Cervical Cancer

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Outline

- Epidemiology, Prognosis and Risk Factors
- Diagnosis and Work Up, Staging
- Management
  - Early Stage
  - Advanced Stage
  - Recurrent Disease

Epidemiology and Risk Factors

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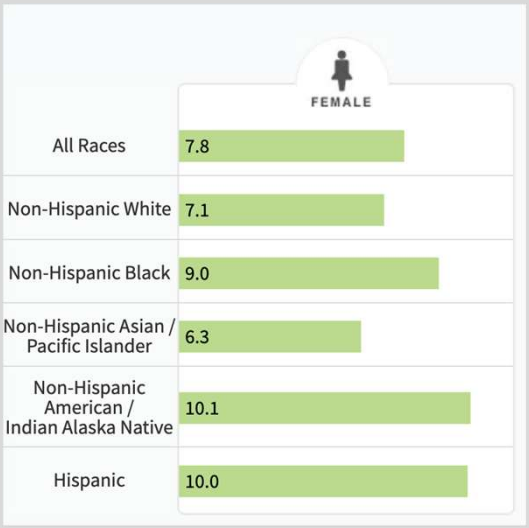
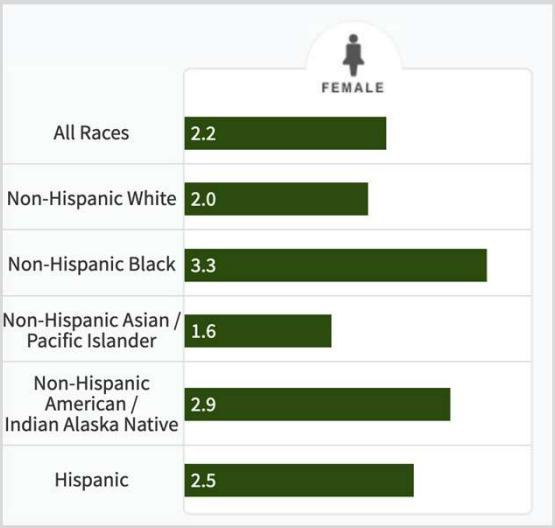
Epidemiology

- **United States**
  - #3 GYN cancer diagnosis and cause of death in U.S.
  - ~14000 cases annually and 4300 deaths annually
  - Median age of diagnosis is 50
- **World Wide**
  - #4 cause of cancer death in women worldwide, with 84% of cases diagnosed in resource-limited settings
  - #1 most common cancer in developing world

Race and Ethnic Disparities

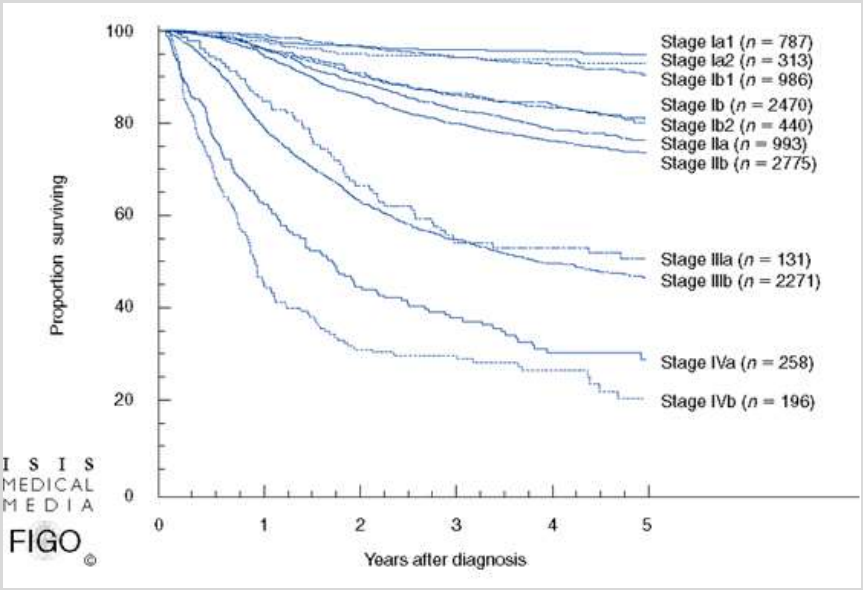




Incidence of diagnoses and deaths per 100,000 women in US from 2016-2020

SEER 2022

Prognosis by Stage



SEER Data 2022

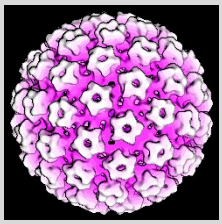
Risk Factors

- HPV infection (99.7% of Invasive Cervical Cancers)
- Environment – Developing countries ↑
- Habits – Tobacco ↑ (bigger RF for SCC)
- Race – Non-Caucasian ↑
- Sexual – Multiple partners ↑, early intercourse ↑
- Screening – Lack of any or recent Pap smear ↑
- Medications – Oral contraceptives ↑, DES
- Infectious – HPV ↑
- Immunosuppression – HIV, transplant
- DES (clear cell vaginal cancers, prescribed 1940-1971)

Pap Smear Guidelines

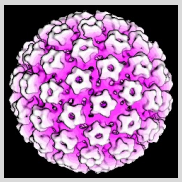
- Begin testing at age 21
- Age 21-29: Cytology alone q3 years (ACS recommends to begin age 25 with HPV screen alone)
- Age 30-65: Cytology + HPV q5 years (preferred), Primary HPV test (q5 years), Cytology q3 years

Human Papillomavirus



- Major role in cervical cancer (99.7%)
- **HPV 16 (SCC), HPV 18 (AC)**
  - Cause of 70% of cervical cancers worldwide
- 40+ HPV subtypes, 15 are oncogenic
  - 31, 33, 45, 52 and 58 cause additional 20%
- Non-enveloped DNA virus
- Minority of infections lead to cancer
- Promoters
  - Smoking
  - Immune suppression
  - Oral contraceptives

Human Papillomavirus



- 80% of adults will acquire HPV
  - Mostly transient
  - Virus alone is insufficient for carcinogenesis
- Steps in Carcinogenesis
  - Infection with oncogenic strain of the metaplastic epithelium at the cervical TZ
  - Persistence of HPV
  - Progression from persistent viral infection → precancer/dysplasia
  - Development of carcinoma → invasion through basement membrane

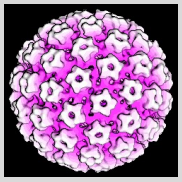
Question

- Contemporary estimate of time from HPV infection to development of invasive cancer?

Answer

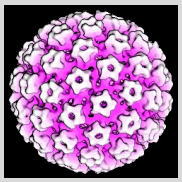
- Contemporary estimate of time from HPV infection to development of invasive cervical cancer?
  - ~15 years
  - **Opportunities for screening/vaccination**

HPV Clearance



- In women 15–25 years of age ~80% of HPV infections are transient.
  - Gradual development of cell-mediated immune response
- Incidence of HPV clearance – **70% in 1 year and 91% in 2 years**
  - Median duration of infection = 8 months
  - Certain HPV types are more likely to persist (HPV 16 and HPV 18)
- In immune-competent women CIN3 clears in **35%**

HPV Vaccination



- **Gardasil 9** – protects against HPV 6,11,16,18,31,33,45,52,58
  - Protects against most common viruses for invasive SCC and anogenital warts (90% HPV 6/11) – **97.4% efficacy**
  - Recommended 11-12 years, can be given as early as 9 years
    - Most effective in HPV naïve patients
  - Approved through age 45
  - Schedule:
    - 9-15 years: TWO doses - 0, 6-12 months later
    - 15 years or older: THREE doses – 0, 1-2 months, 6 months
    - Any immunocompromised patient: THREE doses – 0, 1-2 months, 6 months

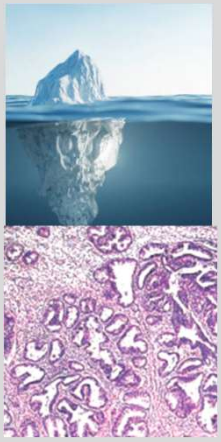
Diagnosis and Staging

Management of High Grade Cervical Dysplasia

- Colposcopy
- Biopsy a visible lesion or suspicious area
- Consider random (4 quadrant) biopsies
  - Detected 18-32% with CIN2+
- LEEP/Cold Knife Cone (CKC) if no suspicious areas or discrepancy
- If CIN3 on biopsy then CKC (or LEEP) + ECC
  - To rule out underlying invasion
  - To treat CIN3
- May be treated with a hysterectomy after ruling out invasive cancer

Management of Adenocarcinoma in Situ (AIS)

- Atypical glandular cells (AGC) is pap precursor – 3 to 4% will go on to have AIS, 1-2% invasive AC
- Increased risk for ”skip lesions” and higher endocervical lesions
- Median age = 38 years
- Treatment is traditionally hysterectomy after childbearing
- Conization alone is appropriate in selected situations (i.e. desires fertility, negative margins)
- 10-25% persistent disease with negative margins;
  - 2.5% AIS recurrence with negative margin, 20% with positive margin
  - 5% invasive cancer with positive margins, <0.1% if negative



Diagnosis

- Asymptomatic
  - Cervical cancer screening or during pelvic exam
- Symptomatic
  - Irregular/heavy bleeding
  - Postcoital bleeding
  - Pelvic pain/pressure
  - Bladder/bowel complaints
  - Flank pain, leg pain, leg swelling
- Pelvic exam +/- Colposcopy
  - Biopsy (diagnostic)
  - No pap for a cervical mass (screening test)
  - Masses may be exophytic, ulcerative, endophytic (endocervical canal, barrel shaped)

Histology

- **Squamous Cell Carcinoma** – 70%
  - HPV16 - 59%
  - HPV18 – 13%
- **Adenocarcinoma** – 25%
  - HPV16 – 36%
  - HPV18 – 38%
- **Other –** very rare
  - Adenosquamous
  - Neuroendocrine/small cell
  - Sarcomas
  - Lymphomas

Diagnostic Studies

- **Historical & Low Resource Settings**
  - IVP (evaluate for urinary obstruction)
  - CXR/skeletal radiographs for metastasis
  - EUA with cystoscopy, proctoscopy
- **Contemporary**
  - **FIGO 2018:** Clinical, surgical and radiographic staging permissable
  - **MRI pelvis** – tumor size, local extent, nodal metastasis
    - Surgical planning
    - Radiation planning (especially if concern for bladder/rectal involvement)
  - **PET** – nodal/distant metastasis
    - Decision for treatment

Staging

- **Stage I** – confined to cervix
- **Stage II** – beyond uterus but not to the side wall or lower vagina
- **Stage III** – spread within the pelvis
- **Stage IV** – invasion in the pelvis/distant mets
  - IVA – invasion of bowel/bladder mucosa
  - IVB – distant metastasis

Staging (FIGO 2018)

- **Stage I – confined to cervix**
  - IA – microscopic, max depth invasion 5mm
    - IAI – invasion <3mm
    - IA2 - invasion between 3-5mm
  - IB – lesion limited to cervix, >5mm invasion
    - IB1 – invasion >5mm, <2cm
    - IB2 – invasion >5mm, 2-4cm
    - IB3 – >4cm

Staging (FIGO 2018)

- **Stage II** – beyond uterus but not to the side wall or lower vagina
  - IIA1 – <4cm
  - IIA2 - >4cm
  - IIB – parametrial involvement
- **Stage III** – spread within the pelvis
  - IIIA – lower third vagina
  - IIIB – pelvic side wall/hydronephrosis
  - IIIC – pelvic (IIIC1) or para-aortic LN (IIIC2)

Patterns of Spread, Nodal Metastasis

- **Direct Extension**
- **Hematogenous/Lymphatic**
  - Ovarian metastasis – SCC: 0.5%, AC 2%
  - Risk of nodal metastasis
    - Increasing depth of invasion (DOI)
    - Increasing stage
      - IA1: 2.1%
      - IA2: 3.9%
    - LVSI
      - Stage I with LVSI – 9.3% vs. 1.7% without
    - Tumor size

Management of Early Stage Cervical Cancer

Important Questions?

- Radiation versus hysterectomy?
- What type of hysterectomy? Radical vs. Simple?
- Who may preserve fertility?
- Who needs treatment after hysterectomy?

Hysterectomy Types

- **Type I:** Simple Hysterectomy
- **Type II**: Modified Radical Hysterectomy
  - Uterine artery: at ureter
  - Uterosacral: ½ between sacrum/sidewall
  - Vagina: upper 1/3
- **Type III:** Radical Hysterectomy
  - Uterine artery: at origin from superior vesical/internal iliac
  - Uterosacral: at sacrum/sidewall
  - Vagina: upper 1/2

Important Considerations

- Factors Associated with Recurrence (**GOG49**)
  - Lymph node metastasis
  - Depth of invasion of tumor
  - Parametrial involvement
  - Served as basis for radical hysterectomy to clear parametrial disease
- Newer data evaluated risk of LN mets and parametrial involvement
  - <2cm tumor, no LVSI, SCC or Adenocarcinoma histology → 1% risk of parametrial involvement
  - Served as basis for thought that a less radical approach could be considered

LANDONI Trial (1997)

- RCT evaluating Radical Hysterectomy (experimental, n=172) vs. Radiation (control, n=171) for Stage IB vs. IIA cervical cancer
  - Adjuvant RT given for those with high risk factors (Stage IIA+, + lymph nodes)
  - Radiation (external beam, 47Gy with brachytherapy; total dose 70-90Gy)
- Primary endpoint: 5 year OS
- **Results**:
  - 5 year OS: 83% for surgery vs. 83% for RT (NS)
  - 5 year disease free survival: 74% for surgery vs. 74% for RT (NS)
  - Severe morbidity: 28% for surgery vs. 12% for RT (p=0.0004)
  - Urologic complications: ~20% in the RH arm and 10% in radiation arm

Landoni, Lancet, 1997

SHAPE Trial

- Multicenter, non-inferiority RCT comparing radical hysterectomy (type II)(n=350) vs. simple hysterectomy (n=350) including LN assessment in patients with early stage cervical cancer
- Inclusion criteria:
  - Tumor size <2cm
  - Depth of invasion <10mm (surgical specimen) or <50% (on MRI)
  - Squamous cell carcinoma, adenocarcinoma, adenosquamous, any grade
  - LVSI was permitted
- Primary outcome: pelvic recurrence at 3 years

Plante, NEJM, 2024

SHAPE Trial

- **Primary outcome**: Pelvic Recurrence
  - 2.52% for simple hysterectomy vs. 2.17% for radical hysterectomy
- **Secondary outcomes**
  - Intra-op surgical complications: 7.1% for SH vs. 6.4% for RH
  - Bladder injury: 0.9% for SH vs. 2.6% for RH
  - Surgical related AE: 42.6% for SH vs. 50.6% for RH (p=0.04)
  - Urinary retention: 0.6% for SH vs. 9-11% for RH (p<0.001)

Plante, NEJM, 2024

CONCERV Trial

- **Goal:** Evaluate feasibility and oncologic outcomes of conservative surgery in early stage low-risk patients
- **Design**: single arm study
- **Primary endpoint:**
  - 2 year cumulative incidence of recurrence
  - Immediate failure rate (residual disease in hysterectomy)
- **Inclusion criteria:**
  - Stage IA2-IB1
  - Squamous cell carcinoma (any grade), adenocarcinoma (G1,2)
  - Tumor size <2cm
  - No LVSI
  - Depth of invasion <10mm
  - Negative imaging
  - Negative conization margins

Plante, NEJM, 2024

CONCERV Trial

- 100 patients
  - Fertility preservation: conization + pelvic lymph node assessment (n=44)
  - No fertility preservation desires: simple hysterectomy with pelvic lymph node assessment (n=40)
  - Inadvertent hysterectomy: pelvic lymph node dissection only (n=16)
- **Results**
  - Positive lymph nodes = 5%
  - Immediate failure rate = 2.5%
  - 2 year recurrence = 3.5%

Plante, NEJM, 2024

Summary of Recommendations

- **If surgical candidate:**
- **Stage IA1, no LVSI:** Simple hysterectomy, no lymph node assessment
- **Stage IA1, + LVSI:** Simple hysterectomy with pelvic lymph node assessment
- **Stage IA2 – IB2** (meets conservative surgery guidelines)
  - Fertility desired: Conization + pelvic lymph nodes assessment
  - Fertility not desired: Simple hysterectomy + pelvic lymph node assessment
- **Stage IA2, IB2** (not meeting conservative guidelines): Radical hysterectomy, pelvic lymph node assessment
- **If not surgical candidate** --> EBRT

NCCN January 2023

LACC Trial

- Objective to evaluate open versus minimally invasive surgery
- International P3 RCT with stage IA1 with LVSI, IA2, IB1 SCC/AC/AS cervical cancer randomized to
  - Open RH (n=312)
  - MIS RH (n=319) – 84% had laparoscopy
- Results
  - Lower DFS (3 years: 97% vs. 91.2%, HR 3.7)
  - Lower OS (3 years: 99% vs. 93.8%, HR = 6)
  - Outcomes regardless of tumor size, LVSI, histology, BMI, stage, LN involvement

NEJM, Ramirez, 2018

Post-op Adjuvant Treatment

- **Intermediate Risk** - negative nodes, negative margins, negative parametrium
  - Sedlis Criteria (GOG92)
    - Depth of invasion
    - Tumor size
    - LVSI
  - EBRT +/- cisplatin
- **High Risk** - positive nodes OR positive margins OR positive parametrium
  - Peter's Criteria
  - EBRT + VBT with cisplatin

Intermediate Risk (Sedlis' Criteria)	High Risk (Peters' Criteria)
LVSI plus deep stromal invasion (outer third)	Positive surgical margins
LVSI plus middle stromal invasion (one-third) and tumor size ≥ 2 cm	Detection of pathologically-confirmed lymph node metastases
LVSI plus superficial stromal invasion (inner third) and tumor size ≥ 5 cm	Extension into the parametrial tissue
No LVSI but deep or middle stromal invasion and tumor size ≥ 4 cm	

Summary

- **If Primary treatment is surgery**
  - **Low-risk**: Observation
  - **Intermediate-risk**: Pelvic EBRT +/- cisplatin
  - **High-risk:** Pelvic EBRT + cisplatin
- **If Primary treatment is radiation**
  - EBRT + cisplatin (weekly during radiation)

Fertility Sparing Management

- **Radical trachelectomy and lymph node dissection**
- 10-15% of all cervical cancers occur in women during reproductive years
- Variety of techniques published (vaginal, open, MIS)
- Generally must have:
  - Desire for fertility preservation
  - Small (less than 2 cm) tumor
  - Negative LVSI
  - No evidence lymph node metastasis
  - No upper endocervical involvement (ECC)
  - SCC histology, less data on AC or rarer histologies

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Locally Advanced Cervical Cancer

Stage IIA1/2- IVA

- **External beam radiation therapy with weekly cisplatin**
  - 25-28 treatments, M-F x 5 weeks
  - 4500-5040cGy
  - Covers LN, tumor, parametrium +/- extended field for aortic LN
  - Weekly cisplatin 40mg/m2
  - Completion time matters…. >56 days worsens OS
  - Cisplatin is a radiosensitizer
- **Brachytherapy**
- Total point A dose = 80-90Gy
  - 2cm above os, 2cm lateral in plane of the “tandem”

INTERLACE Trial

- **Hypothesis**: adding induction chemotherapy before cis/RT improves PFS/OS.
- **Inclusion**: FIGO2008, 1B1 (+ nodes), IB2, IIA, IIB, IIIB, IVA cervical cancer without para-aortic LN involvement
- **Primary endpoint:** PFS/OS
- **Experimental Arms**
  - Induction Chemo: Carbo AUC 2, Taxol 80 weekly x 6 weeks and then standard chemoRT (n=250)
  - Standard: Cis 40mg/m2 with EBRT + Brachy for total dose of 78-86 Gy (n=250)

INTERLACE Trial

Outcome	Induction Chemo + Chemoradiotherapy	Chemoradiotherapy Alone	p-value	Hazard Ratio (HR)
5-year Progression-free Survival (PFS)	72%	64%	0.013	0.65 (95% CI 0.46–0.91)
5-year Overall Survival (OS)	80%	72%	0.015	0.60 (95% CI 0.40–0.91)
Grade 3 or greater adverse events	147 (59%)	120 (48%)	-	-
Haematological toxicities	74 (30%)	32 (13%)	-	-

KEYNOTE A18

- **Hypothesis**: adding Pembro to CisRT improves PFS/OS in high-risk locally advanced CC vs. cisRT alone.
- **Inclusion criteria:** FIGO2014 IB2-IIB2 with node positive disease or stage III-IVA.
- **Primary Endpoint:** PFS, OS
- **Experimental Arms**
  - Pembro + CisRT: Pembro 200 q3 weeks during chemoRT and then 400mg q6 weeks x 15 cycles
  - Standard Cis/EBRT

KEYNOTE A18

Endpoint	Pembrolizumab + CRT	Placebo + CRT	Hazard Ratio (HR)	p-value
24-month PFS	68%	57%	HR 0.70 (0.55–0.89)	0.0020
36-month OS	82.6% (95% CI 78.4–86.1)	74.8% (95% CI 70.1–78.8)	HR 0.67 (0.50–0.90)	0.0040
Median OS	Not reached	Not reached		
Grade 3+ Adverse Events	78%	70%		

Summary

- **If Primary treatment is surgery**
  - **Low-risk**: Observation
  - **Intermediate-risk**: Pelvic EBRT +/- cisplatin
  - **High-risk:** Pelvic EBRT + cisplatin
- **If Primary treatment is radiation**
  - EBRT + cisplatin (weekly during radiation)

Management of Recurrent Disease

Recurrent Disease

- **Central pelvic recurrence**
  - Potential for cure
  - Pelvic exenteration – Overall survival 50%
- **All others (including Stage IVB)**
  - Treatment to palliate symptoms
  - Chemotherapy
  - Radiation for palliation of pain
  - Surgery in very selected group
  - Clinical trials

Chemotherapy for IVB/Recurrent Disease

- **1st Line Therapy – KEYNOTE 826**
  - Cisplatin + Paclitaxel
    - If prior cisplatin, can give Carboplatin
  - +/- Bevacizumab (Avastin) – mAb against VEGF (blocks blood vessels)
  - +/- Pembrolizumab (Keytruda) – immunotherapy, anti-PD-1 inhibitor
    - 88% patients PD-L1 positive
    - FDA approved in PD-L1+ pts

Tisotumab Vedotin

- **Population** = Recurrent/metastatic cervical cancer after disease progression to SOC chemo/immunotherapy
- **Experimental Arm** = Tisotumab Vedotin (2.0mg/kg q3 weeks)
- **Control:** Investigators choice = Topotecan, Vinorelbine, Gemcitabine, Irinotecan, Pemetrexed

Metric	Tisotumab Vedotin	Chemotherapy	P-Value	Hazard Ratio
Median Overall Survival (OS)	11.5 mths (9.8 to 14.9)	9.5 mths (7.9 to 10.7)	0.004	0.70 (0.54 to 0.89)
Median Progression-Free Survival (PFS)	4.2 mths (4.0 to 4.4)	2.9 mths (2.6 to 3.1)	<0.001	0.67 (0.54 to 0.82)
Confirmed Objective Response Rate (ORR)	17.8% (13.3 to 23.1)	5.2% (2.8 to 8.8)	<0.001	Odds ratio, 4.0 (2.1 to 7.6)

Tisotumab Vedotin

Antibody drug conjugate (ADC) targeting Tissue Factor with MMAE (Auristatin derivate, microtubule disrupting agent) payload

Tisotumab Vedotin

- **Tisotumab Vedotin:**
  - Grade ≥3 adverse events: 52.0%
  - Most common adverse events: nausea (33.2%), conjunctivitis (31.2%), peripheral sensory neuropathy (28.4%)
- **Chemotherapy:**
  - Grade ≥3 adverse events: 62.3%
  - Most common adverse events: nausea (40.2%), anemia (52.3%), neutropenia (22.6%)