 million per year (7%)
- CIS = 50,000 per year
- CXCA = 13,000 per year
  - 4,500 deaths per year
- Overall incidence: 8.7/100,000 women
- Second most common female cancer worldwide
- Among top 5 causes cancer death in developing countries (20-30% of female cancers)
  - Pap decreased cancer by 50% in U.S.!

### Risk Factors
- Age first intercourse
- Multiple partners (>2)
- STD
- HPV
- High risk HPV
- Immunosuppression
- Smoking
- Low socioeconomic status
- > 3 years pap
- High risk partner
- Other
  - Contraceptive hormones
  - Radiation

### HPV
- > 80 subtypes (31 anogenital)
- HPV stronger association with cancer
- Epidemic past 20 yrs
- HPV DNA found > 95% of SCC
- Not only factor
- 43% college women HPV+ (but <5% CIN)

### Human Papilloma Virus
- Non-enveloped DNA encased in capsid
  - Integration disrupts E2 leading to increased E6/E7 transcription
  - E2 transcriptional regulation of HPV genes
  - E7 binds pRb
  - E6 binds p53
  - Late genes encode capsid proteins
HPV Types

High Risk HPV Testing

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
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<tbody>
<tr>
<td>6, 11, 26, 42, 44, 54, 70, 73</td>
<td>31, 33, 35, 39, 51, 52, 55, 58, 59, 66, 68</td>
<td>16, 18, 45, 56</td>
</tr>
</tbody>
</table>

- Low Risk: never found alone in invasive cancer
- HPV-16: more common in squamous lesions
- HPV-18: more common in endocervical lesions

In The Zone

- Cervix mullerian duct origin
- Lined by columnar epithelium
- 18-20 wks. gestation colonized by squamous epithelium
- Squamocolumnar Junction = Transformation Zone
- Zone changes position depending on hormonal influence

Understanding The Cervical Transformation Zone

Screening Is Good

- Cervical cancer #1 in incidence & mortality in women prior to 20th century
- Screening for premalignant lesions knocked it down to #2 worldwide (yipee)
- Dichotomy b/t developing & developed countries
- “Preventable disease”

Bethesda 2001

- Specimen type
- Specimen Adequacy
  - Satisfactory
  - Unsatisfactory due to...
- General Categorization
  - Negative, Epithelial cell abnormality, other
**Bethesda 2001**

- Interpretation and Result
  - Negative for Intraepithelial Lesion or Malignancy
  - Organisms
    - Trich, Candida, BV, HSV, etc
  - Other
    - Reactive inflammation, IUD, radiation, Atrophy

**Bethesda 2001**

- Squamous Cell
  - Atypical Squamous Cells
    - ASC-US
    - ASC-H
  - LSIL (HPV, mild dysplasia)
  - HSIL
    - Moderate dysplasia
    - Severe dysplasia

**Bethesda 2001 Abnormalities**

- Squamous Cell
  - Squamous Cell Carcinoma
- Glandular Cell
  - Atypical Endocervical, Endometrial, Glandular cells
    - AG-NOS
    - AG-favor neoplasia
    - Adenocarcinoma

**Bethesda 2001 Abnormalities**

- Squamous Cell
  - Atypical Squamous Cells
    - ASC-US
    - ASC-H (can’t r/o high grade lesion)
  - LSIL (HPV, mild dysplasia)
  - HSIL
    - Moderate dysplasia
    - Severe dysplasia
    - Squamous Cell Carcinoma

**Dysplasia Natural History**

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>Regress</th>
<th>Persist</th>
<th>Progress to CIN 3</th>
<th>Progress to Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN1</td>
<td>57%</td>
<td>32%</td>
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<td>CIN2</td>
<td>43%</td>
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<td>22%</td>
<td>5%</td>
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<td>CIN3</td>
<td>32%</td>
<td>56%</td>
<td>N/A</td>
<td>12%</td>
</tr>
</tbody>
</table>

Ostor AG. Int J Gyn Path. 1993
**Infectious Or Neoplastic?**

<table>
<thead>
<tr>
<th>Normal</th>
<th>Infection</th>
<th>Neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>No Neoplasia</em></td>
<td><em>Infection (HPV)</em></td>
<td><em>Neoplasia</em></td>
</tr>
<tr>
<td><em>No Infection</em></td>
<td><em>Normal</em></td>
<td><em>ASCUS</em></td>
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<tr>
<td>* ASCUS</td>
<td>* LSIL</td>
<td>* ASCUS</td>
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<tr>
<td></td>
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<td>* LSIL</td>
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<td></td>
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<td>* HSIL</td>
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</tbody>
</table>

**Bottom Line**

Differentiate

*normal from infectious*

and

*infectious from neoplastic*

**Colposcopy**

- Adequacy? – visualize entire TZ and entire lesion (if any)
- Visualize with Green filter- atypical vascularity
- 3-5% acetic acid solution
  - Dries cells, neoplastic cells with higher nuclear:cytoplasmic ratio

**Colposcopy**

- Lugol’s Solution (1/4 strength)- Shiller’s Test
  - Taken up by glycogen containing normal epithelium
  - Not taken up by atrophic or neoplastic epithelium or columnar epithelium

**Colposcopy**

- Endocervical Curettage (ECC)
  - Identify dysplasia within endocervical canal
  - Controversial
  - Some studies show cytobrush sampling more sensitive although less specific
Colposcopic Findings

- Acetowhite Changes
  - Increased N:C ratio
  - Abnormal intracellular keratins
  - Intracellular dehydration

Before Acetic Acid

After Acetic Acid

Colposcopic Findings

- Abnormal vascularity
  - Punctuation and Mosaicism
    - HPV capillary proliferative effect
    - Intraepithelial pressure created by expanding neoplastic tissue
    - Tumor angiogenesis factor
  - Atypical blood vessels
- Margins
  - Rolled, peeling edges or internal demarcation between areas of differing appearance are abnormal

Punctuation And Mosaicism

- Epithelial proliferation squeezes capillaries up to surface

Where’s the Dysplasia?

Coarse Mosaicism & Punctuation

Abnormal Vascularity

Punctuation
Colposcopic Warning Signs Of Invasion

- Friable epithelium with contact bleeding
- Irregular surface contour
- Surface ulceration or erosion
- Atypical blood vessels

Colposcopic Warning Signs Of Invasion

- Extremely abnormal punctuation and mosaicism
- High grade lesions occupying 3 or 4 quadrants
- High grade lesions extending into canal either >5mm or beyond colposcopic view

Lugol’s

Is this Normal?

Nabothian Cyst

Cancer

Lugol’s Iodine Application

Tischler Biopsy Instrument

Interventional Techniques

- Excision
  - Cold Knife Cone
  - Loop Electrosurgical Excision Procedure (LEEP, LLETZ, LOOP)
- Laser Cone
- Ablation
  - Cyrotherapy
  - Laser vaporization therapy
**Cold Knife Cone**
- Lugol’s to delineate lesion
- Stay sutures at 3 and 9 o’clock for traction & hemostasis
- Intracervical vasopressin for hemostasis
- Sound endocervical canal to guide excision
- Conical excision with #11 blade

**Cold Knife Cone**
- Tag 12 o’clock for orientation
- +/- ECC or D&C
- Cauterize base
  - Sturmdorf sutures not advisable because of risk of burying residual disease

**LEEP**
- Visualize cervix with non-conductive speculum with suction attachment
- Lugol’s to define lesion
- Paracervical and intracervical block with Lidocaine
- 35-55W or either cutting or blend

**LEEP**
- Excise area 7-10mm deep at center
  - Maximum depth of involved glands 5.2mm
- Ball electrode cautery to base and periphery with coag current
- +/- ECC
- Monsel’s as needed for hemostasis
Side Effects Of LEEP

• Bleeding (now & later)
• Infection
• Damage to adjacent organs
• Cervical incompetence
• Cervical stenosis

HPV Testing- ALTS Distribution

All Paps

Pap normal 92%

ASCUS 8%

HSIL 0.5%

LSIL 2%

ASCUS 5%

High risk HPV pos 97%*

High risk HPV pos 86%

High risk HPV pos 53%

CIN+ 15%

HPV Triage reduces Colpo of ASCUS by 50%

*Missing or false neg values

ASC-US Summary

• If using Thin Prep/HPV testing
  – ASC-US → HPV test and colpo if (+)
    • If (-) then repeat HPV test only in 1 yr. (or repeat Pap)
  – >ASC-US → Colpo
• If not using ThinPrep/HPV
  – Colpo for ASC-US*2
  – If ASC-H or greater → Colpo

See www.asccp.org

Atypical Glandular Cells of Undetermined Significance (AGUS)

• Where are glandular cells?
  • Endometrium
  • Endocervix
Difficult to differentiate HSIL from AGUS on Pap

**Significance Of AGUS**

<table>
<thead>
<tr>
<th>Pap</th>
<th>Any HSIL (including squamous)</th>
<th>High Grade Glandular Lesion</th>
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<tbody>
<tr>
<td>AGUS Reactive</td>
<td>5-39%</td>
<td>1-8%</td>
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<td>AGUS NOS</td>
<td>9-41%</td>
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<tr>
<td>AGUS favor neoplasia</td>
<td>27-96%</td>
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**AGUS Summary**

- Colpo with ECC for everyone
- Endometrial Bx if >35 or history of irregular bleeding (suspicion of endometrial hyperplasia or CA)

See www.asccp.org

**Special Circumstances-Postmenopausal**

- Vaginal atrophy causes cells to resemble HSIL or ASCUS
  - Predominance of smaller basal cells
- If atrophy present, treat with vaginal Estrogen for 6 weeks and re-evaluate

See www.asccp.org
ASC-H
- ASC- Can’t rule out high grade lesion
  - 87% High-risk HPV positive
  - 30% CIN2 or CIN3 on biopsy
- Immediate Colposcopy

See www.asccp.org

ASCUS
= 8%

HPV pos
89%

HPV pos
97%

CIN
2+
15%

HPV pos
53%

CIN
2+
25%

HPV pos
97%

HPV pos
89%

HPV pos
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CIN
2+
Management of Women with Low-grade Squamous Intraepithelial Lesions

- Post-menopausal Women
  - Additional after-risk
  - ≥ ASCUS

- ≥ ASCUS
  - Biopsy if lesion suspicious for high-grade or invasive disease
  - NO ECC
  - No treatment unless invasive cancer found

HIV Patients
- Pap every 6 months
- Colpo for all abnormalities ≥ ASCUS
- Higher risk for severe dysplasia and cancer
- More likely to have abnormal cytology
  - ASCUS 42%
  - HSIL 5%
  - LSIL 17%
  - ASCUS 20%

Pregnant Patients
- Referral to Colpo same as non-pregnant
- Colposcopy
  - Preferably by examiner experienced with pregnant colpos
  - Biopsy if lesion suspicious for high grade or invasive disease
  - NO ECC
- NO ECC
  - No treatment unless invasive cancer found

Treatment of Dysplasia
- CIN1
  - Expectant management if colpo satisfactory
    - 10% risk of CIN2/3 progression
  - Consider ablative or excisional procedure if persistent (But recommend conservative f/u)
    - Sample endocervix prior to ablative procedure
Treatment of Dysplasia

• CIN1
  – Follow-up
  • Repeat Pap 6 mo or HPV test at 12 mo
  • Refer back to colpo for ≥ASCUS

CIN2 or CIN3

• Excision or Ablation
  (if colpo satisfactory)
  – Excision preferred if CIN recurrent
• Observation acceptable in very select circumstances

Normal ⟷ Infection ⟷ Neoplasia

CIN2 or CIN3

• Special Circumstances
  – Pregnancy- observation of CIN2/3 ok
  – Adolescent- observation of CIN2 ok & very selectively CIN3
• Repeat Pap 6 mo. or HPV at 12 mo.
  – Refer to colpo for ≥ASCUS

Positive Endocervical Margin After CIN2/3 Excision

• 15-30% rate of recurrence
• Colpo at 6 mo. preferred (according to guidelines)
  – Repeat Pap at 6 & 12 mo. likely ok
• Hysterectomy acceptable if repeat cone not possible
• Hysterectomy for recurrent CIN2/3 acceptable

CIN2 or CIN3

<table>
<thead>
<tr>
<th>BX</th>
<th>Regress</th>
<th>Persist</th>
<th>CIN 3</th>
<th>Cancer</th>
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<tbody>
<tr>
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Excisional Procedure

• Inadequate colposcopy
• + ECC
• 2 step difference (Pap, CXBX)
• HSIL
• Microinvasion (+/-)
• Persistent dysplasia
Candidates For Excision Or Ablation

- Ablation therapy
  - Visualization of entire transformation zone
  - No suggestion of invasive disease
  - No suspicion of glandular disease
  - Corresponding cytology and histology (≤1 grade difference)
    - i.e. HSIL-Mod Pap and CIN1

Candidates For Excision Or Ablation

- Excision
  - Unsatisfactory colpo
  - Suspicion of invasion or glandular abnormality

Cryosurgery

- Nitrous Oxide
  - -65 to -85°C at cryotip
  - Cell death at −20 to -30°C
- Lethal Zone
  - 2mm proximal to start of iceball
  - Thus to ensure 5mm depth of freeze, lateral spread freeze of 7mm required
- Water-soluble gel to tip
- Freeze-thaw-freeze technique

Treatment Success

- Persistence
  - 3-5% for CIN2/3
  - No difference b/t treatments
- Recurrence
  - 13-19%
    - Higher if age>30, HPV16 or 18, or prior treatment

Treatment Success

- Complications
  - Cervical stenosis (Cryo)
  - Cervical incompetence (large specimens)
    - Preterm labor
  - Infection (<1%)
  - Bleeding (2-5%)

Compressed nitrogen gas flows through a cryo probe making the metal cold enough to freeze and destroy the abnormal cervical tissue.
“You tell them I’m coming, and I’m bringing Lugol’s with me!!!”

-Wyatt Earp

Invasive Cervical Cancer

Invasive Cervical Cancer: Typical Patient
- 45 – 55 y.o. woman
- First child delivered before the age of 20
- Vaginal discharge: thin, watery, blood tinged
- Intermittent painless metrorrhagia or spotting
- Postcoital bleeding
- Last pap was several years ago

Symptoms Of Advanced Disease
- Heavy continuous bleeding
- Foul smelling discharge
- Flank or leg pain, sciatic pain
- Dysuria, hematuria, rectal bleeding
- Unilateral leg edema
- Massive hemorrhage

Diagnosis
Differential Diagnosis

- Vaginitis
- Ectropion
- Cervical Polyp
- Primary Herpes
- Infection/Cervicitis
- MUST DO BIOPSY OF ANY SUSPICIOUS LESION

Cervical Cancer

Poor Prognostic Factors

- Depth of invasion
- Parametrial involvement
- CLS involvement
- Gross vs occult
- Pelvic node involvement
- Adenocarcinoma
- Size of tumor (> 3-4 cm)

Delgado et al, GOG study, Gynecologic Oncology, 35:314-320, 1989

Cervical Cancer

FIGO STAGING FOR STAGE I CERVICAL CANCER

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Carcinoma confined to the cervix</td>
</tr>
<tr>
<td>IA</td>
<td>Identified only microscopically, no gross disease</td>
</tr>
<tr>
<td>IA1</td>
<td>Depth ≤ 3.0 mm, horizontal spreads ≤ 7.0 mm</td>
</tr>
</tbody>
</table>
| IA2   | Depth ≤ 5.0 mm (> 3.0 mm)
|       | Horizontal spread ≤ 7.0 mm |
| IB    | Clinical lesions confined to the cervix |
|       | (or microscopic lesions > IA) |
| IB1   | Clinical lesions ≤ 4.0 cm in size |
| IB2   | Clinical lesions > 4.0 cm in size |

Creasman WT, Gynecol Oncol; 58, 157-158 (1995); FIGO, Montreal (1994)

Cervical Cancer

Routes of Spread

- Pelvic lymphatics
- Direct extension:
  - Vagina
  - Parametrium
  - Bladder, Rectum
- Hematogenous
- Intraperitoneal
Cervical Cancer
Pretreatment Evaluation

• History and Physical examination
  - Lesion size
  - Configuration
• CBC, liver function studies
• CXR
• IVP
• CT scan abdomen and pelvis?

Cervical Cancer
Pretreatment Evaluation

• Staging (EUA)
• Histology of Lesion (review slides)
• Cystoscopy/Proctoscopy selectively
• PET/CT Fusion Selectively

Microinvasive <1mm Depth

• Of 3683 patients reported with < 1mm invasion:
  – Incidence of Lymph Node Metastases was essentially 0%
  – Death rate <0.1%
  – Invasive recurrences approx 0.4%

Ostor AG, Rome RM: Int J Gynecol Ca 4:257, 1994

Management of Microinvasive Cervical Cancer
0-3 mm invasion:
• Conization is reasonable if patient desires preservation of childbearing
• Hysterectomy is also reasonable
• Preservation of ovaries
• LND not indicated

Cervical Conization

Management of Microinvasive Cervical Cancer
3-5 mm invasion:
• 2 – 6% risk of nodal metastases
• 4% risk of invasive recurrence
• 2% of patients die of the disease

### Management of Microinvasive Cervical Cancer

3-5 mm invasion:
- Management options include Conization with LND, Hysterectomy with LND, Radical Trachelectomy with LND or Radical Hysterectomy with LND
- Treatment individualized based on histology
- Conservative management becoming more common

### Cervical Cancer Management I-B – II-A

- Radical hysterectomy:
  - Uterus
  - Upper third of vagina
  - Parametrial tissues
  - Uterosacral ligament
  - Cardinal ligament
  - Pelvic lymphadenectomy
  - +/- para-aortic lymphadenectomy

### Cervical Cancer Management I-B – II-A

- Most appropriate for younger, thin patients
- Smaller tumors (< 4 cm)
- Reasonable for any medically fit, reasonably sized patient with a small tumor

### Cervical Cancer Management I-B – II-A

- Postoperative teletherapy still advisable in selected cases
- Radical Trachelectomy with uterine preservation may be an option in select patients who want to preserve fertility
### IB1 vs IB2 Cervical Cancer

**Complications of Radical Hysterectomy**

<table>
<thead>
<tr>
<th></th>
<th>IB1 n (%)</th>
<th>IB2 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>91 (50.3)</td>
<td>25 (52.1)</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>9 (5.0)</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Medical minor</td>
<td>78 (43.1)</td>
<td>19 (38.6)</td>
</tr>
<tr>
<td>Surgical major</td>
<td>1 (0.5)</td>
<td>3 (6.2)</td>
</tr>
<tr>
<td>Other major</td>
<td>2 (1.1)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

p = 0.0775 (NS)

Finan MA et al, Gynecol Oncol 1996
**Locally Advanced Cervical Cancer**

<table>
<thead>
<tr>
<th>Bulky Tumor</th>
<th>Smaller Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 4 cm</td>
<td>&lt; 4 cm</td>
</tr>
<tr>
<td>Nodal metastases</td>
<td>80%</td>
</tr>
<tr>
<td>Local recurrences</td>
<td>40%</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>50%</td>
</tr>
</tbody>
</table>


**Cervical Cancer**

**Pelvic Nodal Involvement**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients % + Pelvic Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB</td>
<td>1160</td>
</tr>
<tr>
<td>II A</td>
<td>90</td>
</tr>
<tr>
<td>II B</td>
<td>341</td>
</tr>
<tr>
<td>III</td>
<td>96</td>
</tr>
<tr>
<td>IVA</td>
<td>23</td>
</tr>
</tbody>
</table>

**Cervical Cancer**

**Para-aortic Nodes**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patients</th>
<th>% + Para-aortic Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB</td>
<td>1579</td>
<td>4</td>
</tr>
<tr>
<td>II A</td>
<td>212</td>
<td>11</td>
</tr>
<tr>
<td>II B</td>
<td>602</td>
<td>20</td>
</tr>
<tr>
<td>III</td>
<td>546</td>
<td>27</td>
</tr>
<tr>
<td>IVA</td>
<td>80</td>
<td>31</td>
</tr>
</tbody>
</table>

**Tumor Diameter & Recurrence Interval**

- 431 patients with IB and II A cervical cancer treated with radical hysterectomy
- Overall survival = 82%
  - 85% with negative nodes
  - 50% with positive nodes

- Median time to recurrence is related to tumor size:
  - Less than 2 cm: 44 mos.
  - 2-4 cm: 23 mos.
  - Greater than 4.0 cm: 17 mos.

- Tumors greater than 4.0 cm assoc. with local recurrence


**Tumor Diameter & Recurrence Interval**
- Negative nodes assoc. with local recurrence
- Positive nodes: local and distant recurrence


---

**IB Cervical Cancer**
- 98 patients underwent laparotomy for IB/IIA disease
- Bulky tumor (> 4 cm) → 80% nodal metastases
- Smaller tumor (< 4 cm) → 16% nodal metastases
- Factors associated with prognosis are:
  - Size of cervical lesion
  - Lymph node metastases
  - CLS involvement
  - Depth of invasion


---

**IB Cervical Cancer**
GOG study with 645 patients
- IB, negative paraaortic nodes and grossly negative pelvic nodes
- 3 independent prognostic factors:
  - Clinical tumor diameter
  - CLS involvement
  - Depth of invasion


---

**IB Cervical Cancer**
GOG study with 645 patients
- Pelvic nodal status did not affect disease free interval (may be a result of careful patient selection)
- Tumor diameter and disease free interval at 3 years:
  - Occult 94.6%
  - < 3 cm 85.5%
  - > 3 cm 68.4%


---

**Cervical Cancer**
Nodal Metastases
- 185 patients treated with radical hysterectomy, all had nodal metastases
- 150 Stage IB, 35 Stage IIA
- 95 patients had single node involved, remainder had multiple nodes
Cervical Cancer

Nodal Metastases

• Multivariate analysis
• Identified risk groups based on tumor size and nodal disease
• Older age = poor survival


Cervical Cancer

Nodal Metastases (cont.)

<table>
<thead>
<tr>
<th>Risk Groups</th>
<th>Number of Nodes</th>
<th>Lesion size</th>
<th>10 yr survival</th>
<th>Postop XRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 1 cm</td>
<td>1.1 - 4 cm</td>
<td>&gt; 4 cm</td>
</tr>
<tr>
<td>Low Risk (n=13)</td>
<td>≤ 2 LR</td>
<td>92%</td>
<td>61%</td>
<td></td>
</tr>
<tr>
<td>Low Intermediate Risk (n=66)</td>
<td>&gt; 2 LIR</td>
<td>70%</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>High Intermediate Risk (n=66)</td>
<td>&gt; 2 HIR</td>
<td>56%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>High Risk (n=20)</td>
<td>&gt; 2 HR</td>
<td>13%</td>
<td>85%</td>
<td></td>
</tr>
</tbody>
</table>


Treatment: Stage IB2

Treatment Options:

• Radical Hysterectomy
• Radical Hysterectomy plus postoperative adjuvant radiation
• Radiation therapy plus adjuvant extrafascial hysterectomy
• Radiation therapy

Controversy With 1B Rx

• Stage IB encompasses a wide range of tumor diameters
• Tumor diameter is related to survival
• IB ranges from less than 1 cm tumor to > 8 cm tumor

Controversy With 1B Rx

• Cell type: squamous, adenocarcinoma vs adenosquamous
• Wide range of treatment options: surgery, radiation, combined modalities
• Which type of treatment is best?
**IB Cervical Cancer**

- 100 patients, Radical Hysterectomy, randomly selected
- Studied prognostic factors:
  - Histopathologic
    - Grade
    - Stromal Reaction
    - Depth of invasion
  - Clinical
    - Age
    - Race
    - Lesion size
  - Character of Tumor - Stromal Border
  - Number of mitoses
- Purpose was to define "risk groups" to classify patients


**IB Cervical Cancer**

3 risk groups identified:

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Tumor diameter</th>
<th>Depth of invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt; 2 cm</td>
<td>any depth</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt; 2.1 cm</td>
<td>&gt; 1.5 cm</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 3.0 cm</td>
<td>&gt; 1.5 cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Pos Nodes</th>
<th>Recurrence</th>
<th>5 yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>75</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>14</td>
<td>29</td>
<td>36</td>
</tr>
<tr>
<td>High</td>
<td>11</td>
<td>36</td>
<td>64</td>
</tr>
</tbody>
</table>

Survival by Nodal Status

Survival by Nodal Status

IB1 VS IB2 Cervical Cancer

**SURVIVAL**

**IB1**

- 18/181 patients (9.9%) are dead
- 5 year survival 90.0%

**IB2**

- 9/48 patients (18.7%) are dead
- 5 year survival 72.8%

p = 0.0265* Mantel-Cox test

Cervical Cancer

Management:

* I-B, II-A Large Tumors

- XRT
- Radical hysterectomy
- Combined treatment
- Neoadjuvant chemotherapy

IB1 VS IB2 Cervical Cancer

**SURVIVAL**

**IB1**

- 18/181 patients (9.9%) are dead
- 5 year survival 90.0%

**IB2**

- 9/48 patients (18.7%) are dead
- 5 year survival 72.8%

p = 0.0265* Mantel-Cox test


**Stage IB2 Cervical Cancer**

**XRT & Adjuvant Extrafascial Hysterectomy**

- GOG Prospective Study 1984-1991
- 282 patients randomized to conventional XRT versus XRT followed by extrafascial hysterectomy

Finan MA, et al; Gynecol Oncol 1996

Follow - up (months)

Cumulative Survival (%)

IB1

IB2

Survival by Nodal Status

Survival by Nodal Status

Piran MA, et al; Gynecol Oncol 1996
Stage IB2 Cervical Cancer
XRT & Adjuvant Extrafascial Hysterectomy

- Survival:
  - 61.4% for XRT alone
  - 64.4% for XRT plus surgery (ns)
- Recurrence:
  - 43.3% for XRT alone
  - 34.5% for XRT plus surgery (ns)

Substantial reduction in risk of local recurrence in XRT plus surgery group at 5 years (25.8% versus 14.4%)
The addition of hysterectomy to standard radiation therapy does not improve survival but may reduce the risk of local recurrence (longer follow up is needed) Keys H, et al. GOG, Abstr. SGO 1997

IB1 VS IB2 Cervical Cancer

- Patients with Stage IB2 disease did have a significantly worse 5 year survival when compared to Stage IB1 patients
- The current staging system is not an independent predictor of survival

Finan MA, et al; Gynecol Oncol 1996

IB1 VS IB2 Cervical Cancer

- Stage appears to impact survival through nodal status
- Those patients with Stage IB2 tumors but with negative nodes had a significantly better survival than those with positive nodes

Finan MA, et al; Gynecol Oncol 1996
Appropriate treatment is either radiation or radical hysterectomy/radical trachelectomy.

Radical hysterectomy appropriate even with positive lymph nodes.

Radical hysterectomy appropriate even with positive lymph nodes.

Individualize treatment.

Tailor treatment to patient.

Further study is needed for bulky tumors treat patients on protocol.

Cervical Cancer

Adenocarcinoma: Is it really worse?

Stage IB analysis of survival by treatment:

5 year survival

<table>
<thead>
<tr>
<th></th>
<th>Surgery alone</th>
<th>Surgery &amp; XRT</th>
<th>XRT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell</td>
<td>93%</td>
<td>73%</td>
<td>76%</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>95%</td>
<td>66%</td>
<td>71%</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>69%</td>
<td>87%</td>
<td>79%</td>
</tr>
</tbody>
</table>

SCCa and Adenocarcinoma patients treated with Surgery alone had a significantly better survival than women treated with Surgery and XRT or XRT alone (p<0.001).

Adenosq patients had similar survival in all treatment groups (p=0.5).


Conclusion from study of 11,157 patients:

Multivariate analysis revealed that histologic cell type had no impact on survival for patients with IB disease.

Tumor size, nodal mets and treatment other than surgery alone were all independent prognostic factors in Stage IB disease.

Patients with adenocarcinoma and positive nodes had a very poor survival (33.3%).

Surgery and XRT seemed to result in higher cure rate for patients with adenosquamous tumors.


Proportion Surviving

Cervical Cancer Stage I
Positive Lymph Nodes

Squamous Carcinoma of Cervix
Stage Ib Survival by Treatment

Post-Op Adjuvant Radiation
- 195 patients treated with radical hysterectomy
- 164/195 (85%) with negative nodes, 7.3% recurred
- 30/195 (15%) had positive nodes 10/30 (33%) recurred
- 20/30 Postop XRT 10/30 No XRT
- 5/20 recurred 5/10 recurred
- No pelvic recurrences 2 pelvic 3 distant


Post-Op Adjuvant Radiation
- 90% of recurrences occur within 24 months
- Patients with pelvic node metastases accounted for 45% of the recurrences yet they were only 15% of the study group

Cervical Cancer
Surgery vs Radiation*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Radiation</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>91.5</td>
<td>86.3</td>
</tr>
<tr>
<td>IIA</td>
<td>83.5</td>
<td>75.0</td>
</tr>
<tr>
<td>IIB</td>
<td>66.5</td>
<td>58.9</td>
</tr>
<tr>
<td>IIIA</td>
<td>45.0</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>36.0</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>14.0</td>
<td></td>
</tr>
</tbody>
</table>

*5 year survival
Cervical Cancer
I-B, II-A: Surgery vs. XRT

Surgery:
• Avoids permanent radiation injury to normal organs (ovaries, vagina, bladder, rectum, etc.)
• Avoids possibility of XRT induced 2nd pelvic malignancies
• Accurate staging
• Pregnancy, IBS, prior XRT, PID, adnexal mass

Cervical Cancer
Primary Radiation Therapy

• Avoids a major operation
• Potentially gives better “tumor-free” margin
• Survival rates similar to surgery
• Can be used for stage I-B – IV
• Should always include weekly cisplatin chemotherapy

Brachytherapy
For Cervical Cancer

A = 2 cm above os & 2 cm lateral, B = 3 cm lateral to A
Treatment options for cervical cancer:
- Surgery (Stages 1A, 1B & 2A)
- Radiation therapy + weekly cisplatin
  Chemotherapy - all stages
- Combined therapy

Brachytherapy
For Cervical Cancer

Radiation Therapy: 2 components
- External Radiation (Teletherapy)
- Internal Radiation (Brachytherapy)
Brachytherapy For Cervical Cancer

• Brachytherapy:
  – Maximize dose directly to tumor site
  – Minimize radiation dose to surrounding organs
  – Protect bladder, rectum, small bowel, etc.

Brachytherapy For Cervical Cancer

• Important points for Brachytherapy:
  – Drain bladder
  – Foley with 50% Hypaque in balloon
  – The tandem and ovoids are NOT RADIOACTIVE.
  – Flange used on tandem to mark location of cervix

Brachytherapy For Cervical Cancer

• Important points (continued):
  – Plastic caps used on ovoids (colpostats) to “push” normal tissues away from sources
  – Colpostats must contain “baskets” to hold radiation sources

Brachytherapy For Cervical Cancer

• At end of Case:
  – All patients MUST have Foley catheter
  – Suture occasionally placed in vulva to secure system to patient

Brachytherapy For Cervical Cancer

• At end of Case:
  – Thighs are frequently marked with pen or marker to document location of system
  – When moving patient from OR table to bed, protect Brachytherapy System
Brachytherapy For Cervical Cancer

- Postoperatively:
  - Patients go to Radiation Oncology (after recovery) to have X-Rays taken
  - System is loaded with radioactive seeds after patient arrives on floor postoperatively

Cervical Cancer

Systemic factors contributing to complications

- Age
- Atherosclerosis
- Diabetes
- CHF
- Collagen vascular disease

Cervical Cancer

Adhesion factors contributing to complications

- Salpingitis
- Peritonitis
- Appendicitis
- Diverticular disease
- Previous pelvic surgery

XRT Plus Concomitant Chemotherapy For Cervical Cancer

- USF study, 67 patients (cervix n=56, vagina n=7, vulva n=4)
- Cervix Stages IB-IVA (most were advanced stages)
- XRT combined with: Mitomycin-c and 5-Fu
  
  Cisplatin and 5-Fu
  or 5-Fu alone

- 57 (85%) complete clinical response
- 6 (9%) partial response
- 2 (3%) stable disease
- Overall survival 22% at 5 years
- GOG randomized study with Cisplatin 5-Fu and XRT vs XRT alone, results pending (IIB-IVA)

Cervical Cancer - Neoadjuvant Chemotherapy

• Randomized, prospective trial of bulky stage IB and IIA, IIB & III cervical cancer
• Neoadjuvant chemo (NACT) consisted of cisplatin as single agent or combination total dose > 300 mg/m² over 6-8 weeks

Cervical Cancer - Neoadjuvant Chemotherapy

• Patients randomized to NACT followed by radical surgery vs exclusive XRT

<table>
<thead>
<tr>
<th></th>
<th>NACT &amp; Radical Surgery</th>
<th>XRT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>199</td>
<td>187</td>
</tr>
<tr>
<td>Age (median)</td>
<td>48</td>
<td>51</td>
</tr>
<tr>
<td>Stage IB-IIB</td>
<td>40%</td>
<td>41%</td>
</tr>
<tr>
<td>Stage III</td>
<td>60%</td>
<td>59%</td>
</tr>
<tr>
<td>Tumor &gt; 5 cm</td>
<td>53%</td>
<td>53%</td>
</tr>
</tbody>
</table>


Cervical Cancer - Neoadjuvant Chemotherapy (cont.)

• Complications of chemotherapy:
  N & V 76% Severe in 15%
  Myelotoxicity 69% Severe in 14%

• Complications of radical surgery and/or XRT:
  Lymphocyst 20%
  Bladder dysfunction 12%
  Proctitis/cystitis 58%
  GI toxicity 36%

Cervical Cancer - Neoadjuvant Chemotherapy (cont.)

• Median follow up only 20 months (range 1-73)
• 3 yr disease free survival: NACT & Radical Surgery 47% & XRT alone 41%
• 3 yr survival overall NACT & Radical Surgery 66% & XRT alone 60%


Locally Advanced Cervical Cancer (3 & 4)

Neoadjuvant Chemotherapy

Tumor resistance to neoadjuvant chemotherapy may imply cross resistance to radiotherapy

Stages 2 – 4

• Standard Rx includes both XRT and chemotherapy
• Whole pelvis +/- extended field
• Brachytherapy
• Weekly Cisplatin chemotherapy:
  Cisplatin 40 mg/m² weekly X 5 – 7 doses
### Summary
- Stage 1a1 1a2: CKC vs Hyst +/- nodes
- Stage 1B1: Surgery or XRT
- Stage 1B2: Multiple options – individualize to the patient
- Stage 2 – 4: XRT + weekly cisplatin chemotherapy

### Future Programs:
Manage Your Stress Before It Manages You
Thursday, October 23, 2008
2:00-4:00 p.m. Central Time

HIV Serology Update 2008
Tuesday, October 28, 2008
9:00-11:00 a.m. Central Time