

# **Cervical Dysplasia and Invasive Cervical Cancer**

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



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

## **Faculty**

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Chief, Gynecologic Oncology**



## **Objectives**

- Overview of cervical cancer
- Understand Role of HPV
- Apply algorithms from [www.asccp.org](http://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  | • Low socioeconomic status |
| • Multiple partners (>2) | • > 3 years pap            |
| • STD                    | • High risk partner        |
| • HPV                    | • Other                    |
| • High risk HPV          | – Contraceptive hormones   |
| • Immunosuppression      | – Radiation                |
| • Smoking                |                            |



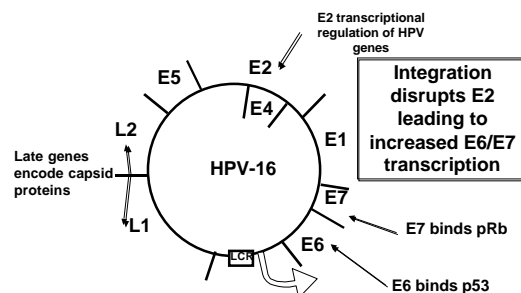
PRESS REPORTS SUGGEST THAT CAFFEINE COULD PROVIDE PROTECTION AGAINST A RANGE OF CANCERS

## 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



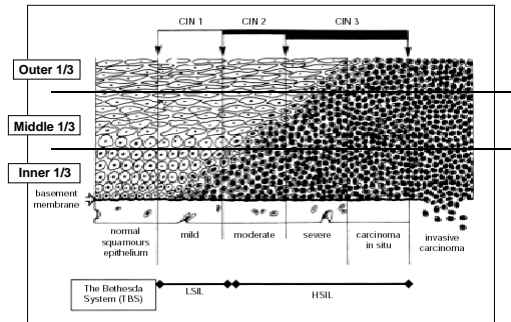
## HPV Types

### High Risk HPV Testing

Low Risk	Intermediate Risk	High Risk
6, 11, 26, 42, 44, 54, 70, 73	31, 33, 35, 39, 51, 52, 55, 58, 59, 66, 68	16, 18, 45, 56

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

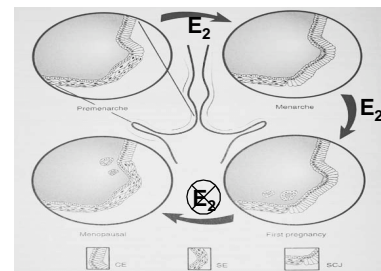
## Cervical Dysplasia Schematic



## “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



From: Practical Gynecologic Oncology 3rd Ed. Berek & Hacker

## Screening Is Good

- Cervical cancer #1 in incidence & mortality in women prior to 20<sup>th</sup> 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

- 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

### Bethesda 2001 Abnormalities

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

### Dysplasia Natural History

Biopsy	Regress	Persist	Progress to CIN 3	Progress to Cancer
CIN1	57%	32%	11%	<1%
CIN2	43%	35%	22%	5%
CIN3	32%	56%	N/A	12%



Ostor AG. Int J Gyn Path. 1993

## Infectious Or Neoplastic?

Normal  $\longleftrightarrow$  Infection  $\longleftrightarrow$  Neoplasia

- No Neoplasia
- No Infection

*Pap* Normal  
ASCUS  
LSIL

- Infection (HPV)
- No Neoplasia

Normal  
ASCUS  
LSIL  
HSIL

- Neoplasia
- Infection

ASCUS  
LSIL  
HSIL

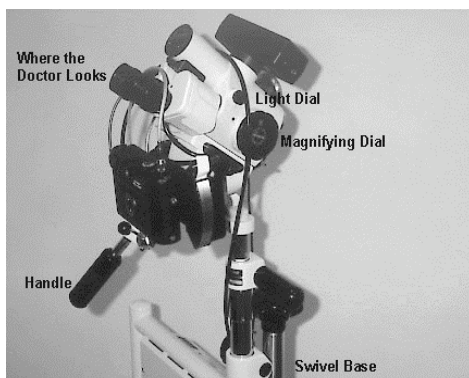
## Bottom Line

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

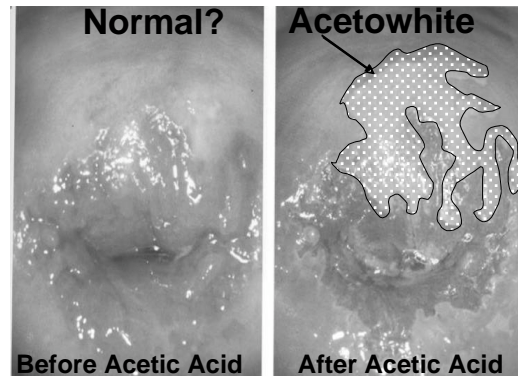
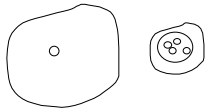
## Colposcopy

- 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



## Colposcopic Findings

- Abnormal vascularity

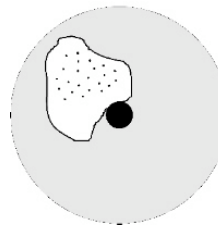
- Punctuation and Mosaicism
  - HPV capillary proliferative effect
  - Intraepithelial pressure created by expanding neoplastic tissue
  - Tumor angiogenesis factor
- Atypical blood vessels

- Margins

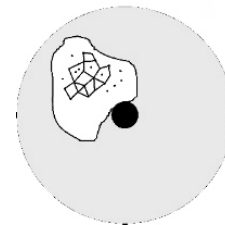
- Rolled, peeling edges or internal demarcation between areas of differing appearance are abnormal

## Punctuation And Mosaicism

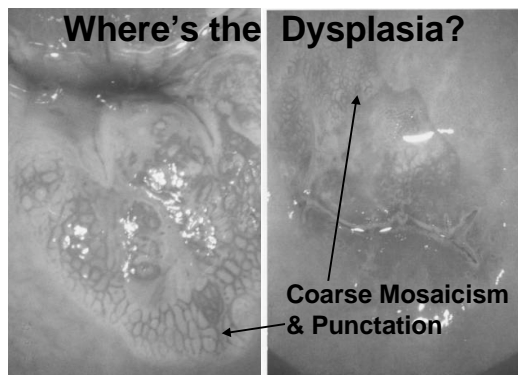
### Punctuation



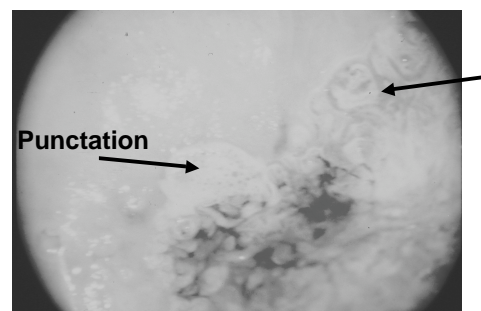
### Mosaicism



- Epithelial proliferation squeezes capillaries up to surface



## Abnormal Vascularity



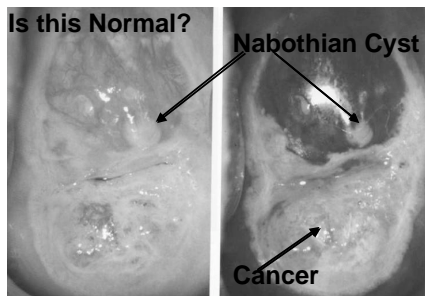
### Colposcopic Warning Signs Of Invasion

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

### Colposcopic Warning Signs Of Invasion

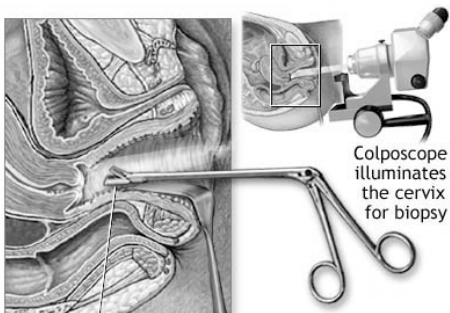
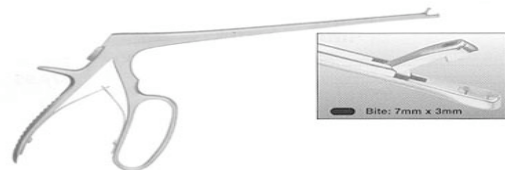
- Extremely abnormal punctation and mosaicism
- High grade lesions occupying 3 or 4 quadrants
- High grade lesions extending into canal either >5mm or beyond colposcopic view

### Lugol's



Lugol's Iodine Application

### Tischler Biopsy Instrument



ADAM

### Interventional Techniques

- Excision
  - Cold Knife Cone
  - Loop Electrosurgical Excision Procedure (LEEP, LLETZ, LOOP)
  - Laser Cone
- Ablation
  - Cryotherapy
  - Laser vaporization therapy

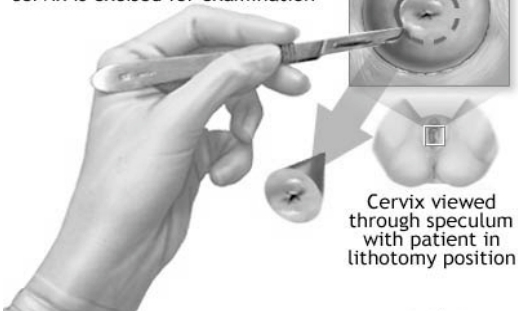
### Cold Knife Cone

- 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

Cold cone biopsy:  
a large area of tissue around the  
cervix is excised for examination



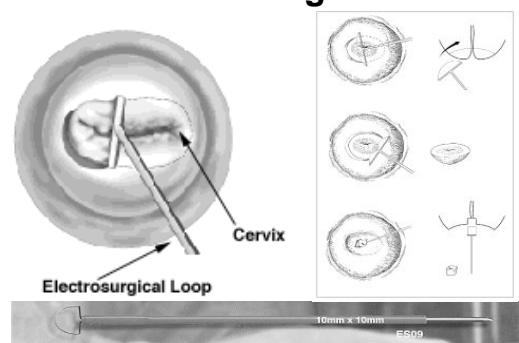
### LEEP

- 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

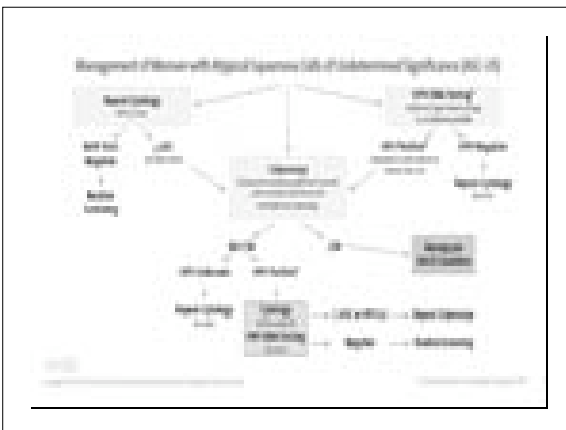
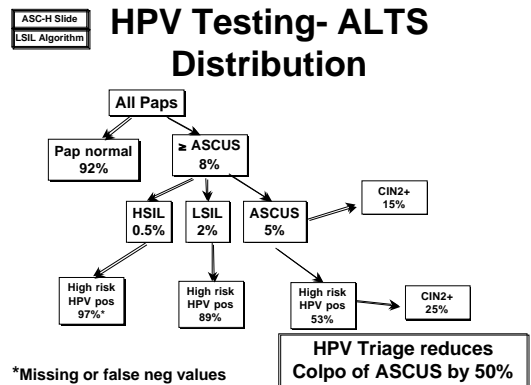
### LEEP Diagram





## Side Effects Of LEEP

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

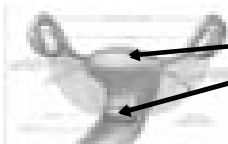


## ASC-US Summary

- 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

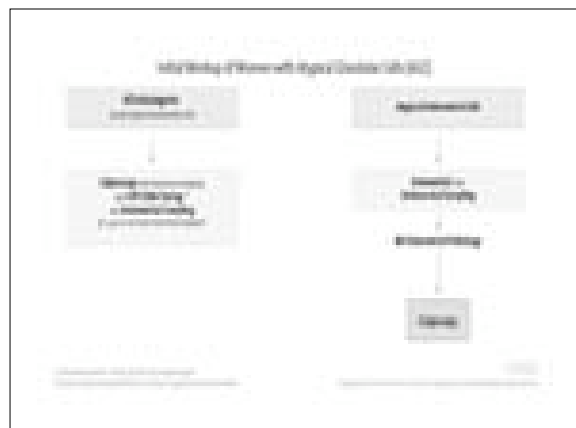
See [www.asccp.org](http://www.asccp.org)

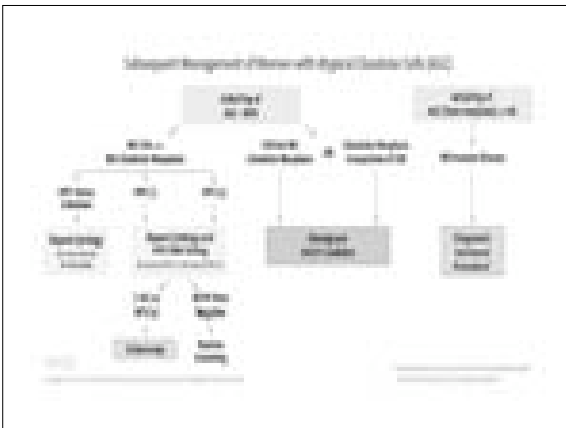
## Atypical Glandular Cells of Undetermined Significance (AGUS)



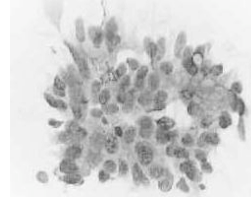
• Where are glandular cells?

- Endometrium
- Endocervix

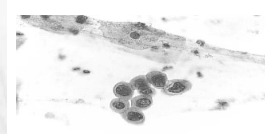




## AGUS



AGUS



HSIL

Difficult to differentiate HSIL from AGUS on Pap

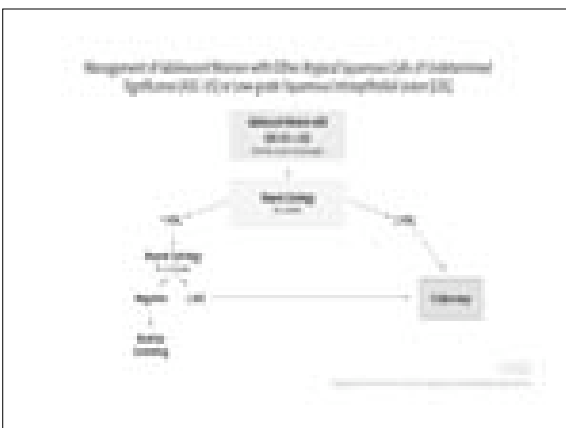
## Significance Of AGUS

Pap	Any HSIL (including squamous)	High Grade Glandular Lesion
AGUS Reactive	5-39%	1-8%
AGUS NOS	9-41%	0-15%
AGUS favor neoplasia	27-96%	10-93%

## AGUS Summary

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

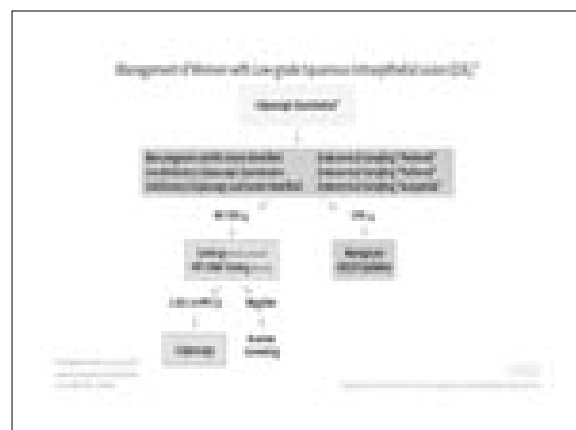
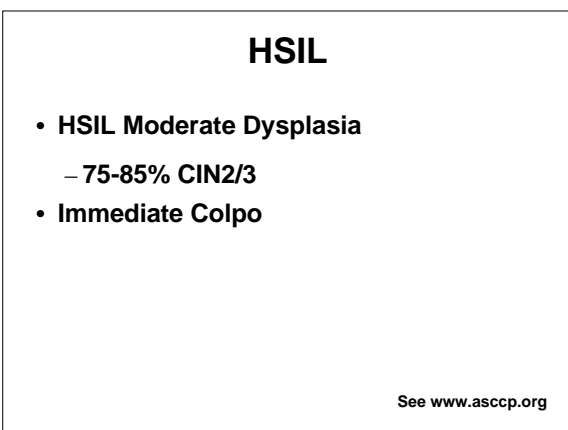
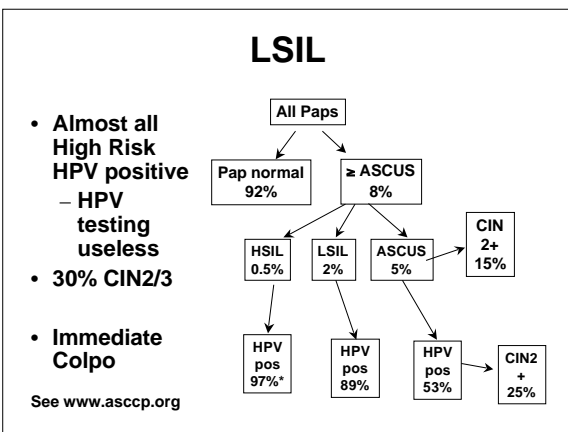
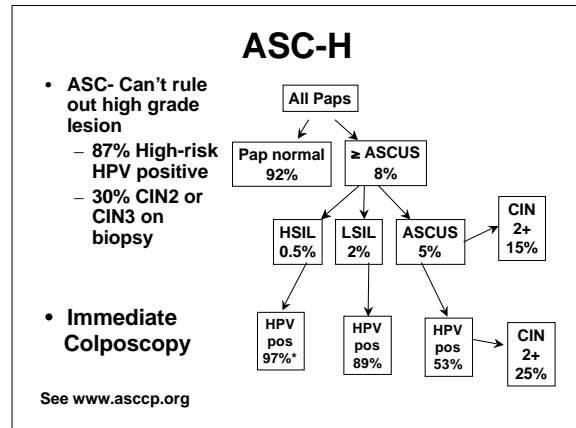
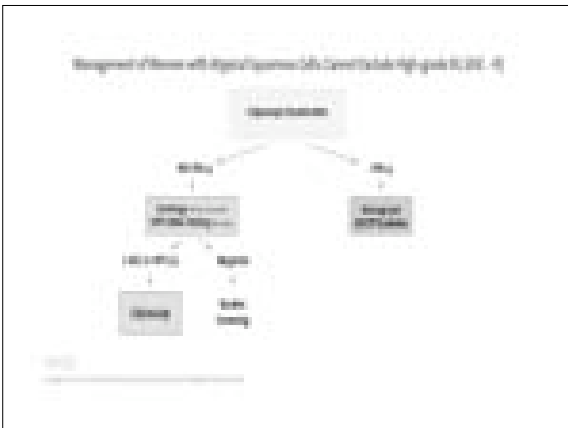
See [www.asccp.org](http://www.asccp.org)

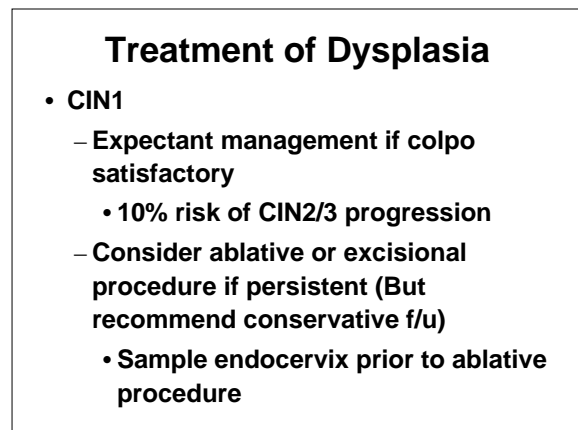
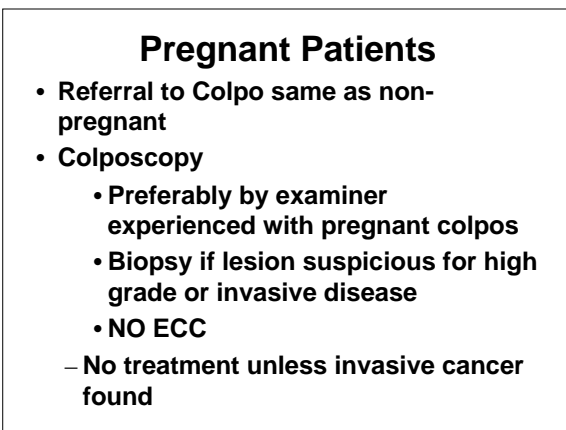
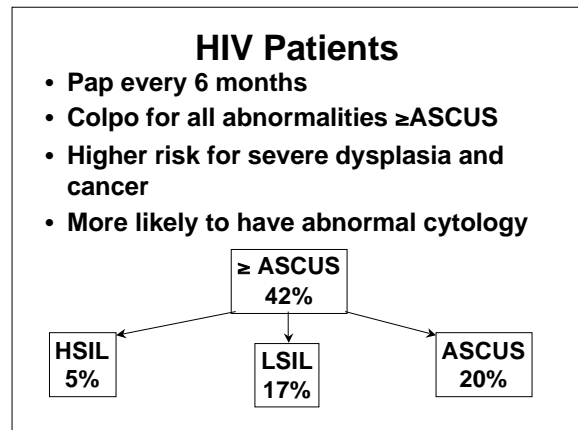
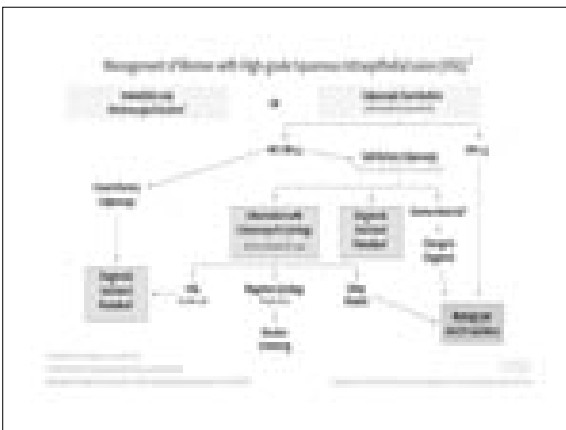
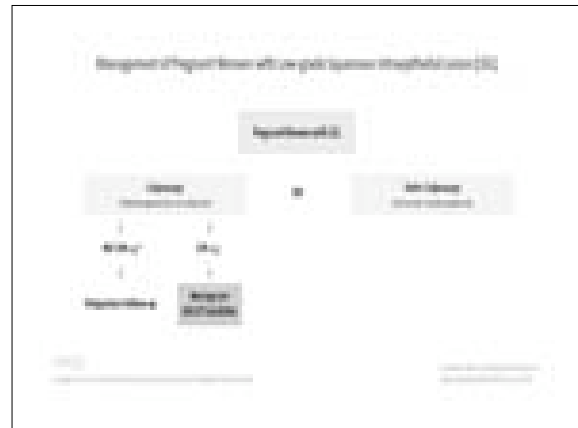
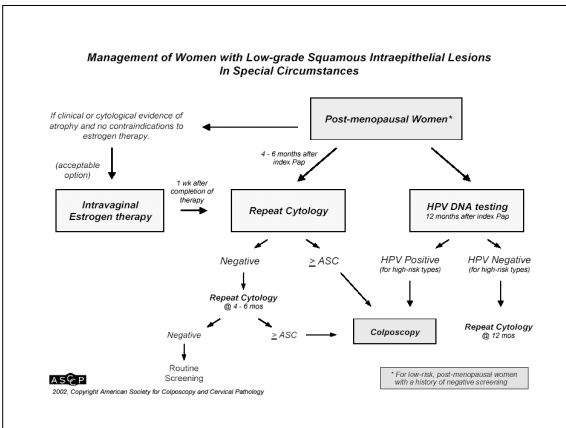


## Special Circumstances- Postmenopausal

- 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](http://www.asccp.org)





## Treatment of Dysplasia

- CIN1
  - Follow-up
    - Repeat Pap 6mo or HPV test at 12mo
    - Refer back to colpo for  $\geq$ ASCUS

Normal  $\longleftrightarrow$  Infection  $\longleftrightarrow$  Neoplasia

## CIN2 or CIN3

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

## 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  $\geq$ ASCUS

## CIN2 or CIN3

BX	Regress	Persist	CIN 3	Cancer
CIN1	57%	32%	11%	<1%
CIN2	43%	35%	22%	5%
CIN3	32%	56%	N/A	12%

## 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

## Excisional Procedure

- Inadequate colposcopy
- + ECC
- 2 step difference (Pap , CXXB)
- 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 ( $\leq 1$  grade difference)
    - ie HSIL-Mod Pap and CIN1



### Candidates For Excision Or Ablation

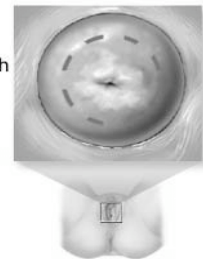
- Excision
  - Unsatisfactory colpo
  - Suspicion of invasion or glandular abnormality



### 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

Compressed nitrogen gas flows through a cryo probe making the metal cold enough to freeze and destroy the abnormal cervical tissue



Cervix as viewed through speculum with patient in lithotomy position

ADAM.

### 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%)

**“You tell them I’m coming,  
and I’m bringing  
Lugol’s  
with me!!!”**

**-Wyatt Earp**

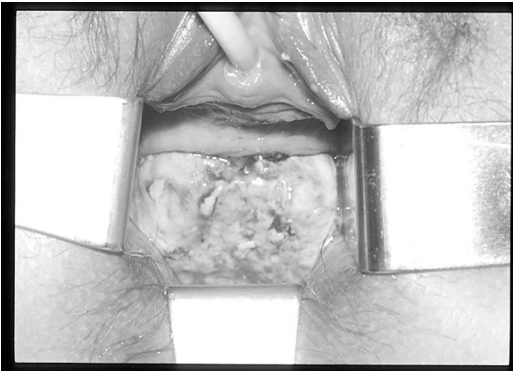
## **Invasive Cervical Cancer**

### **Invasive Cervical Cancer: Typical Patient**

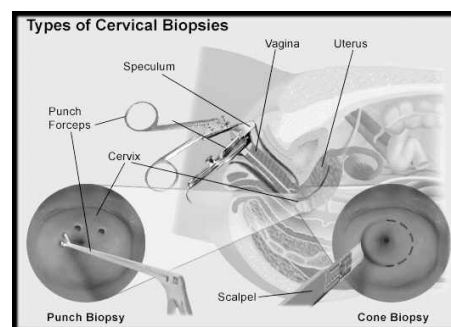
- 45 – 55 y.o. woman
- First child delivered before the age of 20
- Vaginal discharge: thin, watery, blood tinged
- Intermittent painless metrorrhagia or spotting
- Postcoital bleeding
- Last pap was several years ago

### **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



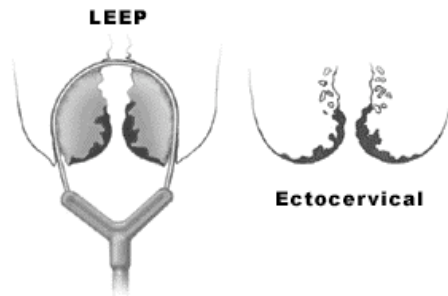
## **Diagnosis**



## Differential Diagnosis

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

## LEEP

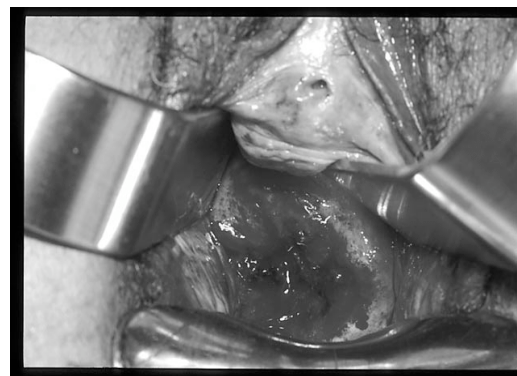


## Cervical Cancer

### 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  
Kamura et al, Cancer, 69:181-186, 1991



## Cervical Cancer

### FIGO STAGING FOR STAGE I CERVICAL CANCER

- I Carcinoma confined to the cervix
- IA Identified only microscopically, no gross disease
- IA1 Depth  $\leq 3.0$  mm, horizontal spreads  $\leq 7.0$  mm
- IA2 Depth  $\leq 5.0$  mm ( $> 3.0$  mm)  
Horizontal spread  $\leq 7.0$  mm
- IB Clinical lesions confined to the cervix  
(or microscopic lesions  $> 1A$ )
- IB1 Clinical lesions  $\leq 4.0$  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**

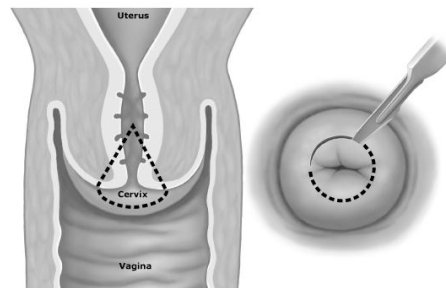
- Staging (EUA)
- Histology of Lesion (review slides)
- Cystoscopy/Proctoscopy selectively
- PET/CT Fusion Selectively

## **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

## **Cervical Conization**



## **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

## **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

Creasman WT, Zano, RJ et al; Am J Obstet Gynecol:178;62,1998

## 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

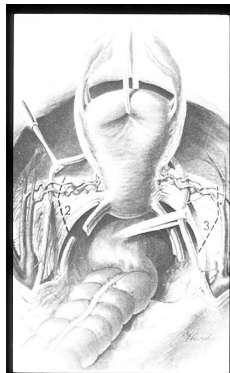
Management I-B – II-A

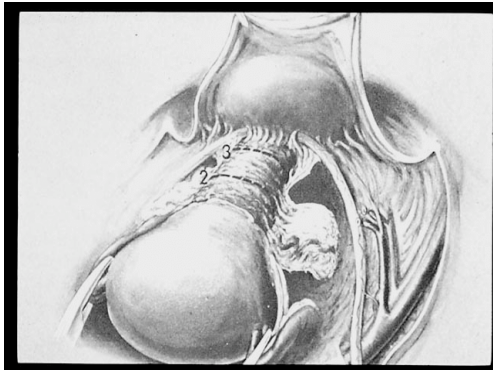
- Most appropriate for younger, thin patients
- Smaller tumors (< 4 cm)
- Reasonable for any medically fit, reasonably sized patient with a small tumor

## 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





## Radical Trachelectomy



## Radical Trachelectomy



## Radical Trachelectomy



## Radical Trachelectomy



## IB1 VS IB2 CERVICAL CANCER

### COMPLICATIONS of Radical Hysterectomy

	IB1 n (%)	IB2 n (%)
None	91 (50.3)	25 (52.1)
Thromboembolic event	9 (5.0)	1 (2.1)
Medical minor	78 (43.1)	19 (39.6)
Surgical major	1 (0.5)	3 (6.2)
Other major	2 (1.1)	0 (0.0)

p = 0.0775 (NS)

Finan MA et al, Gynecol Oncol 1996

### Locally Advanced Cervical Cancer

	Bulky Tumor > 4 cm	Smaller Tumor < 4 cm
Nodal metastases	80%	16%
Local recurrences	40%	5 %
Distant metastases	50%	1%

Chung, et al: Am J Obstet Gynecol, 138, 1980

### Cervical Cancer

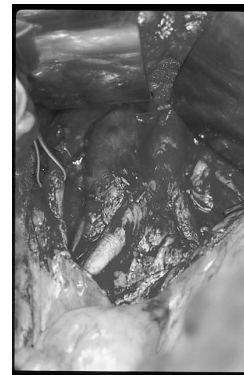
#### Pelvic Nodal Involvement

Stage	Patients	% + Pelvic Nodes
IB	1160	20
IIA	90	26
IIB	341	36
III	96	43
IVA	23	55

### Cervical Cancer

#### Para-aortic Nodes

Stage	Patients	% + Para-aortic Nodes
IB	1579	4
IIA	212	11
IIB	602	20
III	546	27
IVA	80	31



### Tumor Diameter & Recurrence Interval

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

### Tumor Diameter & Recurrence Interval

- 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

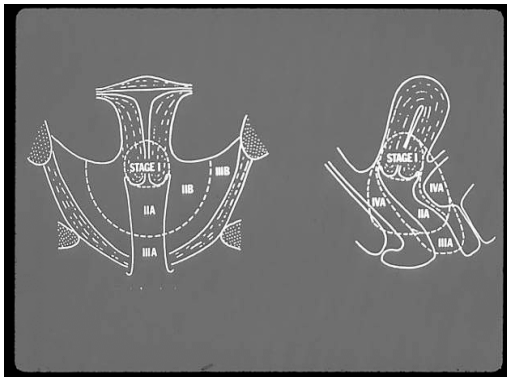
- Negative nodes assoc. with local recurrence
- Positive nodes: local and distant recurrence

Fuller AF, et al. Gynecol Oncol 33, 34-39 (1989).

## 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

Chung, et al. Am J Obstet Gynecol, 135: 550-556 (1980), Hershey, Pennsylvania



## 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%

Delgado G, et al. Gynecol Oncol, 38: 352-357 (1990)

## 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

Alvarez RD, et al. Gynecol Oncol, 35: 130-135 (1989)

## Cervical Cancer

### Nodal Metastases (cont.)

Number of Nodes	Risk Groups		
	Lesion size		
	< 1 cm	1.1 - 4 cm	> 4 cm
≤ 2	LR	LIR	HIR
> 2	LIR	HIR	HR
	10 yr survival		Postop XRT
Low Risk (n=13)	92%		61%
Low Intermediate Risk (n=66)	70%		56%
High Intermediate Risk (n=66)	56%		50%
High Risk (n=20)	13%		85%

Alvarez RD, et al. Gynecol Oncol, 35: 130-135 (1989)

## Treatment: Stage IB2

### Treatment Options:

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

## Treatment: Stage IB2

### Treatment Options:

- Radiation therapy plus adjuvant chemotherapy
- Neoadjuvant chemotherapy plus definitive surgery ± XRT
- Neoadjuvant chemotherapy plus definitive radiation ± surgery

## 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:
 

<u>Histopathologic</u>	<u>Clinical</u>
Grade	Age
Stromal Reaction	Race
Depth of invasion	Lesion size
CLS	
Character of Tumor - Stromal Border	
Number of mitoses	
- Purpose was to define "risk groups" to classify patients

Gauthier P, et al. Obstet & Gynecol, 66: 569 (1985)

## IB Cervical Cancer

3 risk groups identified:

	<u>Tumor diameter</u>	<u>Depth of invasion</u>
Low Risk:	< 2 cm	any depth
	2.1 - 3 cm	depth ≤ 1.5 cm
Intermediate Risk:	2.1 - 3 cm	> 1.5 cm
	> 3.0 cm	≤ 1.5 cm
High Risk:	> 3.0 cm	> 1.5 cm

	Pos Nodes	Recurrence	5 yr %
<u>Risk Group</u>	<u>(n)</u>	<u>(%)</u>	<u>survival</u>
Low	75	20	8
Intermediate	14	29	36
High	11	36	64

Gauthier P, et al. Obstet & Gynecol, 66: 569 (1985) UAB, Birmingham

## 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

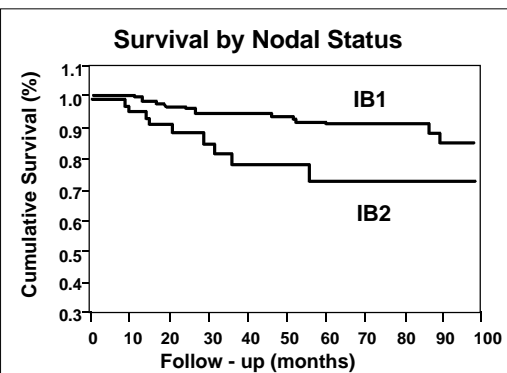
5 year survival 90.0%

IB2

9/48 patients (18.7%) are dead

5 year survival 72.8%

p = 0.0265\*  
Mantel-Cox test



Finan MA, et al; Gynecol Oncol 1996

## 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

### Stage IB2 Cervical Cancer XRT & Adjuvant Extrafascial Hysterectomy

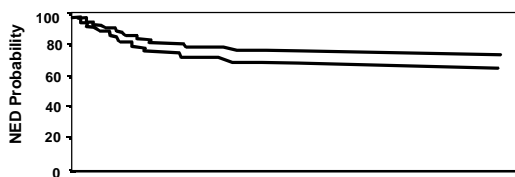
- Survival:  
61.4% for XRT alone  
64.4% for XRT plus surgery (ns)
- Recurrence:  
43.3% for XRT alone  
34.5% for XRT plus surgery (ns)

### Stage IB2 Cervical Cancer XRT & Adjuvant Extrafascial Hysterectomy

- 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)

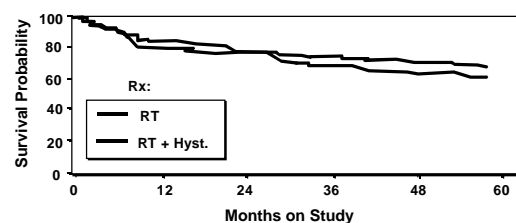
Keys H, et al. GOG, Abstr. SGO 1997

### Progression-Free Interval



Keys, H et al, GOG, Abstr, SGO, 1997

### Survival Time



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



## Treatment: Stage IB1

- Appropriate treatment is either radiation or radical hysterectomy/radical trachelectomy
- Radical hysterectomy appropriate even with positive lymph nodes

## Treatment: Stage IB2

- 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

	Surgery alone	Surgery & XRT	XRT alone
Squamous cell	93%	73%	76%
Adenocarcinoma	95%	66%	71%
Adenosquamous	69%	87%	79%

- 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 ( $p = 0.5$ ).

Shingleton HM, et al. Cancer Suppl, 76: 1948-1955 (1995)

## Cervical Cancer

Adenocarcinoma: Is it really worse?  
Conclusion from study of 11,157 patients:

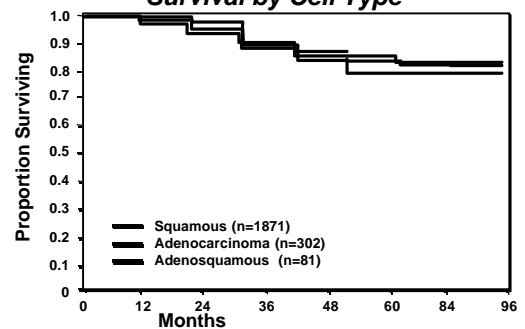
- Multivariate analysis revealed that histologic cell type had no impact on survival for patients with IB disease.
- Tumor size, nodal mets and treatment other than surgery alone were all independent prognostic factors in Stage IB disease.

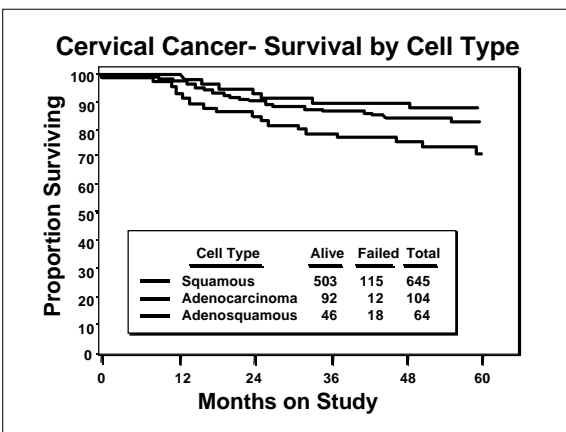
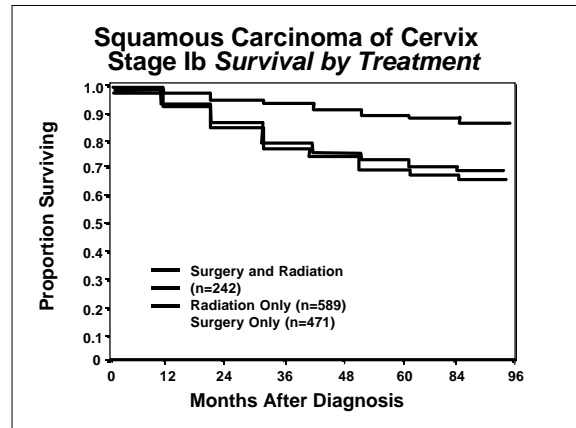
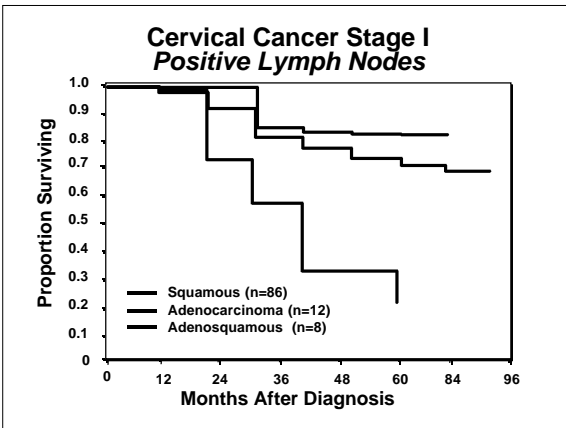
## Cervical Cancer

- Adenocarcinoma: Is it really worse?
- Conclusion from study of 11,157 patients:
- 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.

Shingleton HM, et al. Cancer Suppl, 76: 1948-1955 (1995)

## Cervical Cancer Stage I Survival by Cell Type





## 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

5/20 recurred

No pelvic recurrences

### 10/30 No XRT

5/10 recurred

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

Larson D, et al. Obstet & Gynecol, 69, 378 (1987).

## Cervical Cancer

### Surgery vs Radiation\*

Stage	Radiation	Surgery
I	91.5	86.3
IIA	83.5	75.0
IIB	66.5	58.9
IIIA	45.0	
IIIB	36.0	
IV	14.0	

\*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 2<sup>nd</sup> 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

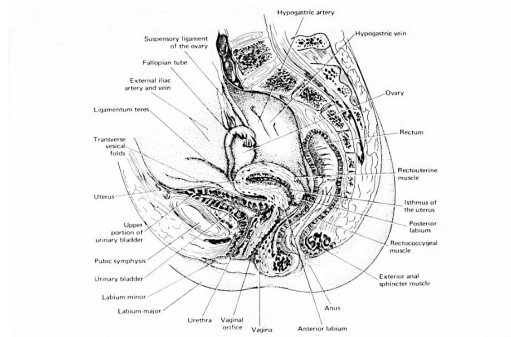
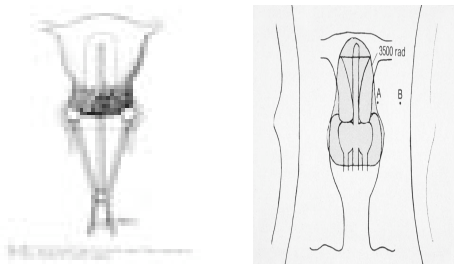
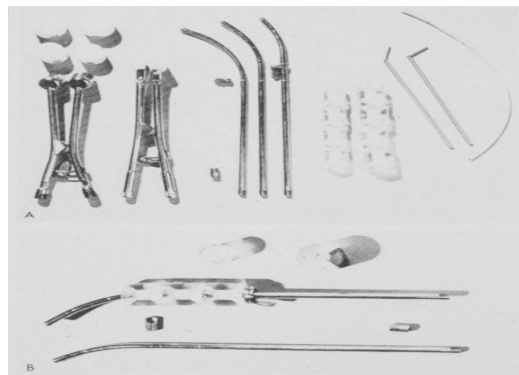


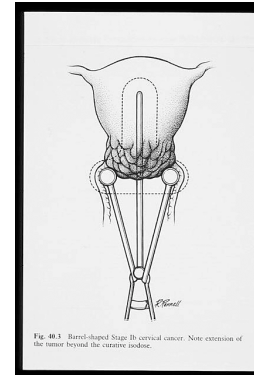
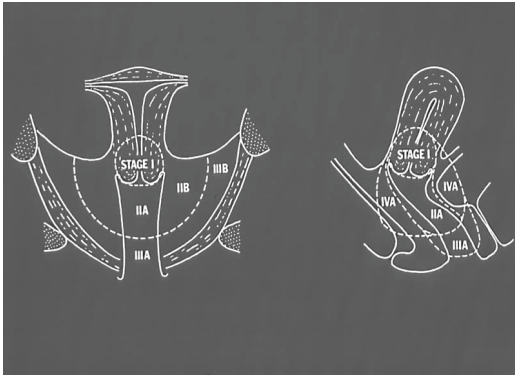
FIG. 4.1. Structural relationships of the vagina. Its axis forms an angle of more than 90 degrees with that of the uterus. [Modified from Clemens CD (ed) Gray's Anatomy, 39th ed., 1985. Courtesy of Lea & Febiger.]

## Brachytherapy For Cervical Cancer

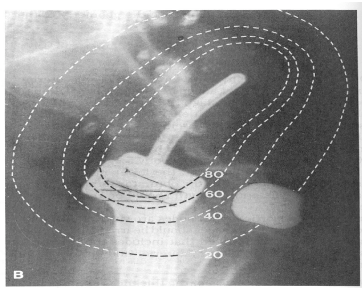


A = 2cm above os & 2 cm lateral, B = 3 cm lateral to A

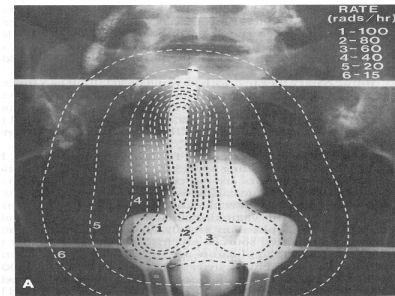




### Rectal / Bladder Points



### Dose Distribution



### Brachytherapy For Cervical Cancer

- 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**

- **Important points (continued):**
  - Tandem and ovoids must be “closed” at end of case
  - Lubricant used on racking to ease removal of system

### **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

Radiation

## Cervical Cancer

### Adhesion factors contributing to complications

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

Radiation

## 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

## XRT Plus Concomitant Chemotherapy For Cervical Cancer

- 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)

Roberts WS, Hoffman MS, et al. Gynecol Oncol, 43: 233 (1991).



### 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/m<sup>2</sup> over 6-8 weeks

### Cervical Cancer - Neoadjuvant Chemotherapy

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

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

Benedetti-Panici P, et al. Abstr SGO 1997, Gynecol Oncol, 64 (2), 292 (1997).

### 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%

Benedetti-Panici P, et al. Abstr SGO 1997, Gynecol Oncol, 64 (2), 292 (1997).

### 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/m<sup>2</sup> 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**