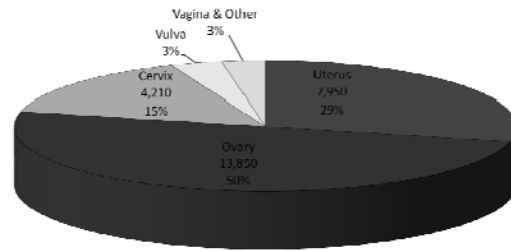


Cervical Cancer

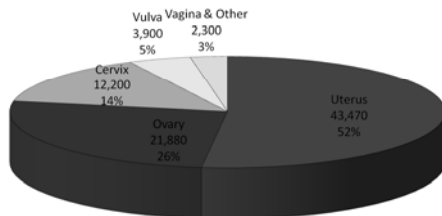
Ritu Salani, M.D., M.B.A.
 Assistant Professor, Dept. of Obstetrics & Gynecology
 Division of Gynecologic Oncology
 The Ohio State University

Estimated gynecologic cancer deaths United States 2010



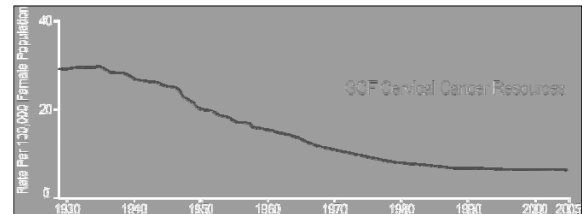
Jemal, A. et al. *CA Cancer J Clin* 2010; 60:277-300

Estimated gynecologic cancer cases United States 2010



Jemal, A. et al. *CA Cancer J Clin* 2010; 60:277-300

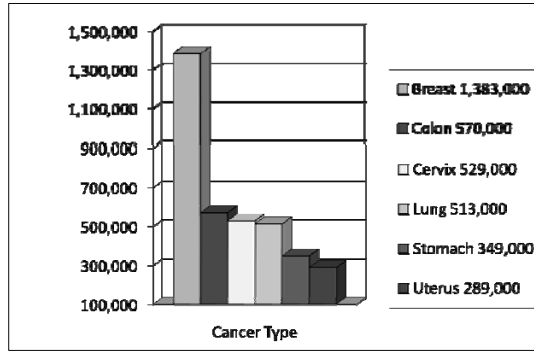
Decreasing Trends of Cervical Cancer Incidence in the U.S.



- 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.

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Cancer incidence worldwide



Cervical Cancer

- Histology
 - Squamous cell carcinoma (80%)
 - Adenocarcinoma (15%)
 - Adenosquamous carcinoma (3 to 5%)
 - Neuroendocrine or small cell carcinoma (rare)

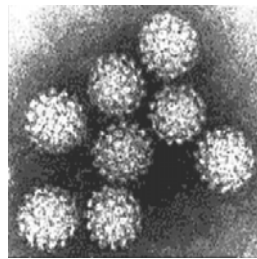
Cervical Cancer

	New cases	Deaths
United States	12,200	4,210
Developing nations	530,000	275,000

- 85% of cases occur in developing nations

¹Jemal, *CA Cancer J Clin* 2010
GLOBOCAN 2008

Human Papillomavirus (HPV)

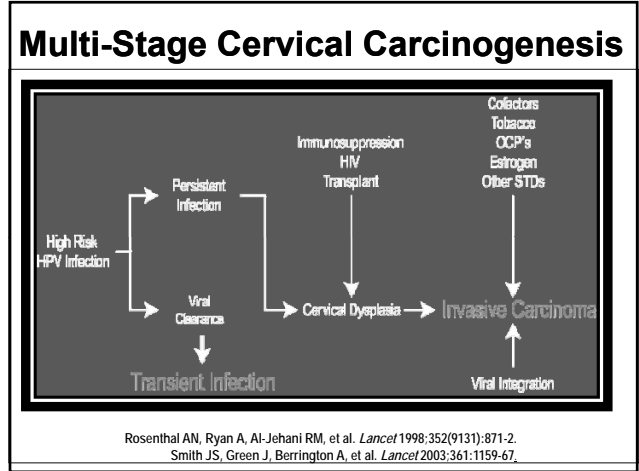
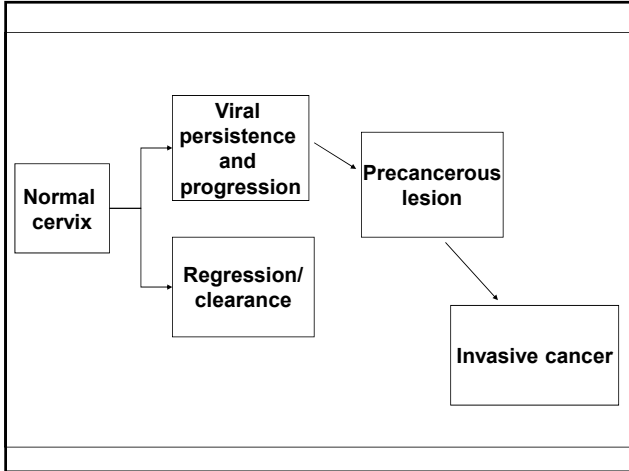


- Etiologic agent of cervical cancer
- HPV DNA sequences detected in more than 99% of invasive cervical carcinomas
- High risk types: 16, 18, 45, and 56
- Intermediate types: 31, 33, 35, 39, 51, 52, 55, 58, 59, 66, 68

HPV 16 accounts for ~80% of cases

HPV 18 accounts for 25% of cases

Walboomers JM, Jacobs MV, Manos MM, et al. *J Pathol* 1999;189(1):12-9.



- ## Risk factors
- Early age of sexual activity
 - Cigarette smoking
 - Infection by other microbial agents
 - Immunosuppression
 - Transplant medications
 - HIV infection
 - Oral contraceptive use
 - Dietary factors
 - Deficiencies in vitamin A and beta carotene

- ## Presentation
- Asymptomatic
 - Vaginal bleeding
 - Post coital bleeding
 - Vaginal discharge
 - Pelvic pain, pressure
 - Vaginal passage of urine or feces

Cervical Cancer

Eric L. Eisenhauer, MD

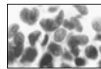
Assistant Professor, Dept. of Obstetrics & Gynecology
Division of Gynecologic Oncology
The Ohio State University

Diagnosis



- Most women with invasive cancer have a visible lesion
 - However, broad range of clinical appearances
- Grossly visible lesions should be biopsied
 - Pap alone is inadequate for visible lesions
- Firm, expanded cervix should undergo biopsy and endocervical curettage
- Women with symptoms or abnormal cytology without a visible lesion should undergo colposcopy and directed biopsy

Screening



- Goal
 - Detect high risk lesions (CIN 2,3+) that could progress to invasive cancer
- Reliability
 - Pap smear has broad range of sensitivity (30-87%)¹
 - Improved with repeated testing
 - Improved with HR HPV testing
- Triage²
 - ASC-H, LSIL, HSIL, AGC, repeat ASC-US
 - Refer for colposcopy and biopsy

¹Smith AE et al. *Cancer* 2000

²ACOG Practice Bulletin 99. *Obstet Gynecol* 2008.

Diagnosis



- Adequate colposcopy
 - Squamocolumnar junction and all lesions completely visualized
 - Biopsy results explain the abnormal cytology
 - Cone biopsy if colposcopy is inadequate
- Limitations of colposcopy
 - Less sensitive than presumed¹
 - Poor correlation between colposcopic impression and biopsy grade²
 - Sensitivity improved with ≥ 2 biopsies³

¹Cox JT et al. *Am J Obstet Gynecol* 2003.

²Ferris DG et al. *Am J Obstet Gynecol* 2006.

³Gage JC et al. *Obstet Gynecol* 2006.

Diagnosis



- **Conclusion**
 - Multiple biopsies
 - Repeat colposcopy if abnormalities persist
 - Cone if inadequate colposcopy

¹Cox JT et al. *Am J Obstet Gynecol* 2003.
²Ferris DG et al. *Am J Obstet Gynecol* 2006.
³Gage JC et al. *Obstet Gynecol* 2006.

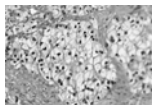
Staging



- **Cervical cancer can spread by:**
 - Direct extension to uterine corpus, vagina, parametria, peritoneum, bladder or rectum
 - Lymphatic spread to pelvic or aortic lymph nodes
 - Hematogenous dissemination
- **Staging is a clinical evaluation to assess the extent to which the cancer has spread**

Diagnosis

Histopathology	<u>Incidence¹</u>
– Squamous cell carcinoma	67%
– Adenocarcinoma	25%
– Adenosquamous carcinoma	5%
– Rare histologies:	3%
• Neuroendocrine carcinoma	
• Adenoid cystic carcinoma	
• Undifferentiated carcinoma	
• Sarcoma or lymphoma	



¹SEER data 2004-2008. <http://seer.cancer.gov/>

Staging

- **Accurate pretreatment staging of cervical cancer determines the therapeutic approach**
- **International Federation of Gynecology and Obstetrics (FIGO) system¹**
 - Physical exam
 - Hysteroscopy
 - Intravenous pyelogram
 - Xray evaluation of lungs and skeleton
 - Biopsy
 - Cystoscopy
 - Proctoscopy
- **Optional testing modalities such as CT and PET scan are widely used in US, and results used to plan treatment²**
- **Most US gyn oncologists still report FIGO stage**

¹Benedet JL et al. *Int J Gynaecol Obstet* 2000.
²Amendola MA et al. *J Clin Oncol* 2005.

FIGO Staging of Cervical Cancer

Stage		
I	Cervical carcinoma confined to uterus	⇒ “Early stage”
IA	Invasive carcinoma diagnosed only by microscopy (microinvasive)	
IB	Clinically visible lesions	⇒ “Locally Advanced”
II	Cervical carcinoma invades beyond uterus but not to pelvic wall or lower third of vagina	
III	Tumor extends to pelvic wall and/or - Involves lower third of vagina - Causes hydronephrosis or nonfunctioning kidney	⇒ “Distant” or “Advanced”
IV	Tumor spreads to other parts of the body, such as the mucosa of the bladder or rectum and/or distant metastasis	

Prognosis

- Stage is the most important prognostic factor
- Lymph node metastasis is the second
 - 5 year survival with stage IB/IIA disease^{1,2}
 - Negative LN – 88-96%
 - Positive LN – 64-74%
 - Number of involved nodes may be important
- HPV subtype 18 may have a worse prognosis
- Smoking may increase the risk for treatment-related complications

¹Delgado G et al. *Gynecol Oncol* 1990.
²Averette HE et al. *Cancer* 1993.

Prognosis

Stage Distribution and Survival¹

Stage	Distribution	5 Year Survival
IA	9%	97%
IB	35%	85%
II	30%	68%
III	19%	41%
IV	6%	15%

¹Quinn MA et al. *Int J Gynaecol Obstet* 2006.

Cervical Cancer

Ritu Salani, M.D., M.B.A.
Assistant Professor, Dept. of Obstetrics & Gynecology
Division of Gynecologic Oncology
The Ohio State University

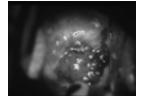
Treatment

- Based on stage of disease
- Categories
 - Early stage
 - Locally advanced
 - Advanced/Metastatic disease

Treatment-Early stage

FIGO IA, IB1, nonbulky IIA1

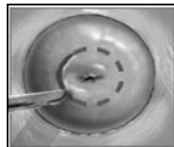
- Surgery versus chemoradiation
 - Outcomes comparable
 - Decision based on
 - Childbearing plans/preservation of ovarian function
 - Comorbidities
 - Physician and patient preference
 - Quality of life (QOL) issues (higher in surgery)



Treatment-Early stage

FIGO IA, IB1

- Non-radical surgery
 - Microinvasive disease
 - Conization
 - Simple hysterectomy
 - Fertility-preserving surgery
 - Discussed later

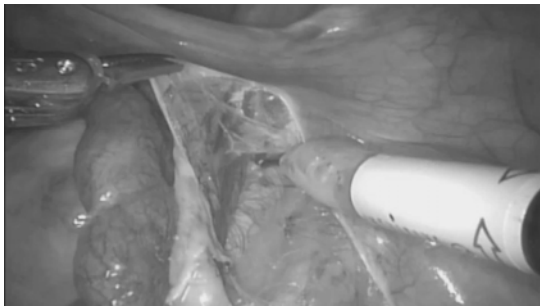


Treatment-Early stage

FIGO IA, IB1, nonbulky IIA1

- Radical hysterectomy
 - Radical hysterectomy refers to the excision of the uterus en bloc with the parametrium (ie, round, broad, cardinal, and uterosacral ligaments) and the upper one-third to one-half of the vagina, with the ovaries left intact.
 - Open, vaginal, laparoscopic, or robotic approach

Video



Adjuvant therapy

- Intermediate risk factors
 - Deep stromal involvement (to the middle or deep one-third)
 - Lymph vascular space invasion
 - Tumor size >4 cm
- High risk factors
 - Positive or close resection margins
 - Positive lymph nodes
 - Microscopic parametrial involvement

Lymphadenectomy

- Pelvic and para-aortic lymph node dissection
 - Resection of bulky pelvic lymph nodes
 - Assessment of lymphatic spread
 - Indication for post-operative chemoradiation
- Not performed for stage IA1 SCC
 - Less than 1% risk of nodal metastases
- Stage IA2, IB1, IB2, and IIA disease
 - Lymphadenectomy indicated

Treatment-Early stage

FIGO IA, IB1, nonbulky IIA1

- Primary chemoradiation therapy
 - RT consists of external beam radiation therapy +/- brachytherapy
 - Treatment field includes the whole pelvis
 - Extended field if known or suspected para-aortic metastases
 - The addition of weekly cisplatin to radiation resulted in superior results than RT alone

Complications of treatment

Radical hysterectomy

- Mortality: <2%
- Fistula:
 - Higher with prior RT
 - 1/3 to 1/2 heal spontaneously
- Bladder atony and delay in removal of the catheter: 4%
- Lymphedema

Chemoradiation

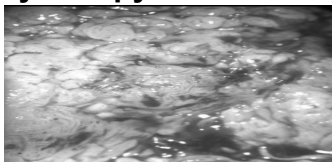
- Major complications 3-15%
- GI toxicity
 - Diarrhea
 - Enteritis
- GU toxicity
 - Frequency
 - Hematuria
- Nerve pain
 - Lumbosacral plexus

Special circumstances

- Role of postchemoradiotherapy hysterectomy
 - Little to no benefit
- Management of incidentally diagnosed cervical cancer after simple hysterectomy
 - Radical parametrectomy and upper vaginectomy, lymph node dissection
 - Radiation therapy

Treatment-Advanced stage FIGO IB2-IVB

- Lymphadenectomy may be performed to determine disease spread and treatment
- Primary chemoradiation followed by brachytherapy



Special circumstances

- Cancer in a cervical stump
 - Post supra-cervical hysterectomy
- Cervical cancer in pregnancy
 - Factors considered
 - Stage of disease
 - Gestational age
 - Patient preference

Cervical Cancer

Eric L. Eisenhauer, MD

Assistant Professor, Dept. of Obstetrics & Gynecology
Division of Gynecologic Oncology
The Ohio State University

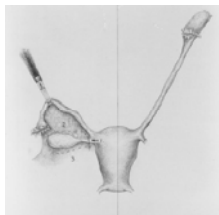
Fertility-sparing surgery

- Eligibility
 - Early cervical cancer < 4 cm
 - No evidence of metastasis
 - Desire for future child-bearing
- Options
 - Cervical conization for non-visible lesions
 - Radical trachelectomy and pelvic lymphadenectomy



Ovarian Transposition

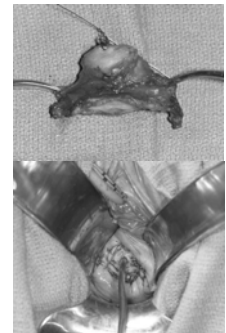
- Standard pelvic radiation doses cause ovarian ablation
- “Transposition”, or “oophoropexy”, can preserve ovarian function by surgically relocating ovaries out of the radiation field¹
- Minimally invasive
- Up to 50% success rate
- Predictive factors²:
 - Reproductive age
 - Radiation doses and fields



¹Tulandi T et al. *Fertil Steril* 1998.
²Stroud JS et al. *Fertil Steril* 2009.

Fertility-sparing surgery

- Radical trachelectomy
 - Removal of cervix, upper vagina and parametrium, but not uterus
 - Abdominal or vaginal
 - Frozen section
 - Cervical cerclage
 - Lower uterine segment reattached to upper vagina



Fertility-sparing surgery

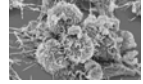
- Fertility outcomes after radical trachelectomy¹
 - As many as 50% of well-selected patients are able to achieve successful pregnancy
 - Rates of 1st and 2nd trimester loss are comparable to general population
 - May have increased incidence of preterm delivery



¹Plante M et al. *Gynecol Oncol* 2005.

Prevention

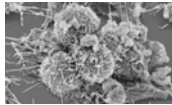
- HPV Vaccines
 - Quadrivalent Vaccine (HPV 16/18 + 6/11)
 - In HPV naïve women, 98% effective to prevent CIN2+¹
 - 95% effective even if all 3 doses were not received
 - Bivalent Vaccine (HPV 16/18)
 - In HPV naïve women, 93% effective to prevent CIN2+²
 - Both are FDA approved
 - Neither contain live virus and are pregnancy category B



¹Future II Study Group. *N Engl J Med* 2007.
²Paavonen J et al. *Lancet* 2009.

Prevention

- HPV Subtypes
 - HPV types 16 and 18 cause 70% cervical cancers
 - HPV types 6 and 11 cause 90% of genital warts



¹Future II Study Group. *N Engl J Med* 2007.
²Paavonen J et al. *Lancet* 2009.

Prevention

- Recommendations for HPV Vaccination
 - Girls and young women ages 9-26
 - Maximum benefit before onset of sexual activity
 - Age-specific recommendations regardless of sexual activity
 - Given as 3 doses at 0, 1-2 and 6 months follow-up
 - Reasonable efficacy even if not all doses administered



Prevention

- **Conclusions**

- Demonstrated efficacy to prevent CIN 2/3, AIS and cervical cancers, as well as anogenital dysplasia and neoplasia
- No evidence of vaccine effect on pre-existing infections



Surveillance

- Clinical evaluation every 3-6 months
- Review of symptoms
- Thorough examination
 - Lymph nodes assessment
 - Speculum examination
 - Rectovaginal
 - Abdominal
- Cytology
 - Low yield

Cervical Cancer

Ritu Salani, M.D., M.B.A.

Assistant Professor, Dept. of Obstetrics & Gynecology
Division of Gynecologic Oncology
The Ohio State University

Post treatment considerations

- Menopausal symptoms
 - Hormonal therapy
- Acute postradiation vaginal mucositis
- Sexual dysfunction
 - Vaginal shortening
 - Decreased vaginal lubrication

Healthy lifestyle

- **Routine cancer screening**
 - Increased risk of developing a second cancer
 - Continued surveillance for development of new lower genital tract disease
- **Exercise**
- **Maintenance of a healthy weight**

Healthy lifestyle

- **Smoking cessation**
 - Over 35% of patients continue to smoke after cervical cancer treatment
- **Bone density monitoring**
 - Assess menopausal status