Gynecologic Malignancies

Kristen D Starbuck

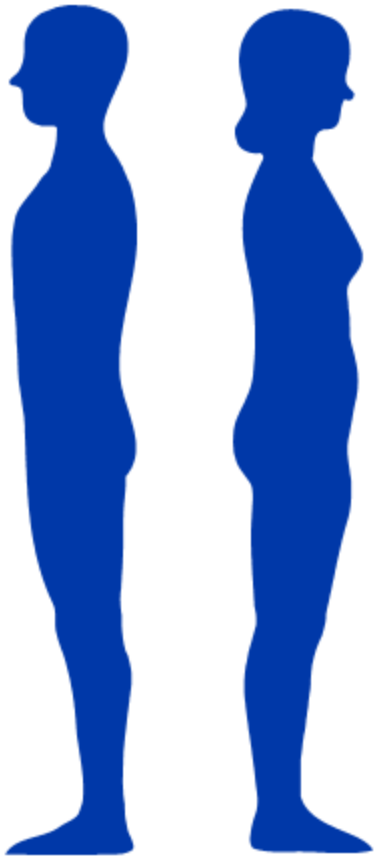
4/20/18

Outline

- Female Cancer Statistics
- Uterine Cancer
- Adnexal Cancer
- Cervical Cancer
- Vulvar Cancer

Estimated New Cancer Cases* in the US in 2016

Males 841,390		Females 843,820	
Prostate	21%	29%	Breast
Lung & bronchus	14%	13%	Lung & bronchus
Colon & rectum	8%	8%	Colon & rectum
Urinary bladder	7%	7%	Uterine corpus
Melanoma of skin	6%	6%	Thyroid
Non-Hodgkin lymphoma	5%	4%	Non-Hodgkin lymphoma
Kidney & renal pelvis	5%	3%	Melanoma of skin
Oral cavity & pharynx	4%	3%	Leukemia
Leukemia	4%	3%	Pancreas
Liver & intrahepatic bile duct	3%	3%	Kidney & renal pelvis
All other sites	22%	21%	All other sites



*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

American Cancer Society®

The Lifetime Probability of Developing Cancer for Females, 2010-2012

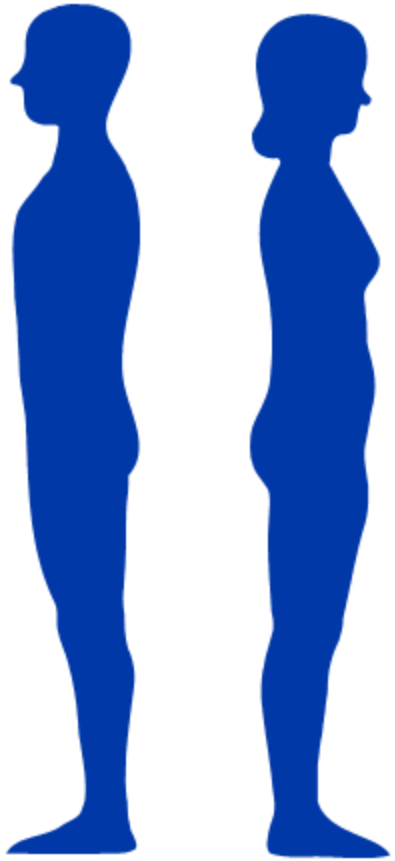
Site	Risk
All sites*	1 in 3
Breast	1 in 8
Lung & bronchus	1 in 17
Colon & rectum	1 in 23
Uterine corpus	1 in 36
Melanoma of the skin†	1 in 52
Non-Hodgkin lymphoma	1 in 53
Thyroid	1 in 58
Pancreas	1 in 67
Ovary	1 in 77
Leukemia	1 in 82

*All sites exclude basal cell and squamous cell skin cancers and in situ cancers except urinary bladder. †Statistic for white females.
Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.7.3 Statistical Research and Applications Branch, National Cancer Institute, 2015.

American Cancer Society®

Estimated Cancer Deaths in the US in 2016

Males 314,290		Females 281,400	
Lung & bronchus	27%	26%	Lung & bronchus
Prostate	8%		
Colon & rectum	8%	14%	Breast
Pancreas	7%	8%	Colon & rectum
Liver & intrahepatic bile duct	6%	7%	Pancreas
Leukemia	4%	5%	Ovary
Esophagus	4%	4%	Uterine corpus
Urinary bladder	4%	4%	Leukemia
Non-Hodgkin lymphoma	4%	3%	Liver & intrahepatic bile duct
Brain & other nervous system	3%	3%	Non-Hodgkin lymphoma
All other sites	24%	2%	Brain & other nervous system
		24%	All other sites



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Uterine Cancer

Endometrial Cancer

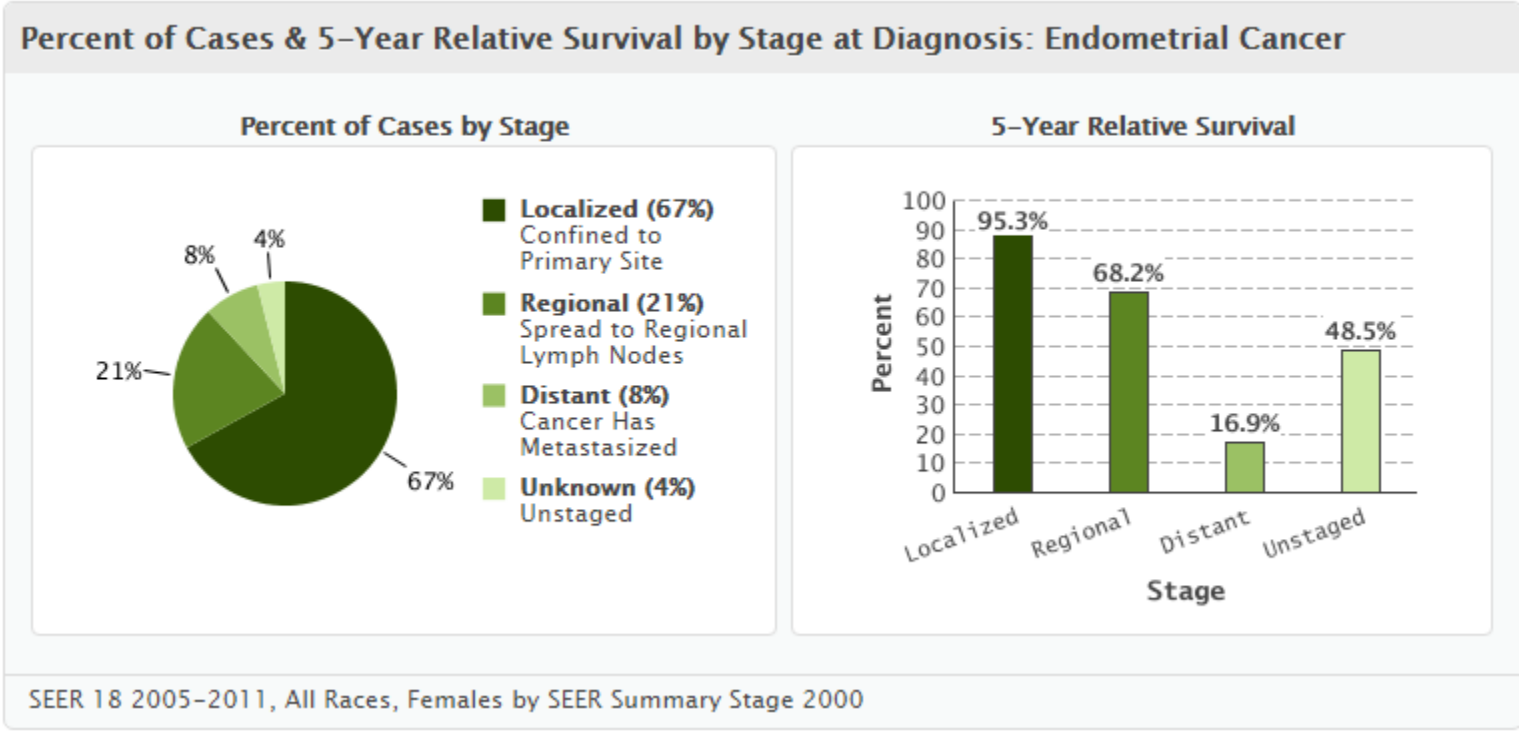
Uterine Sarcoma

Endometrial Cancer

- Epidemiology and Risk Factors
- Histology
- Presentation
- Diagnosis
- Staging
- Therapy
  - Early
  - Locally Advanced
  - Metastatic
  - Recurrent
- Follow-Up
- Future Therapy

Epidemiology

- 60,500 cases expected in 2016
  - 25.3 per 100,000 women
- 10,470 deaths expected in 2016



Epidemiology

Increased Risk

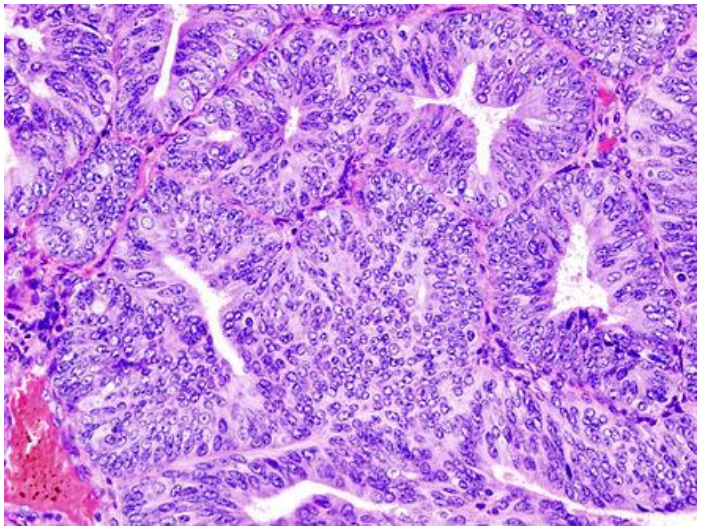
- Age
- Unopposed Estrogens
  - Exogenous
  - Tamoxifen
  - Obesity
- Genetic Risk
  - Lynch Syndrome
  - Cowden Syndrome

Decreased Risk

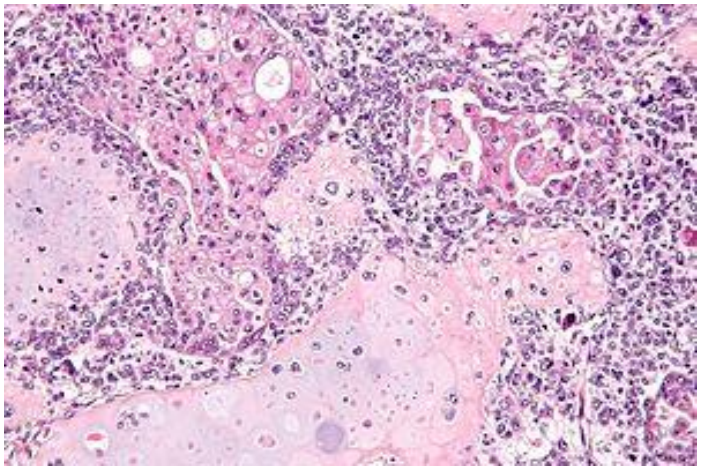
- Progestational Agents
  - Oral Contraceptive Pills
  - Levonorgestrel IUS
- Physical Activity
- Pregnancy
- Breastfeeding

Histology

- Type I
  - Endometrioid, well differentiated
  - Less aggressive
  - Usually localized
  - Good Prognosis



- Type II
  - Clear cell, papillary serous, MMMT (carcinosarcoma), poorly differentiated
  - More aggressive
  - Likely to spread
  - Worse Prognosis



Histology – Molecular Features

Type I

- Diploid
- K-ras overexpression
- PTEN mutations
- Microsatellite instability

Type II

- Aneuploid
- K-ras overexpression
- P53 overexpression

Clinical Presentation

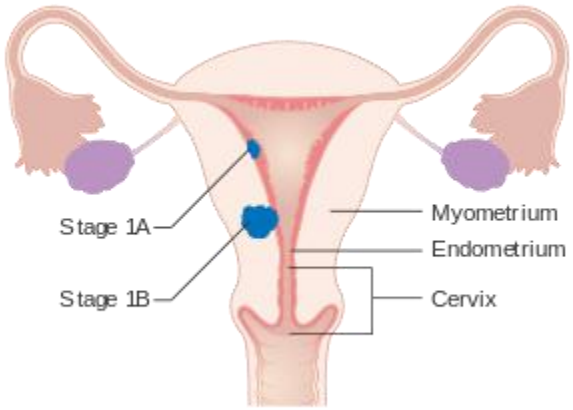
- Abnormal Uterine Bleeding
- Postmenopausal Uterine Bleeding
- Abnormal Vaginal Discharge
- Endometrial cells on a pap smear
- Bloating/pelvic pressure/pain (if advanced disease)

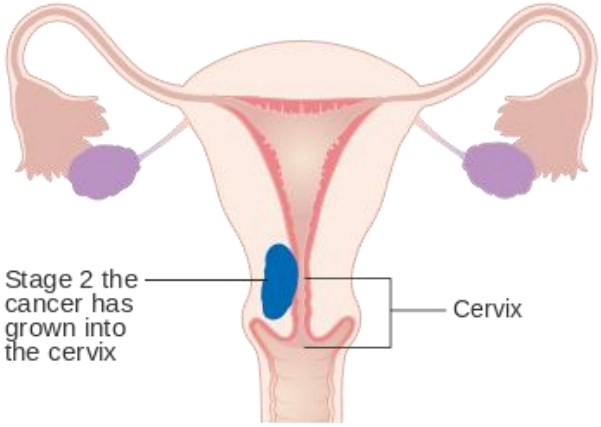
Diagnosis

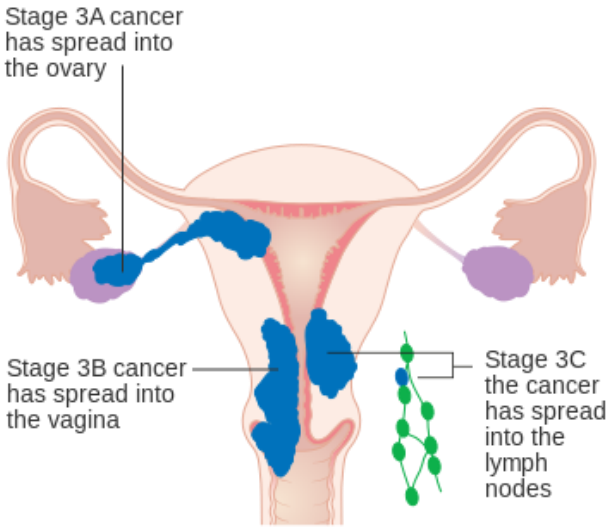
- Ultrasound
- Endometrial Biopsy
- Hysteroscopy
- Dilation and Curettage

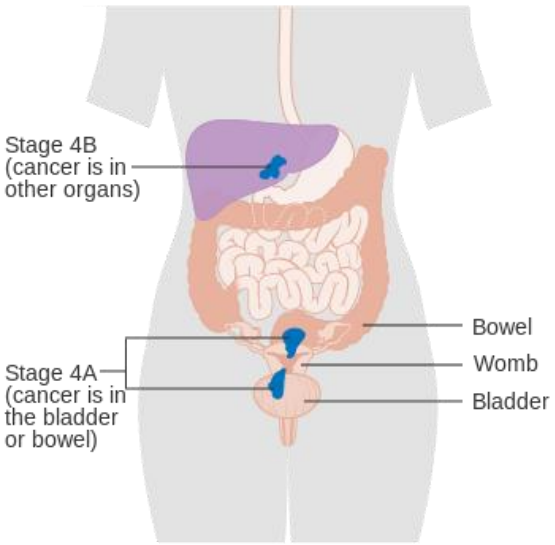
- Hysterectomy +/- BSO +/- Lymph node sampling

Staging









wikipedia

Therapy – Early disease

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Endometrial Carcinoma

NCCN Guidelines Index
Uterine Neoplasms TOC
Discussion

All staging in guideline is based on updated 2010 FIGO staging. (See ST-1)

CLINICAL FINDINGS	ADVERSE RISK FACTORS[m]	HISTOLOGIC GRADE/ADJUVANT TREATMENT[e,n,o]		
		G1	G2	G3
Surgically staged: Stage I[d] — Stage IA (<50% myometrial invasion)	Adverse risk factors not present	Observe	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy
	Adverse risk factors present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy and/or EBRT (category 2B for EBRT)	Observe or Vaginal brachytherapy and/or EBRT
Stage IB (≥50% myometrial invasion)	Adverse risk factors not present	Observe or Vaginal brachytherapy	Observe or Vaginal brachytherapy	Vaginal brachytherapy and/or EBRT or Observe (category 2B for observation)
	Adverse risk factors present	Observe or Vaginal brachytherapy and/or external beam radiation therapy (EBRT)	Observe or Vaginal brachytherapy and/or EBRT	EBRT and/or Vaginal brachytherapy ± chemotherapy[g,p] (category 2B for chemotherapy)

Therapy – Locally advanced disease

National Comprehensive Cancer Network®

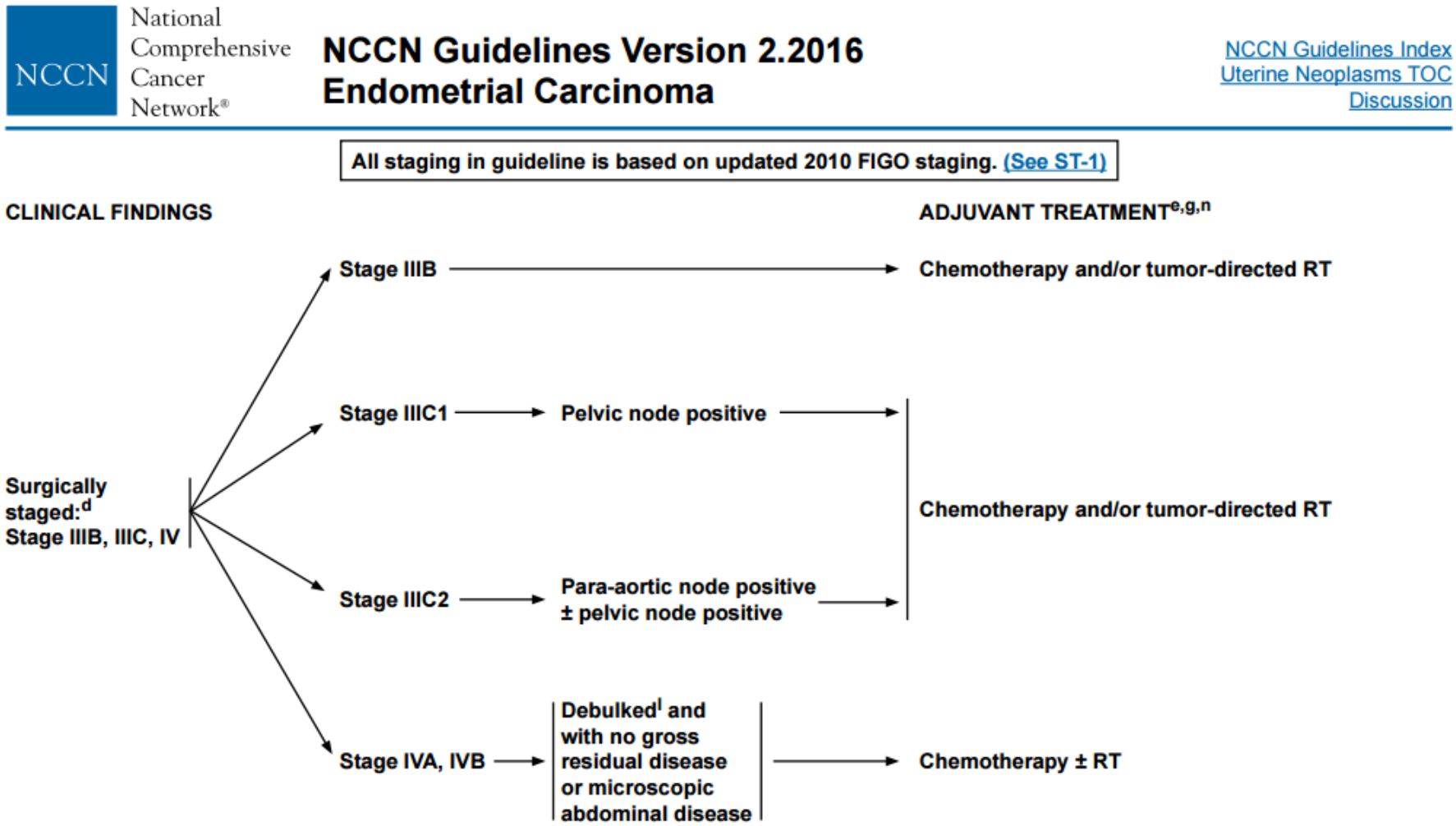
NCCN Guidelines Version 2.2016
Endometrial Carcinoma

NCCN Guidelines Index
Uterine Neoplasms TOC
Discussion

All staging in guideline is based on updated 2010 FIGO staging. (See ST-1)

CLINICAL FINDINGS	HISTOLOGIC GRADE/ADJUVANT TREATMENT[e,g,n,o]		
	G1	G2	G3
Surgically staged:[d] Stage II[q,r] →	Vaginal brachytherapy and/or EBRT	Vaginal brachytherapy and/or EBRT	EBRT ± vaginal brachytherapy ± chemotherapy[p] (category 2B for chemotherapy)
Surgically staged:[d] Stage IIIA →	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or EBRT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or EBRT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or EBRT ± vaginal brachytherapy

Therapy – Metastatic disease



Therapy - Recurrence

- Re-excision
- Radiation
- Systemic Therapies:

HORMONE THERAPY[1]

- Megestrol/tamoxifen (alternating)
- Progestational agents
- Aromatase inhibitors
- Tamoxifen

CHEMOTHERAPY REGIMENS[2,3]

- Multi-agent chemotherapy regimens preferred, if tolerated
  - Carboplatin/paclitaxel[4]
  - Cisplatin/doxorubicin[5]
  - Cisplatin/doxorubicin/paclitaxel[5,6]
  - Carboplatin/docetaxel[7]
  - Ifosfamide/paclitaxel (category 1 for carcinosarcoma)[8]
  - Cisplatin/ifosfamide (for carcinosarcoma)
- Single agents
  - Cisplatin
  - Carboplatin
  - Doxorubicin
  - Liposomal doxorubicin
  - Paclitaxel
  - Topotecan
  - Bevacizumab[9]
  - Temsirolimus[10]
  - Docetaxel[7] (category 2B)
  - Ifosfamide (for carcinosarcoma)

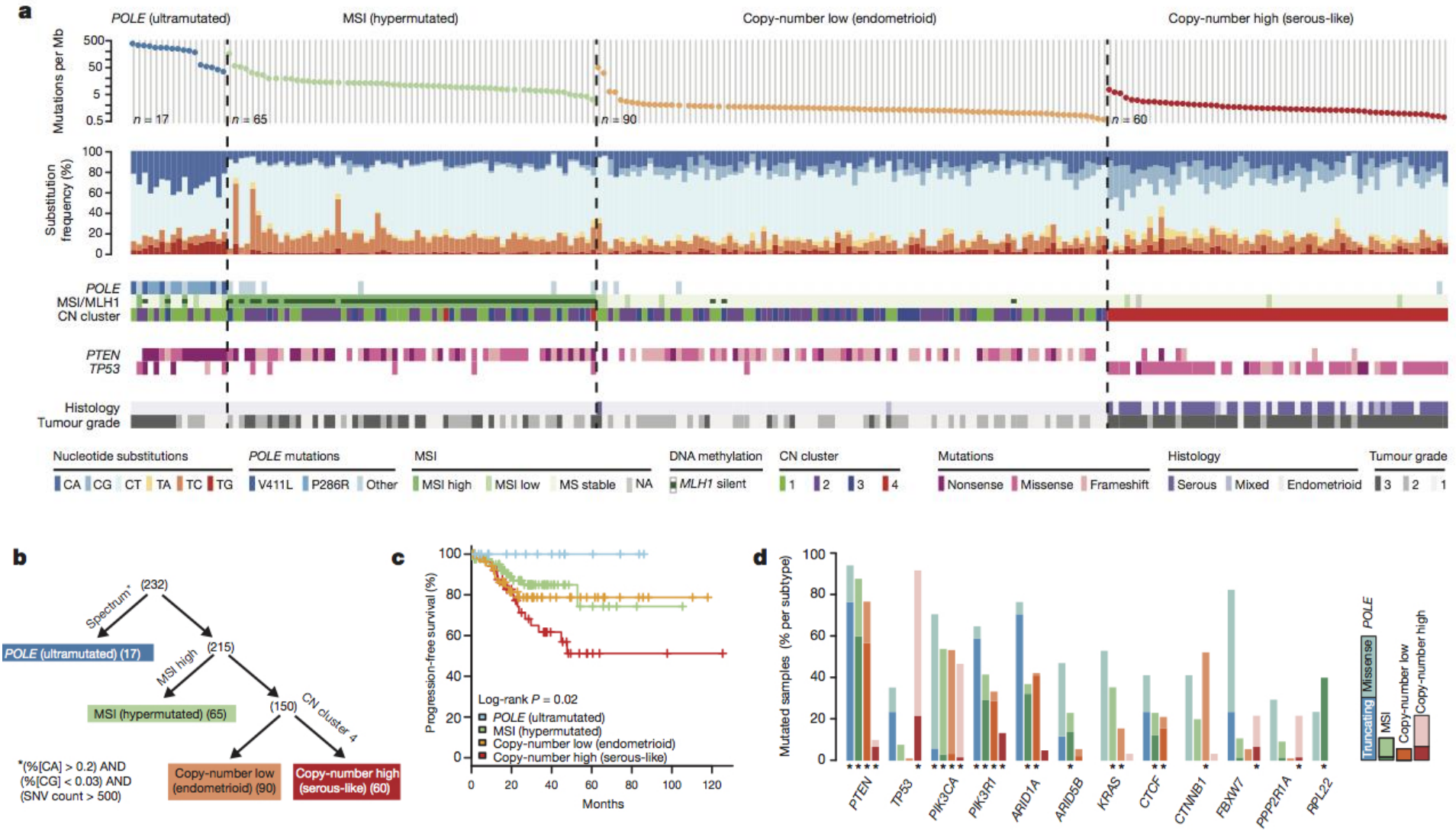
Follow-up

- Regular pelvic examinations
- Symptom awareness
- No role for routine imaging/vaginal cytology

Emerging Therapies

- Sentinel Node Mapping
- Fertility Preservation
- Targeted Therapies

New classification of endometrial cancers- TCGA (endometrioid, serous, mixed)



New classification of endometrial cancers- TCGA (carcinosarcoma)

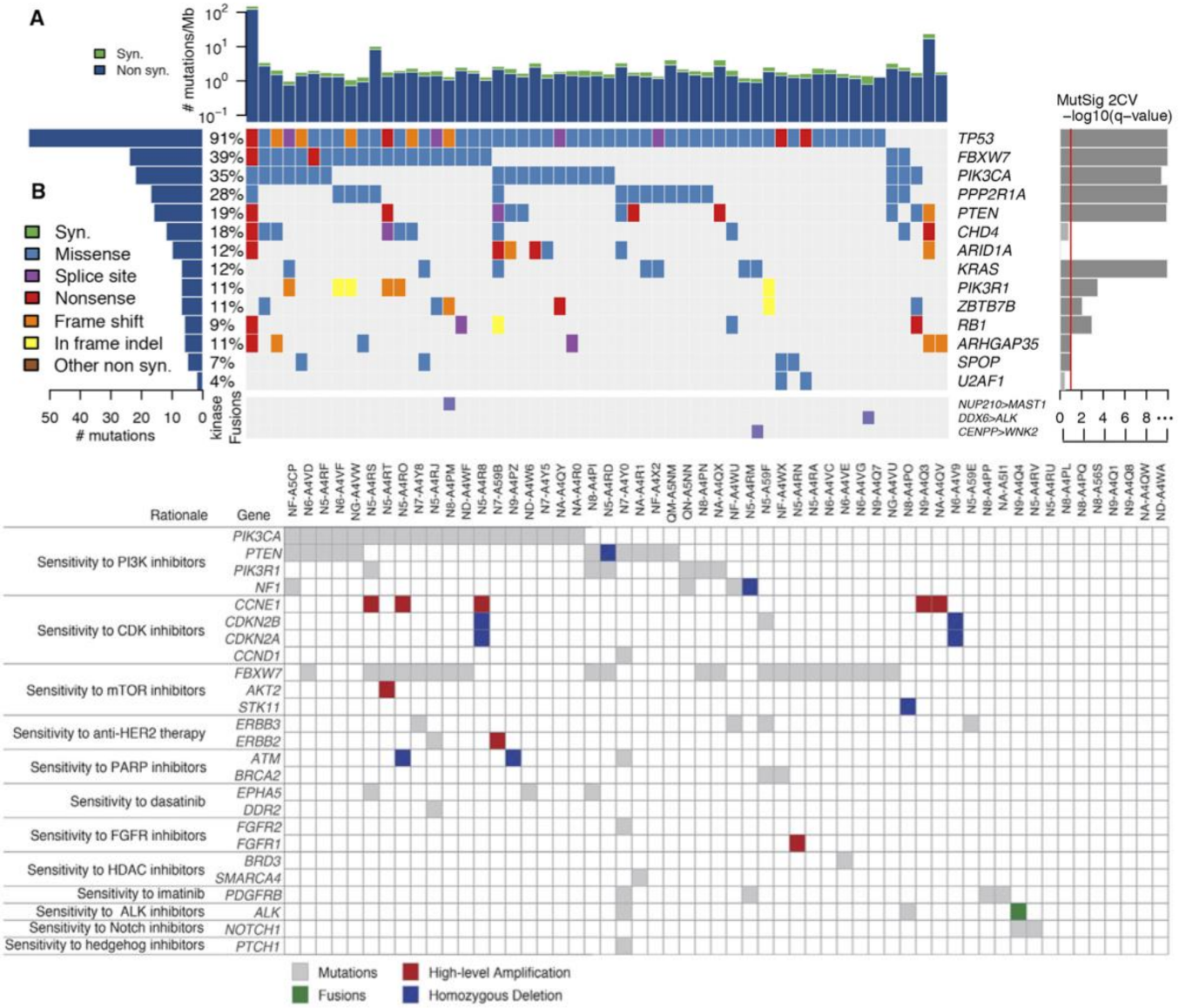


Table 1 Potential changes in practice through molecular categorization

	Immediate?	Future Studies
Overall	• Reproducible categorization • Stratification of trials: past and future, e.g. GOG 210, PORTEC4a	• Characterization of tumours with two or more molecular features • Modeling: which features (clinical, pathological, IHC)* can be added to molecular classification to improve the ability to discern outcomes • Health economic implications • QoL and patient reported outcomes
MMR-D	• Referred for hereditary cancer counselling and testing • Options in immunotherapy	• Further characterization of predictive and prognostic differences within MMR-D: specific mutations, germline vs. somatic, and epigenetic
POLE EDM	• Options in immunotherapy (for rare recurrence or advanced disease unresponsive to conventional Rx)	• Can adjuvant therapy be withheld? Determination of role of treatment in tumors with POLE EDMs: are favorable outcomes independent of therapy? • Possible hormonal management/fertility sparing Rx in young women desiring childbearing
p53 wt	• Lower likelihood metastatic disease: hysterectomy/BSO, managed in community (?)	• Possible hormonal management/fertility sparing Rx in young women desiring childbearing • What additional parameters* can further direct management within this subgroup?
p53 abn	• Fertility sparing Rx not recommended • Complete/aggressive surgical staging • High likelihood will require adjuvant chemotherapy +/- radiation	• Stratification of clinical trials within molecular subgroup

Uterine Sarcoma

- Epidemiology and Risk Factors
- Histology
- Presentation
- Diagnosis/Staging
- Therapy
- Follow-Up
- Future Therapy

Epidemiology

- Median age ranges is 40s to 50s based on histologic type
- Leiomyosarcomas are more common in black women than white women (age adjusted risk is 1.5 vs 0.9 per 100,000)

Risk Factors

- Prior radiation exposure
- Hormone exposure
  - ESS is the only true contraindication to hormone replacement after surgery for a gynecologic malignancy
- Tamoxifen Use
- Hereditary Predisposition
  - HNPCC/Lynch syndrome

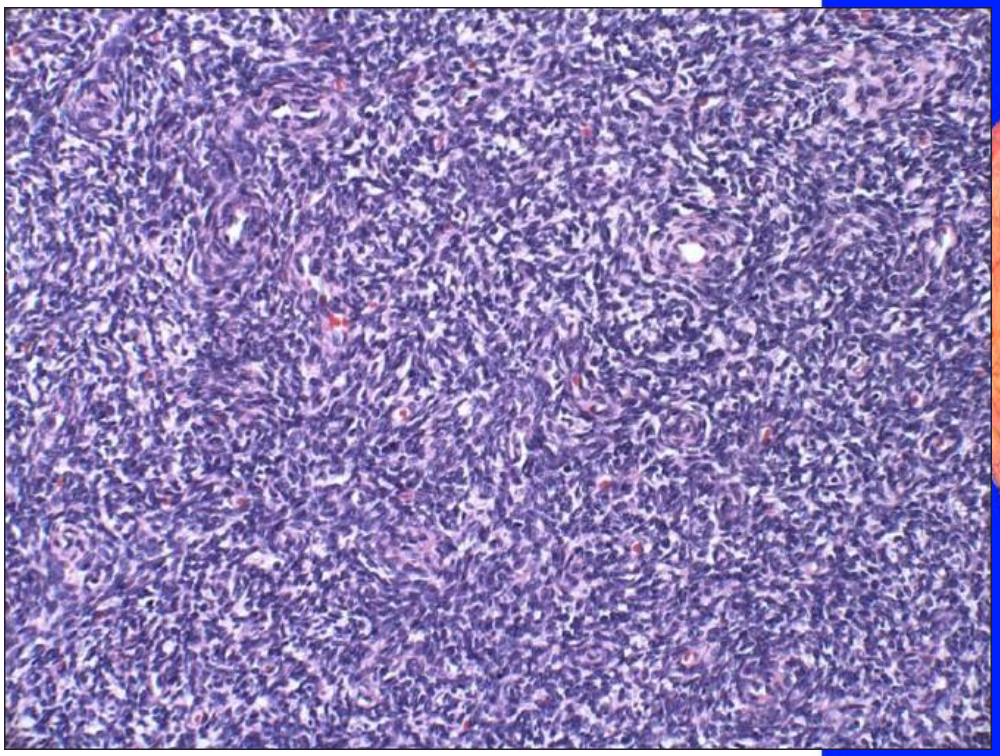
Histology

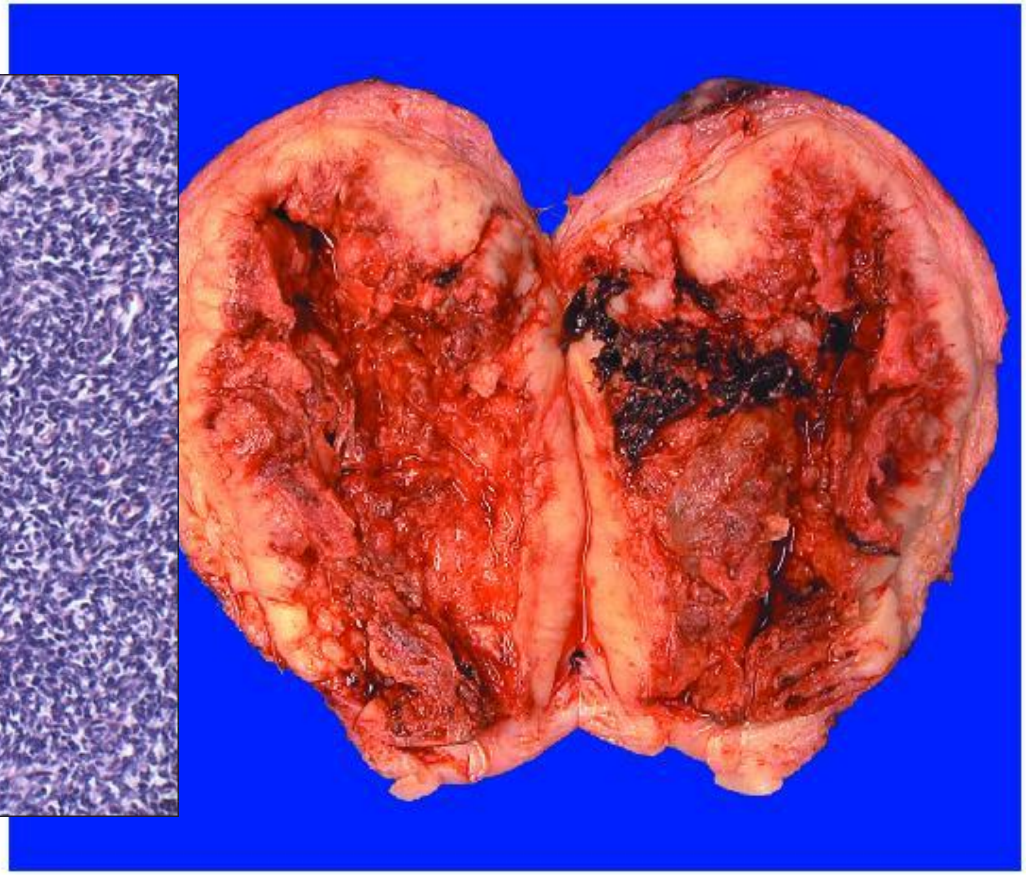
- Leiomyosarcoma
  - Fleshy
  - Nuclear Atypia
  - Tumor Necrosis

- Endometrial stromal sarcoma
  - Low Grade
  - “Bland”
  - Single mass
  - ER/PR positive

Histology

- Undifferentiated Uterine Sarcoma
  - VERY atypical cells





Presentation

- Abnormal vaginal bleeding
- Abdominopelvic mass
- Incidental diagnosis at the time of hysterectomy

Diagnosis/Staging

Staging for uterine sarcomas (leiomyosarcomas, endometrial stromal sarcomas, adenosarcomas, and carcinosarcomas)

(1) Leiomyosarcomas

Stage		Definition
I		Tumor limited to uterus
	IA	<5 cm
	IB	>5 cm
II		Tumor extends to the pelvis
	IIA	Adnexal involvement
	IIB	Tumor extends to extrauterine pelvic tissue
III		Tumor invades abdominal tissues (not just protruding into the abdomen).
	IIIA	One site
	IIIB	> one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis

(2) Endometrial stromal sarcomas (ESS) and adenosarcomas*

Stage		Definition
I		Tumor limited to uterus
	IA	Tumor limited to endometrium/endocervix with no myometrial invasion
	IB	Less than or equal to half myometrial invasion
	IC	More than half myometrial invasion
II		Tumor extends to the pelvis
	IIA	Adnexal involvement
	IIB	Tumor extends to extrauterine pelvic tissue
III		Tumor invades abdominal tissues (not just protruding into the abdomen).
	IIIA	One site
	IIIB	> one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis

Therapy

- Endometrial Stromal Sarcoma
  - Observation
  - Hormonal Therapy
  - Consider Radiotherapy
- LMS/UUS
  - Chemotherapy
  - Radiotherapy

- Lots of negative trials… disappointing results
- Most trials have slow accrual due to rarity of tumors

Therapy

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NCCN Guidelines Version 2.2016
Uterine Sarcoma

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SYSTEMIC THERAPY FOR UTERINE SARCOMA[1]
(Clinical trials strongly recommended)

Combination regimens:
- Docetaxel/gemcitabine (preferred for leiomyosarcoma)
- Doxorubicin/ifosfamide
- Doxorubicin/dacarbazine
- Gemcitabine/dacarbazine
- Gemcitabine/vinorelbine

Single-agent options:
- Dacarbazine
- Doxorubicin
- Epirubicin
- Eribulin
- Gemcitabine
- Ifosfamide
- Liposomal doxorubicin
- Pazopanib
- Temozolomide
- Trabectedin[3]
- Vinorelbine (category 2B)
- Docetaxel (category 3)

HORMONE THERAPY
(For Low-grade ESS or Hormone Receptor Positive (ER/PR) uLMS[2]):
- Medroxyprogesterone acetate (category 2B for ER/PR positive uLMS)
- Megestrol acetate (category 2B for ER/PR positive uLMS)
- Aromatase inhibitors
- GnRH analogs (category 2B for low-grade ESS and ER/PR positive uLMS)

Follow-Up

- Recurrence is common
- Routine exams
- Routine CT scans
- Patient symptom monitoring

Emerging Therapies

- Continued chemotherapy trials
- Biologic therapies
- Numerous genetic mutations in these tumors
  - Targeted therapies
    - Anti-VEGF
    - Multi-kinase inhibitors
    - mTOR inhibitors

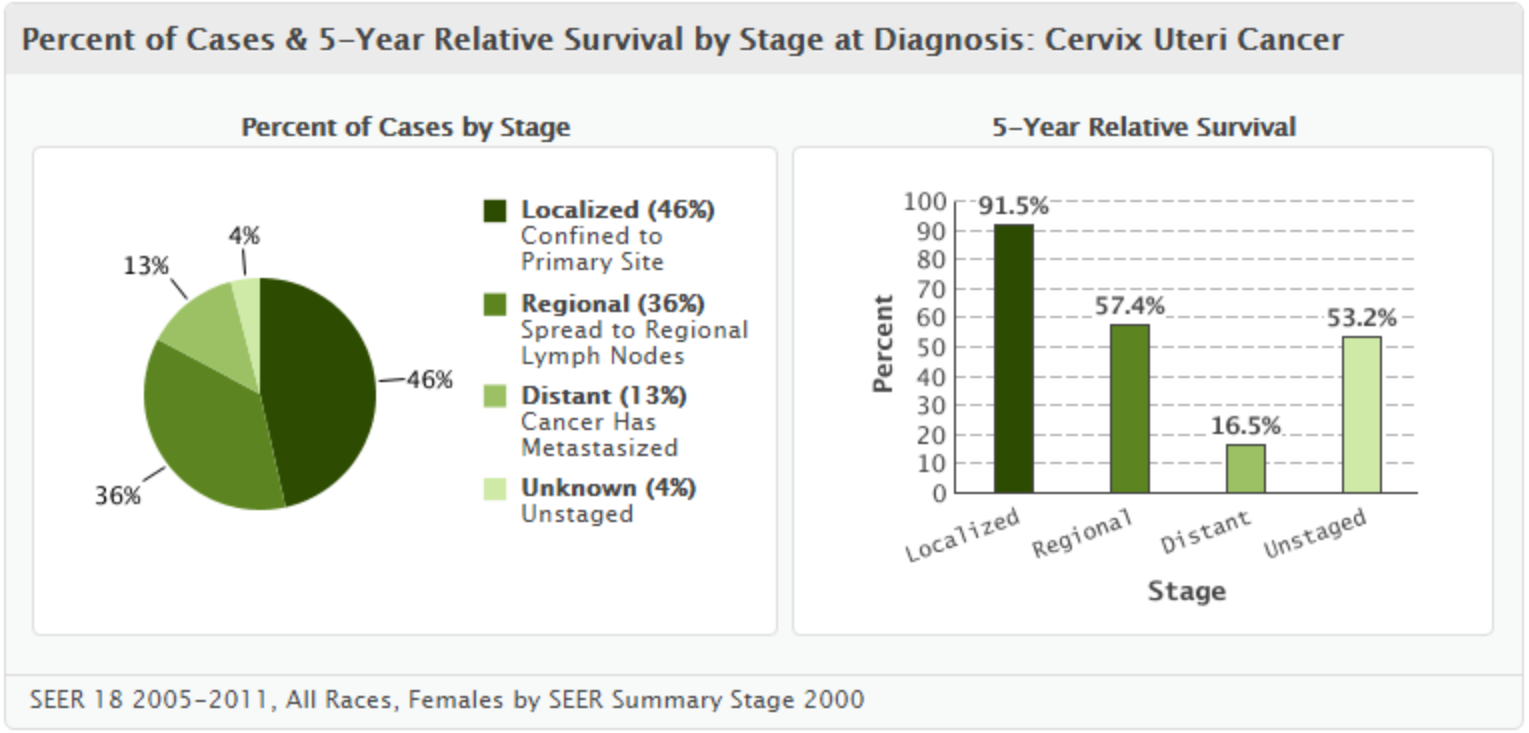
Cervical Cancer

Cervical Cancer

- Epidemiology and Risk Factors
- Histology
- Presentation
- Diagnosis
- Staging
- Therapy
  - Early
  - Locally Advanced
  - Metastatic
  - Recurrent
- Follow-Up
- Future Therapy

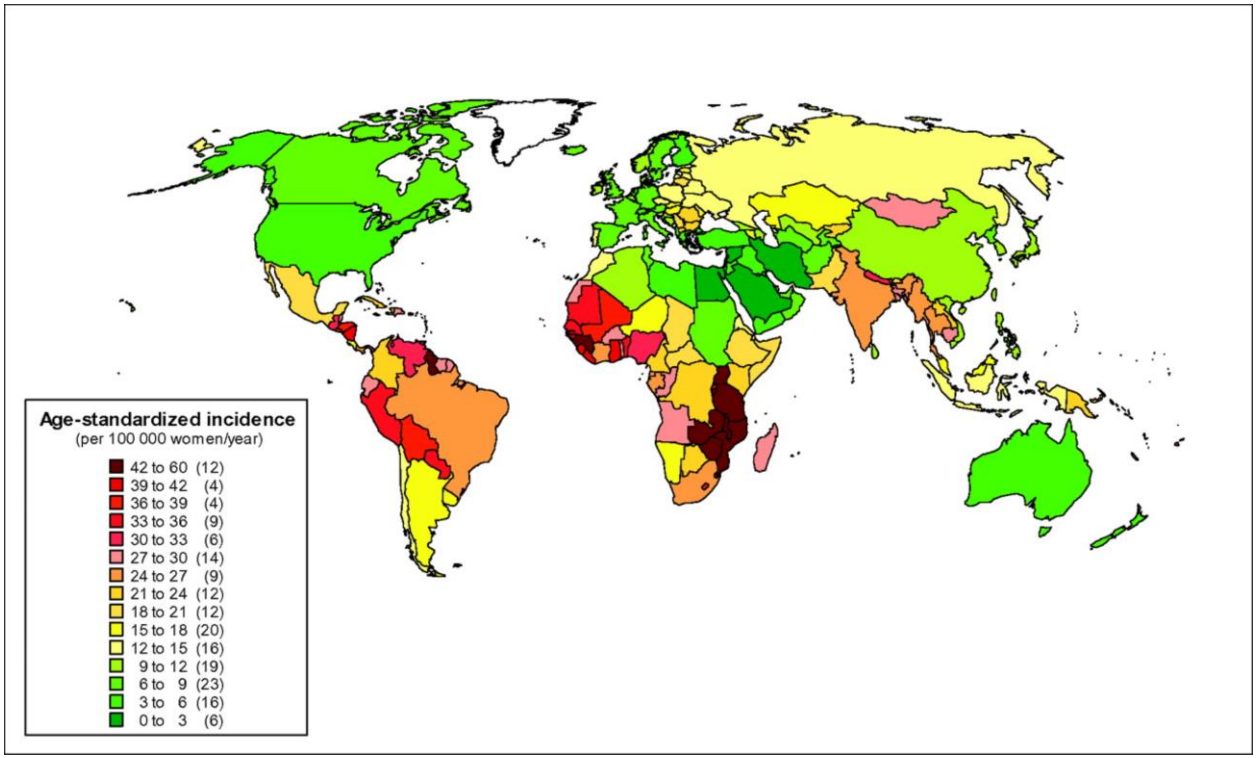
Epidemiology

- 12,990 cases expected in 2016
  - 7.7 per 100,000 women
- 4,120 deaths expected in 2016



Epidemiology- Global

- In 2015, 526, 000 women developed cervical cancer worldwide
- Cervical cancer caused 239, 000 deaths

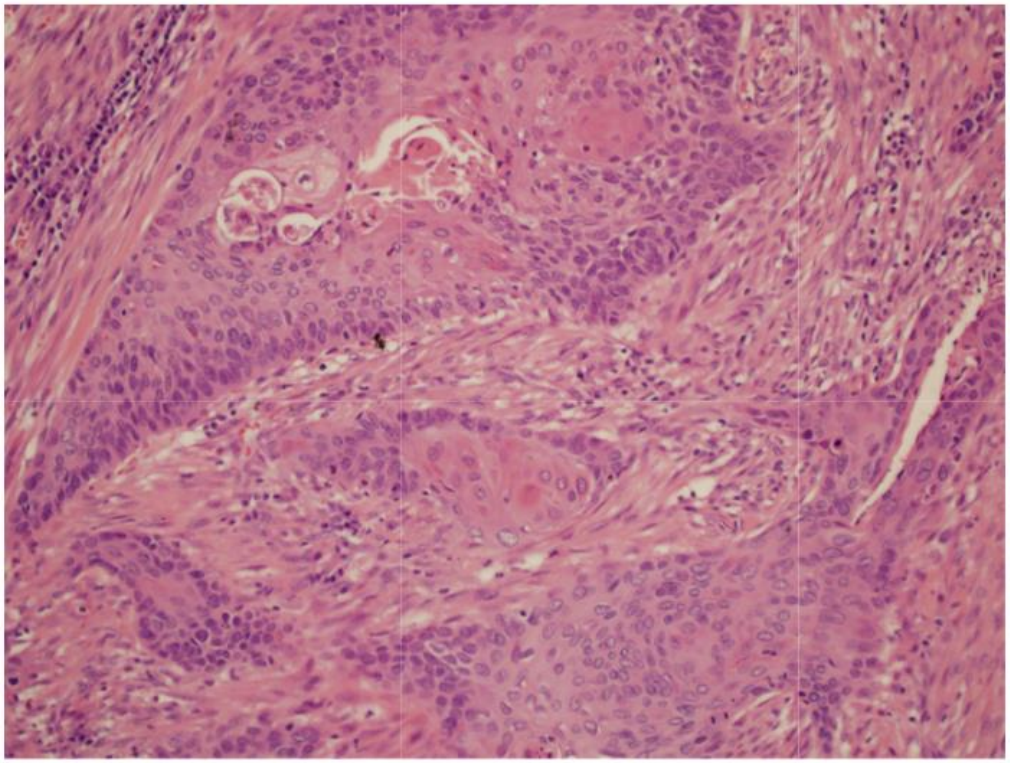


Epidemiology

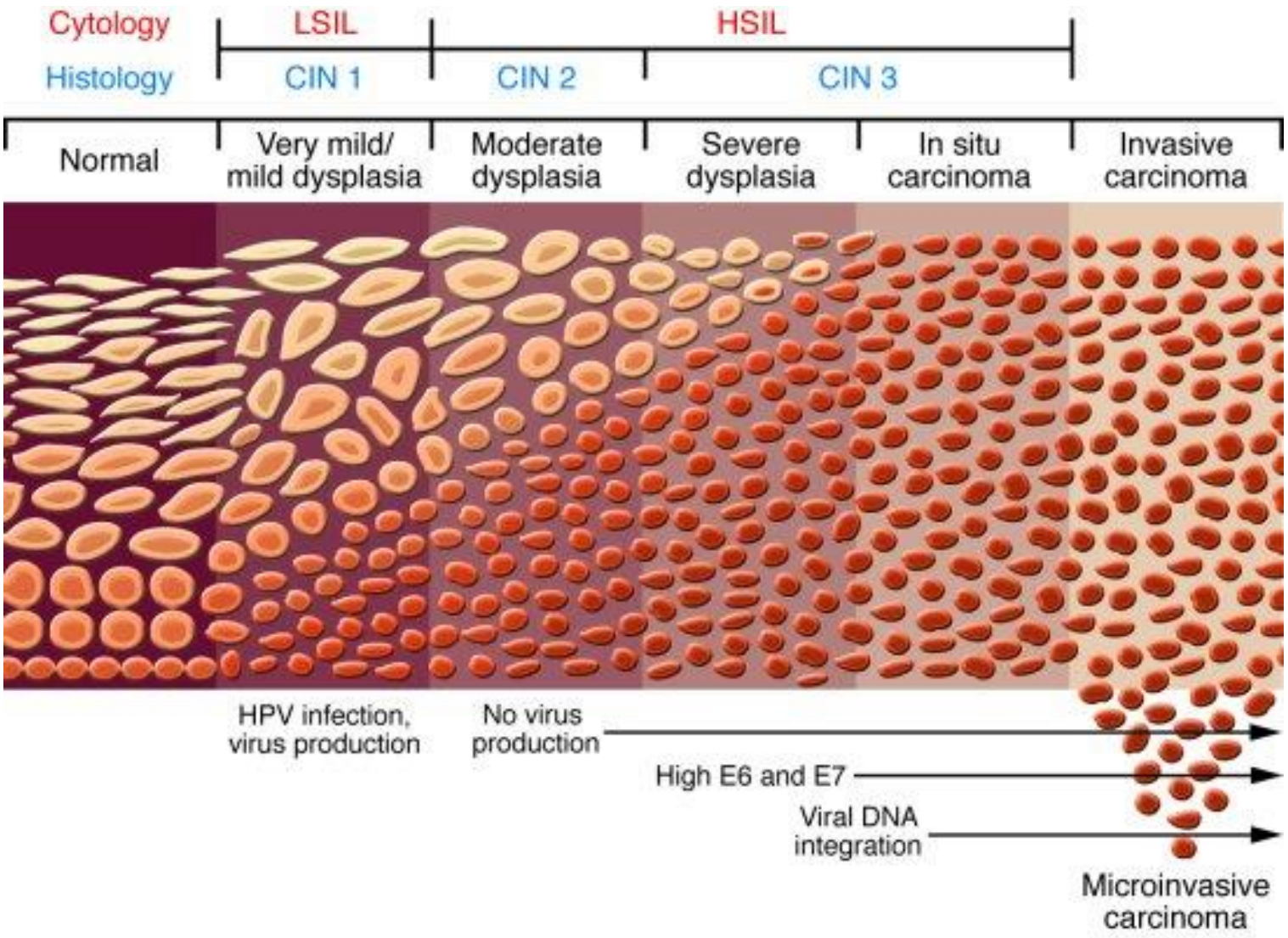
- HPV infection
- High parity
- Increased number of sexual partners
- Young age at time of first sexual intercourse
- Low socioeconomic status
- History of smoking
- Long-term use of oral contraceptives
- Physical inactivity

Histology

- Squamous
- Adenocarcinoma
- Rare histologies
  - Clear cell
  - Serous
  - Glassy Cell
  - Neuroendocrine
  - Mesenchymal tumors

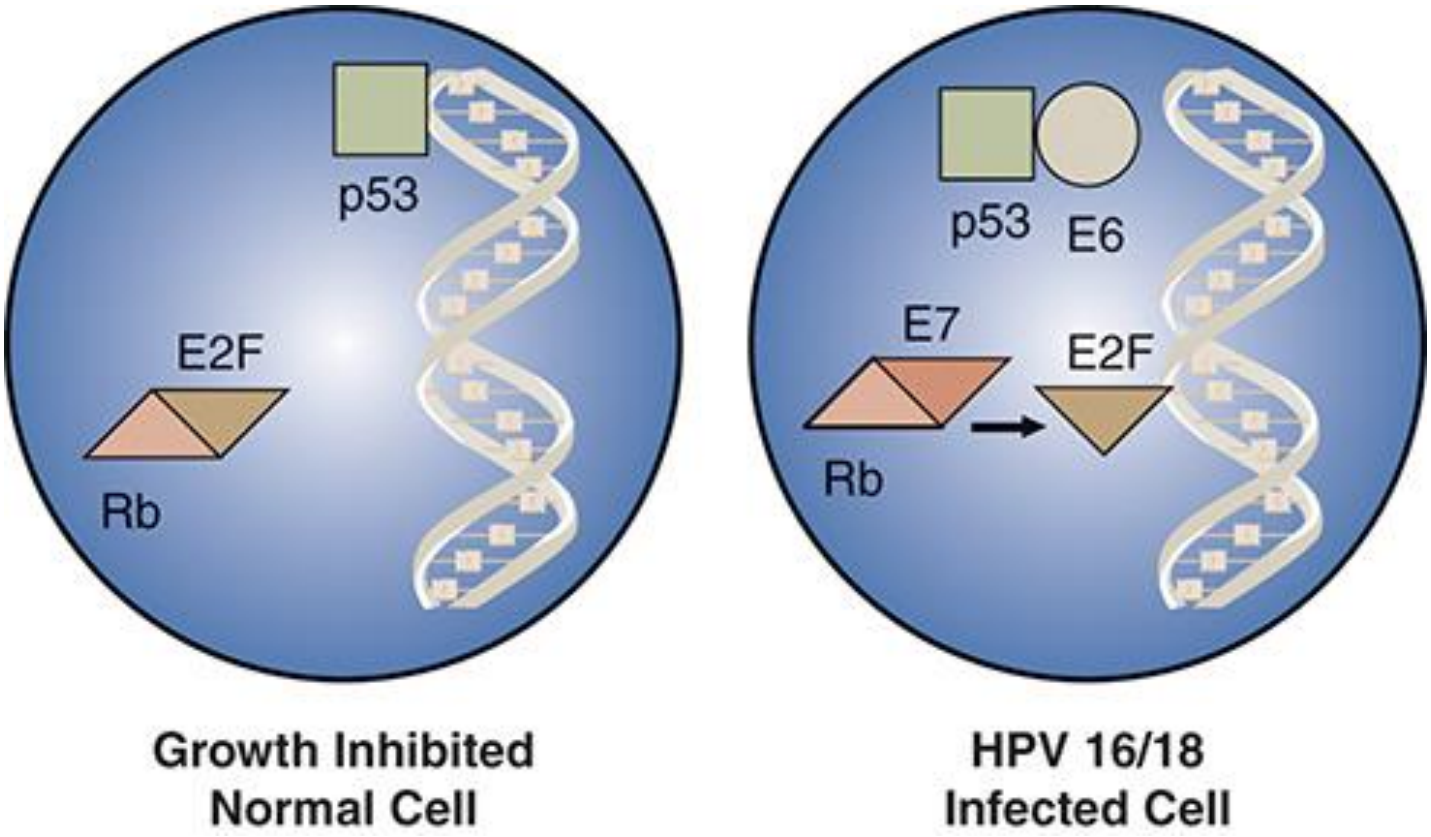


Pathogenesis



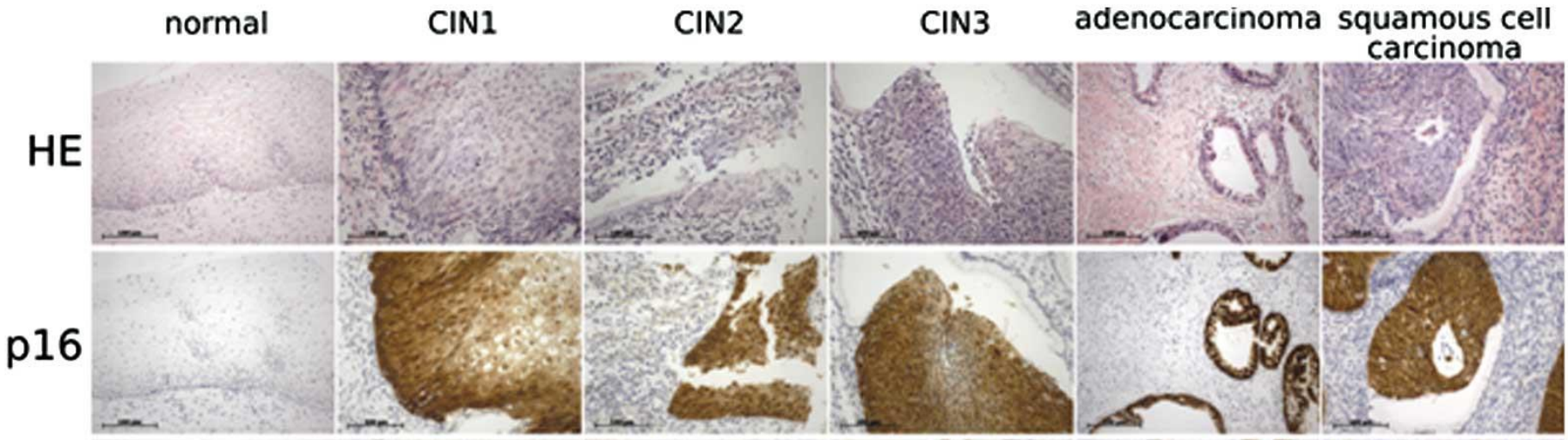
JCI.org

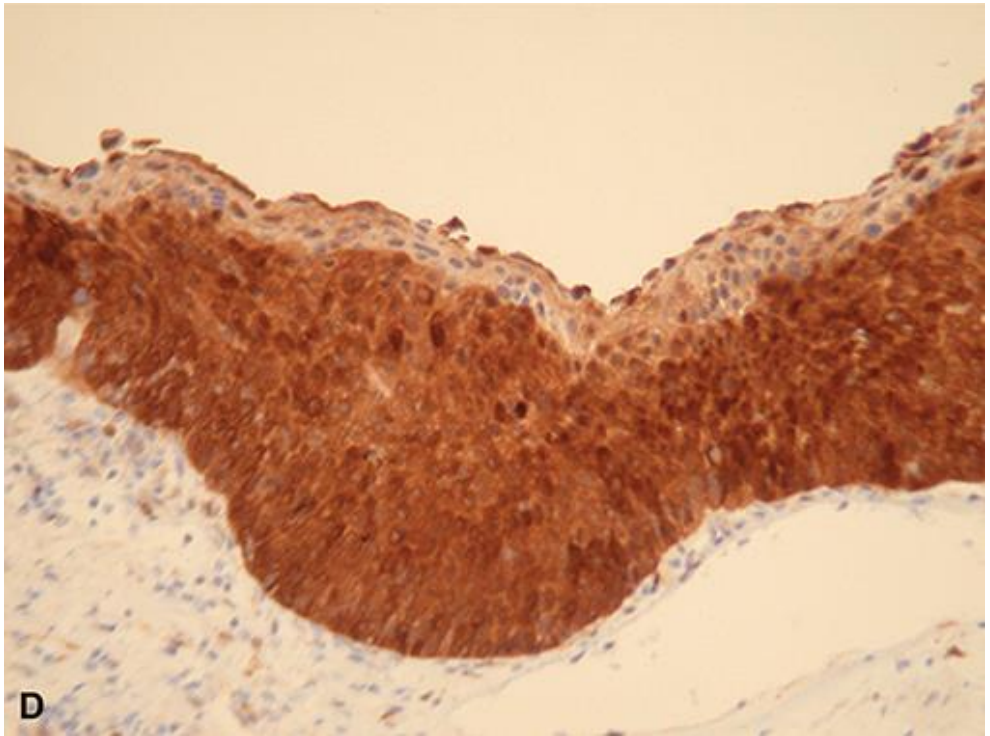
Pathogenesis- HPV



Pathogenesis- HPV

- Cervical cancers arise due to viral inactivation of TP53 and RB tumor suppressors by the HPV E6 and E7 oncoproteins
- TP53 inactivation → genomic instability→ secondary genetic alterations → intratumoral heterogeneity
- MYC and RAS play a significant role in cervical cancer
  - Mutant RAS genes are capable of cooperating with HPV in transforming cells
  - Overexpression of MYC has been demonstrated in one-third of early invasive carcinomas and some cervical intraepithelial neoplasia (CIN) 3 lesions
- CDK inhibitor p16 is strikingly upregulated in most cervical dysplasias and cancers


normal
CIN1
CIN2
CIN3
adenocarcinoma
squamous cell carcinoma
HE
p16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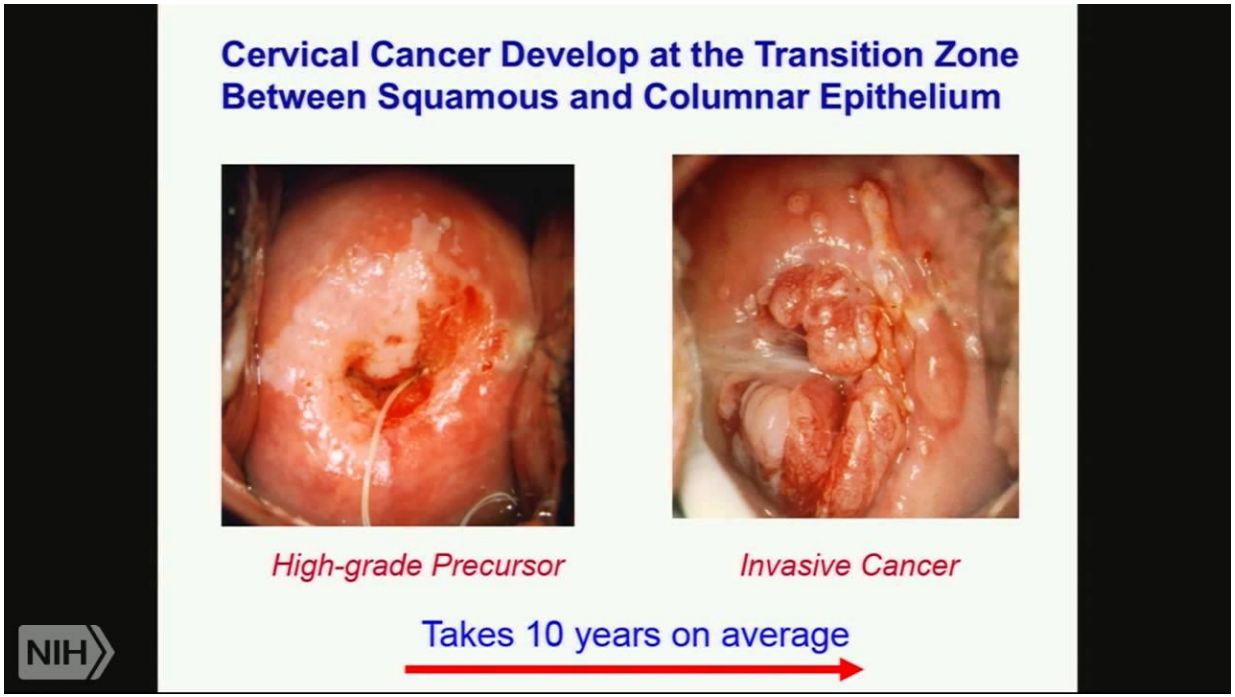
Clinical Presentation

- Post-coital bleeding
- Abnormal uterine bleeding
- Abnormal Pap smear
- Pelvic pain
- Flank pain
- Uncontrolled leakage of urine/stool from vagina

Diagnosis

- Pelvic examination/biopsies
- Cone biopsy
- Chest x-ray
- IVP
- Cystoscopy
- Proctoscopy



Staging

- Clinically staged
- PET CT often used in western countries but not available in the highest prevalence regions of the world

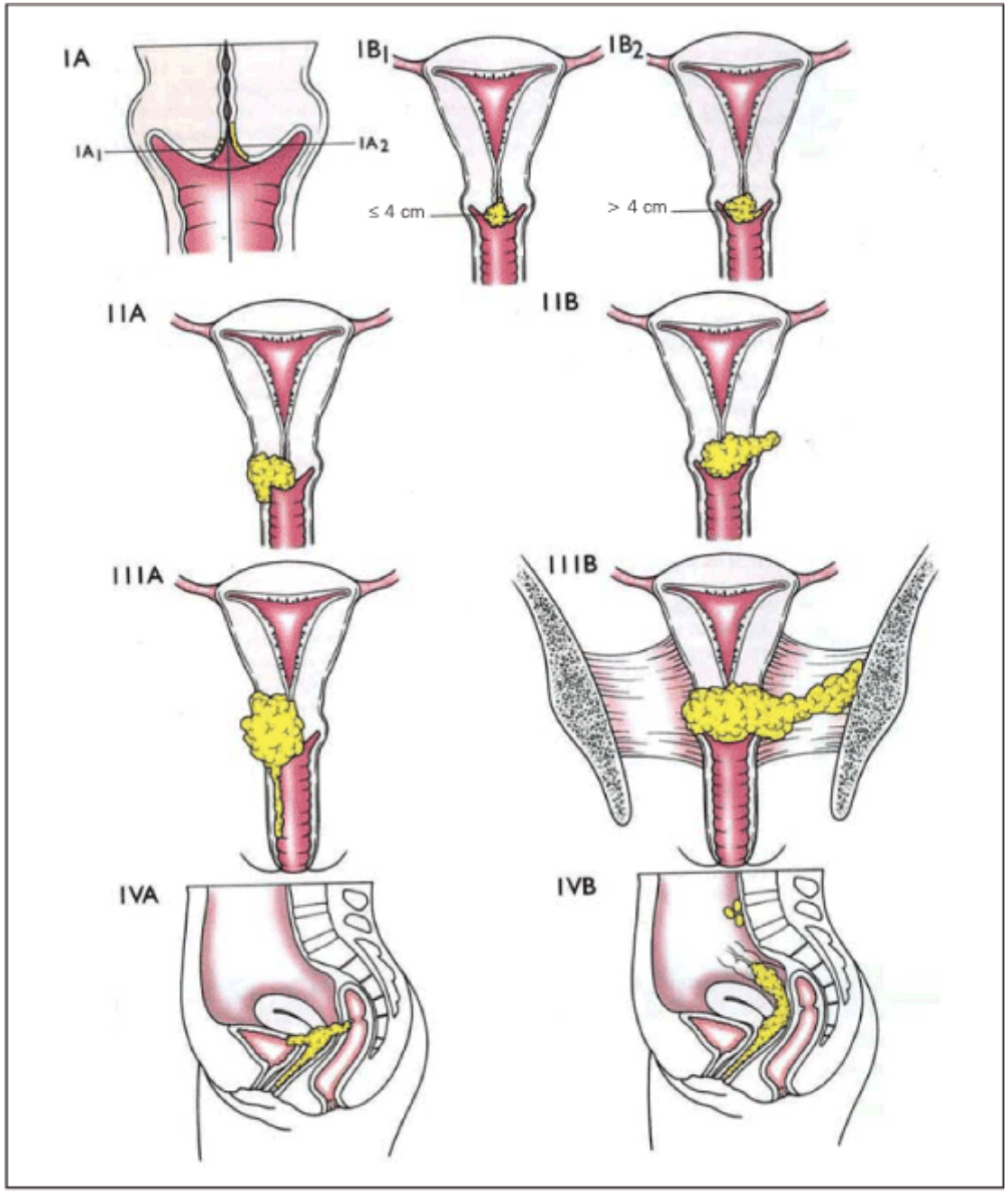


Figure 1. Staging of uterine cervix carcinoma according to FIGO[3].

http://dx.doi.org/10.1590/S0100-39842007000300014

Therapy

- Stage IA1 – Cone biopsy, hysterectomy
- Stage IA2 – modified radical hysterectomy
- Stage IB and IIA – radical hysterectomy OR pelvic RT
  - Add chemotherapy to RT in IB2 and IIA2
  - Can add to RT in IB1 and IIA1
- Stage IIB to IVA – pelvic RT with chemotherapy
- Stage IVB – systemic chemotherapy/clinical trials

Follow-up

- Psychosocial Support
- Routine exams
- Cytologic testing

Emerging Therapies

- Sentinel Node Mapping
- Fertility Preservation
- Targeted Therapies

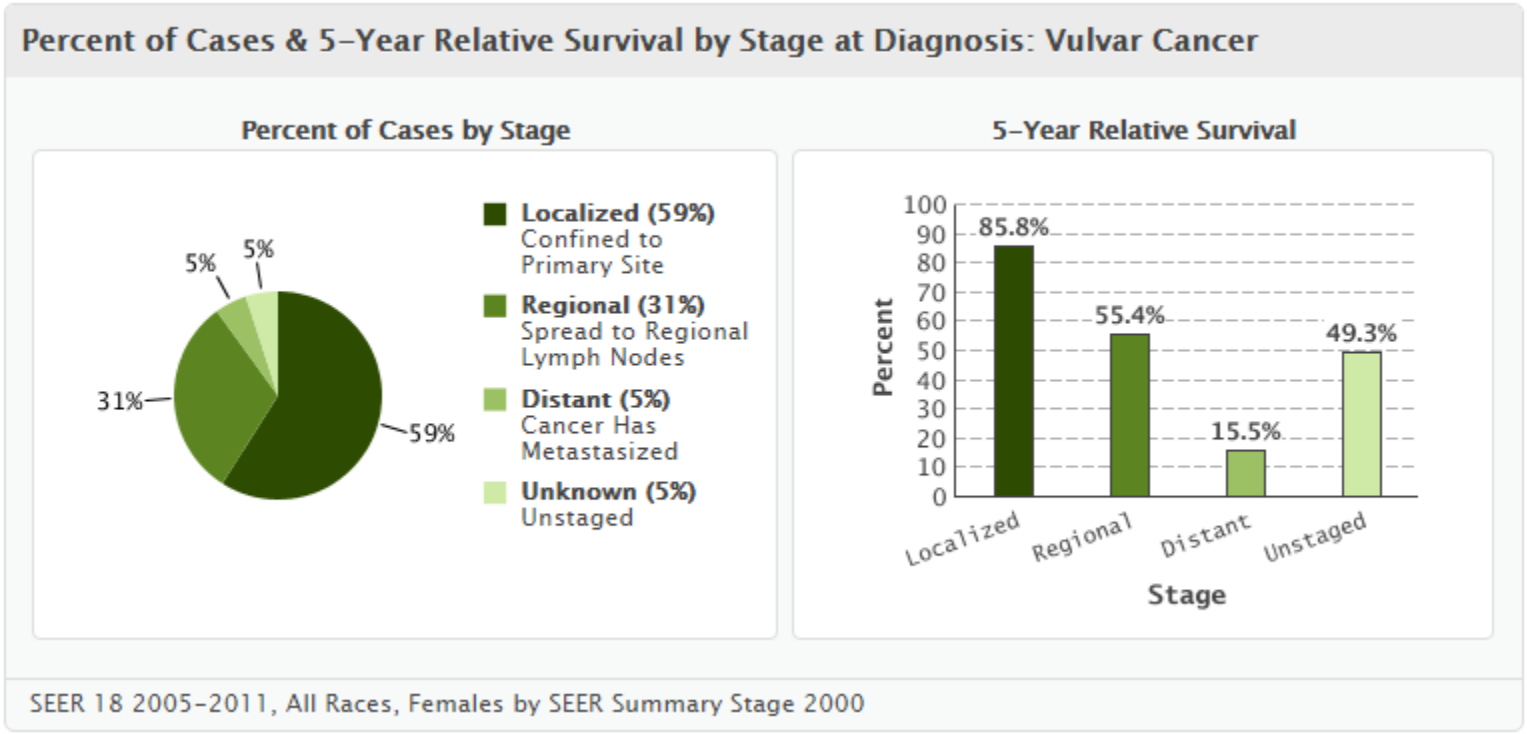
Vulvar Cancer

Vulvar Cancer

- Epidemiology and Risk Factors
- Histology
- Presentation / Diagnosis
- Staging
- Therapy
  - Early
  - Locally Advanced
  - Metastatic
- Follow-Up

Epidemiology

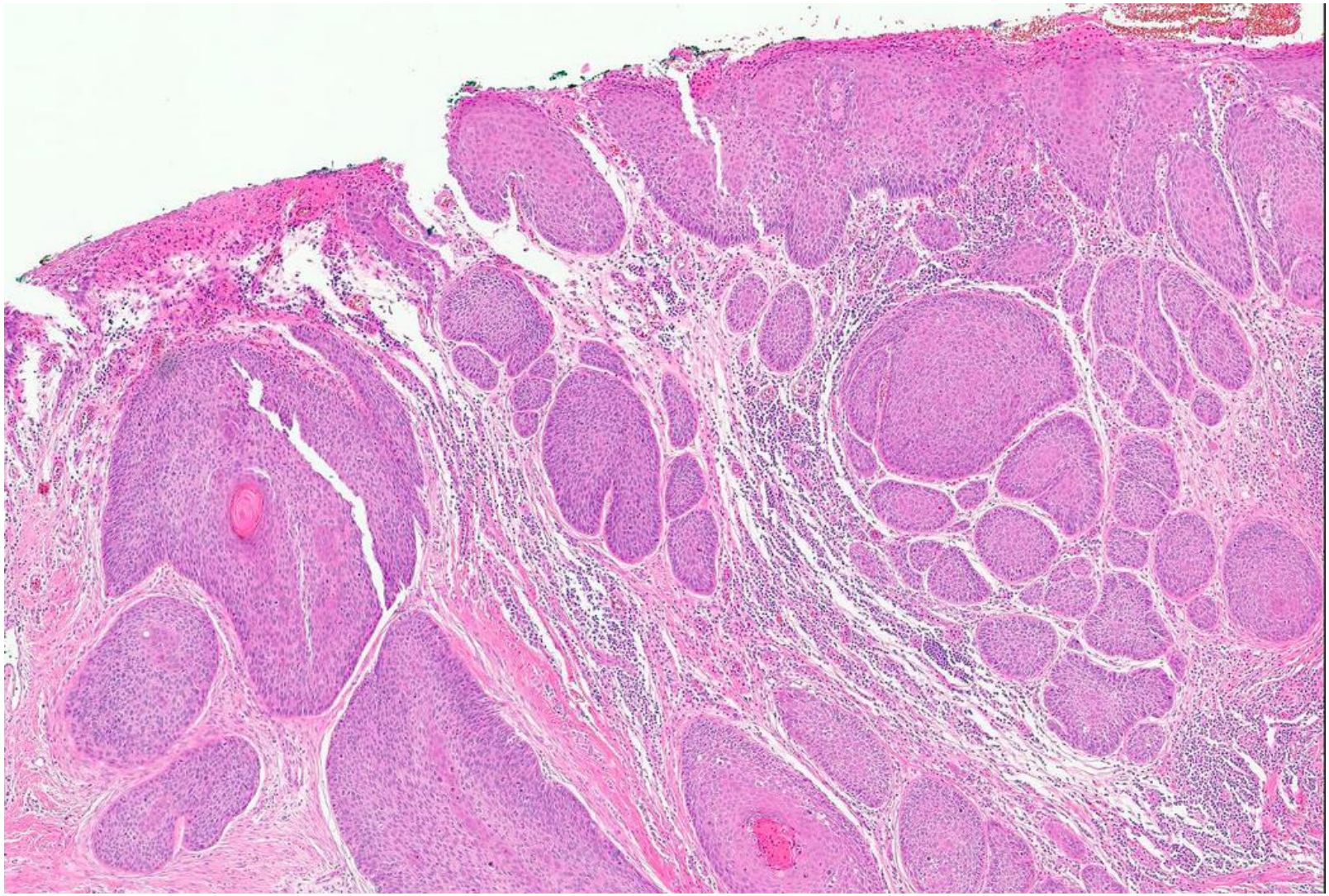
- 5,950 cases expected in 2016
- 1,110 deaths expected in 2016



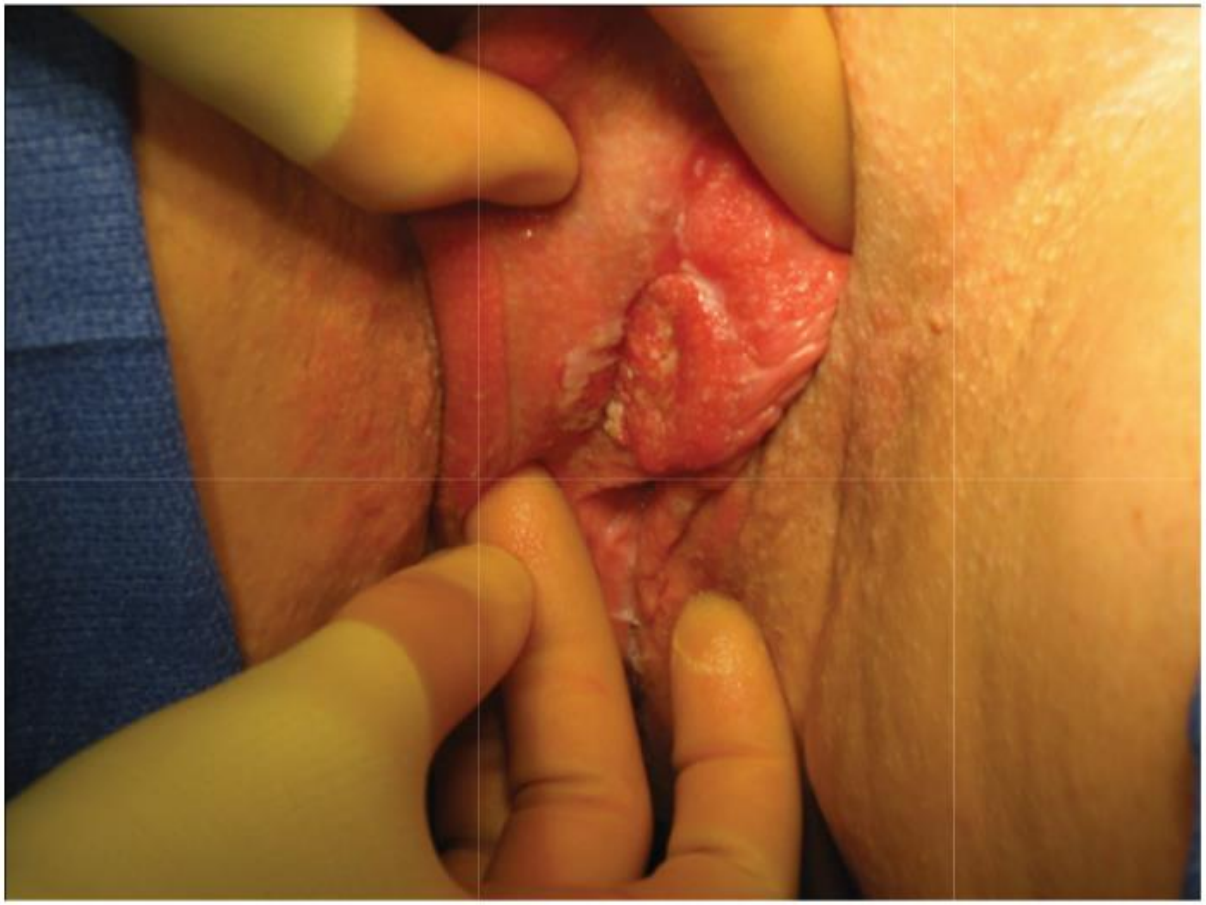
Epidemiology

- Condyloma
- History of squamous dysplasia
- HPV infection in basaloid or warty types
- Common risk factors with cervical cancer
  - Multiple sex partners
  - Early age at initiation of sexual intercourse
  - History of abnormal Pap smears
- HPV associated more common in women < 50 years
- Non-HPV is more common in older women

Histology



Presentation – Early disease



Persistent Irritation
Discoloration
Bleeding

Presentation – Late disease

Severe Pain
Bleeding
Pressure from enlarged masses
Foul odor
Disfigurement

Staging

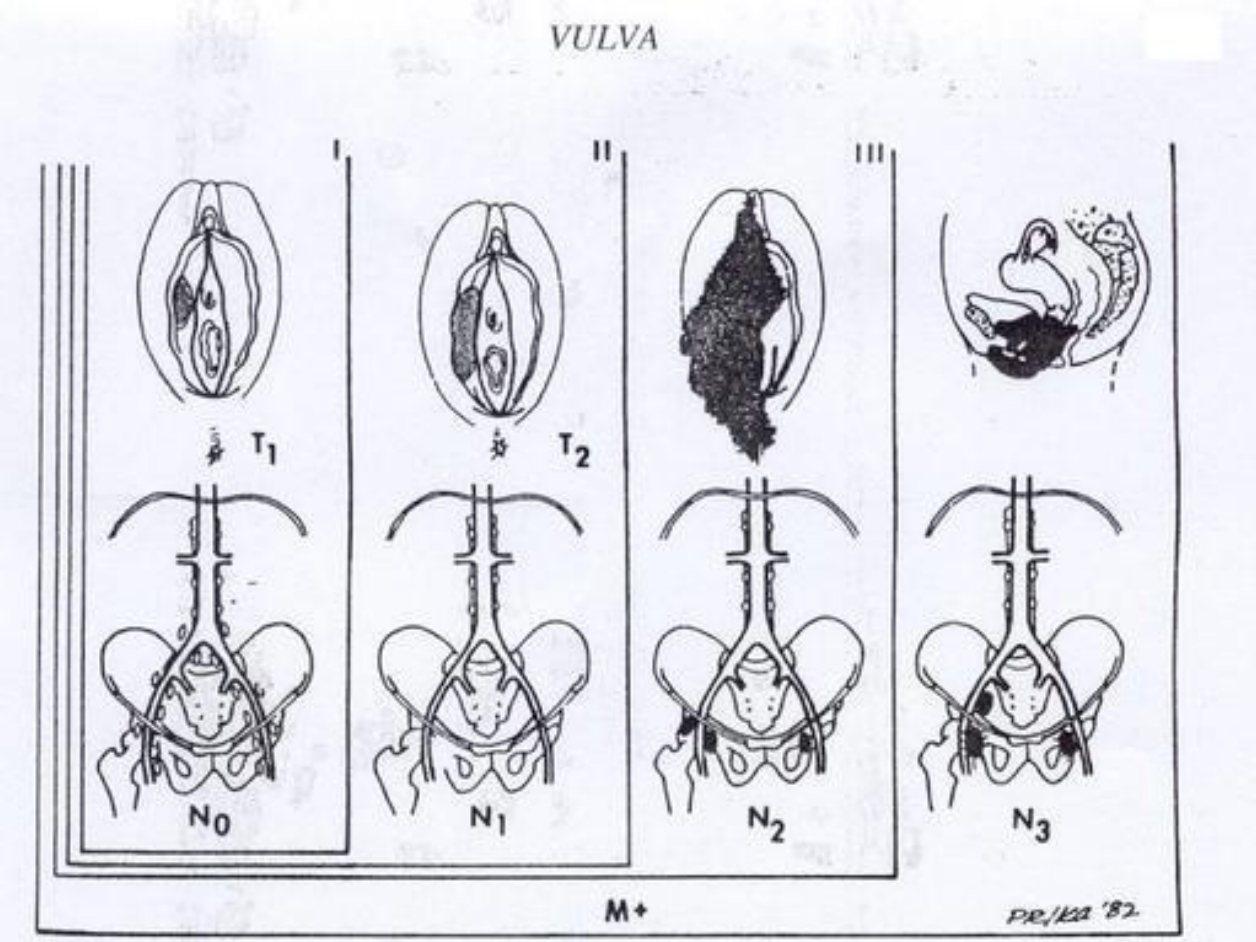


FIG. 50-2. Anatomic staging for vulva cancer. (From DuBeshter B, Lin J, Angel C, et al. Gynecologic tumors. In: Rubin P, ed. *Clinical oncology for physicians and medical students: a multidisciplinary approach*, 7th ed. Philadelphia: WB Saunders, 1993:363–418, with permission.)

Staging

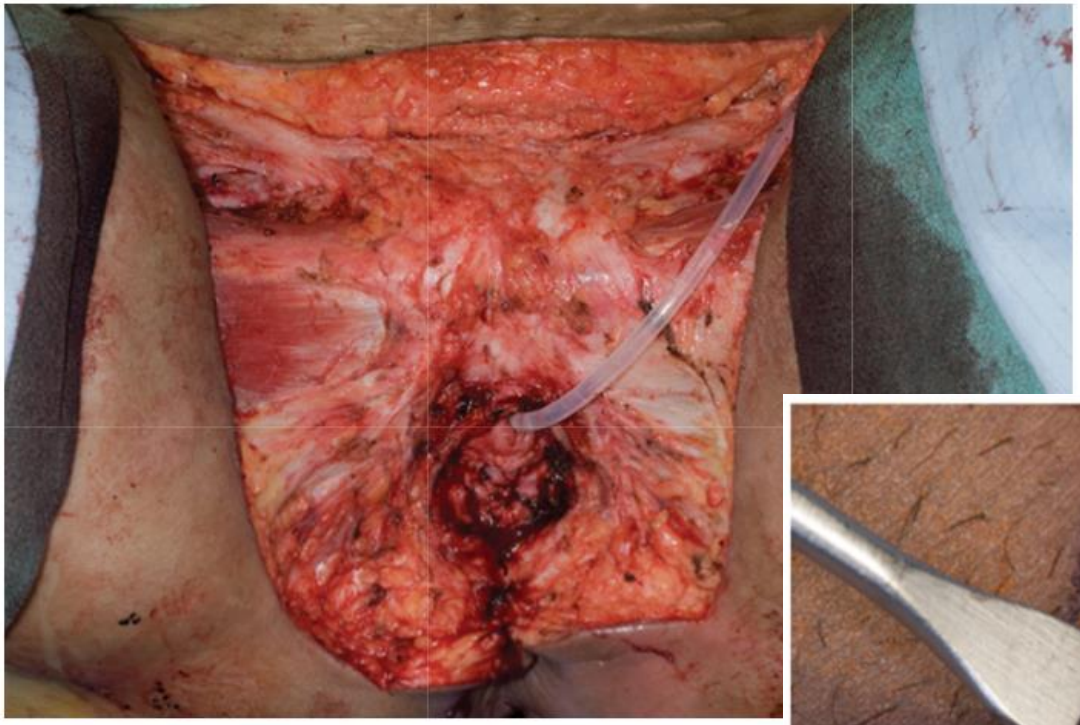
Table 19.2 Integrated 2009 FIGO and AJCC Staging System for Squamous Cell Carcinoma of the Vulva

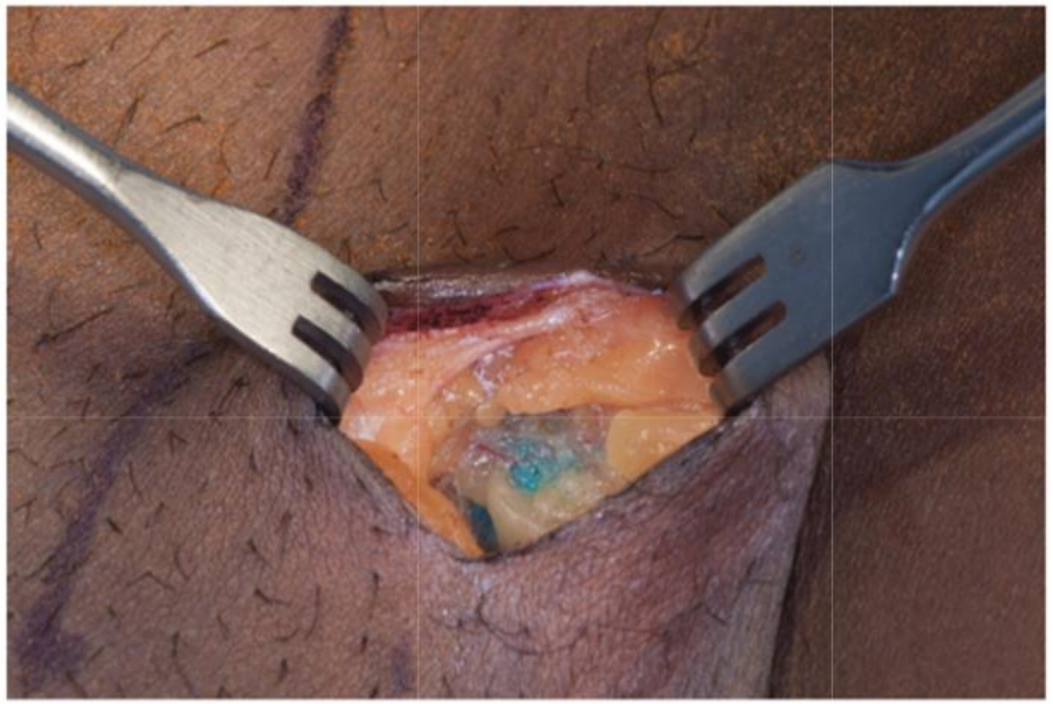
FIGO		AJCC		
		T	N	M
		Tis: No invasion past basement membrane (not in FIGO system)		
I: Tumor confined to the vulva				
IA	Lesions ≤ 2 cm in size, confined to vulva or perineum and with stromal invasion ≤ 1.0 mm, no nodal metastasis	T1a	N0	M0
IB	Lesions > 2 cm in size or with stromal invasion > 1.0 mm, confined to the vulva or perineum, with negative nodes	T1b	N0	M0
II	Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus), with negative nodes	T2	N0	M0
III	Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus), with positive inguinofemoral lymph nodes	T1 or T2	N1-N3	M0
IIIA	(i) 1–2 lymph node metastasis(es) (< 5 mm), or (ii) 1 lymph node metastasis (≥ 5 mm)	T1 or T2	N1a = (i) N1b = (ii)	M0
IIIB	(i) 3 or more lymph node metastases (< 5 mm) or (ii) 2 or more lymph node metastases (≥ 5 mm)	T1 or T2	N2a = (i) N2b = (ii)	M0
IIIC	Positive nodes with extracapsular spread	T1 or T2	N2c N3 = inguinal skin ulceration or fixed nodes	M0
IV	Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures	T3 = any size, involves upper urethra, bladder, rectum, bone		
IVA	Tumor invades: (i) upper urethral and / or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bode, or (ii) fixed or ulcerated inguinofemoral lymph nodes	T3		M0
IVB	Distant metastasis: includes pelvic nodes	T1, T2 or T3		M1

Therapy – Early

- Local excision (simple or radical)

Therapy – Locally Advanced





Therapy – Metastatic

- Systemic cytotoxic therapy is disappointing
- Targeted therapies are under development

Follow-up

- Psychosocial Support
- Routine exams

Summary

- Risk can be reduced by modifying risk factors
- Most cancers are responsive to front-line therapy
- Management of recurrent disease varies by site of origin/histology but is often sub-optimal
- More discoveries are needed to overcome these diseases