



# **Quarterly Webinar Series: Cervical Cancer**

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# Biography

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- ▶ MA, Harvard University
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# Cervical Cancer: Prevention, Screening and Treatment

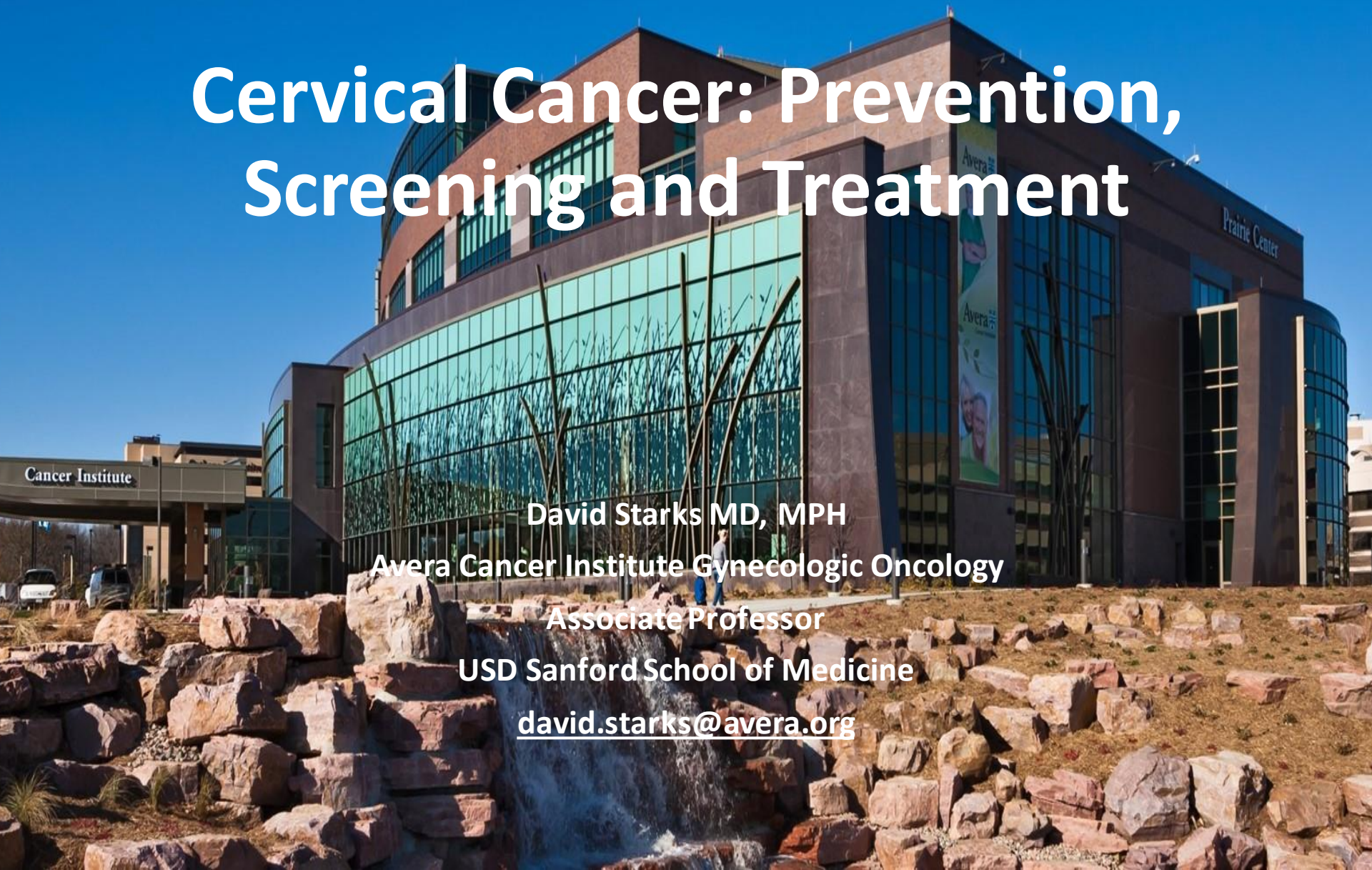
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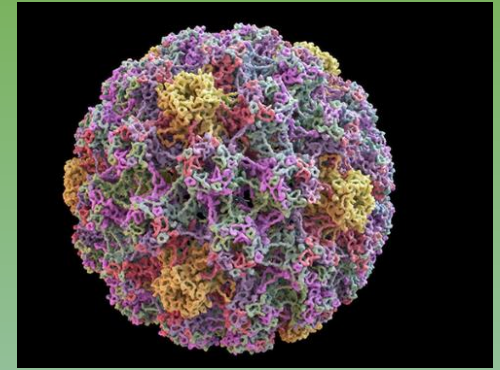
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# Epidemiology

- 13,960 new cases of cervix cancer in US in 2019
- 4,310 deaths from cervix cancer
- Rates are decreasing in the US and resource rich nations
  - Due to success of Pap based screening programs
  - Incidence remains high in Black, Hispanic/Latino, Asian, Native American populations
- Rates are increasing globally
  - 4<sup>th</sup> most common cancer of women worldwide (breast, colon, lung)
  - 604,000 new cases and 342,000 deaths/year
  - Failed/inadequate screening programs, lack of access to treatment
  - HPV vaccine offers hope for decreasing global incidence

# HPV



- Human Papilloma Virus

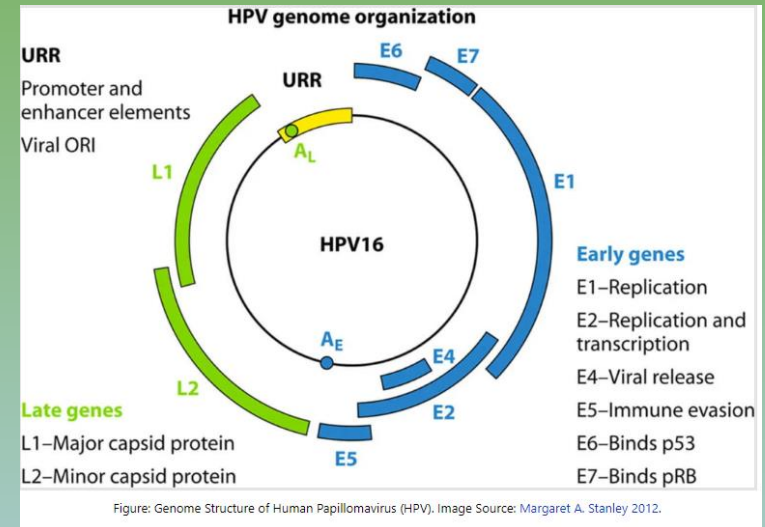
- Small, circular double stranded DNA virus
- HPV genome integrates into the host cell's DNA leading to genomic instability and malignant progression
- More than 100 different types
  - 15 Oncogenic types: HPV 16 (most frequent, squamous & adenocarcinoma), 18 (20-25%, adenocarcinoma), 31, 45, etc...
  - Low risk: HPV 6, 11. Associated with condyloma (genital warts)

- Persistence of HPV infection → cervical cancer

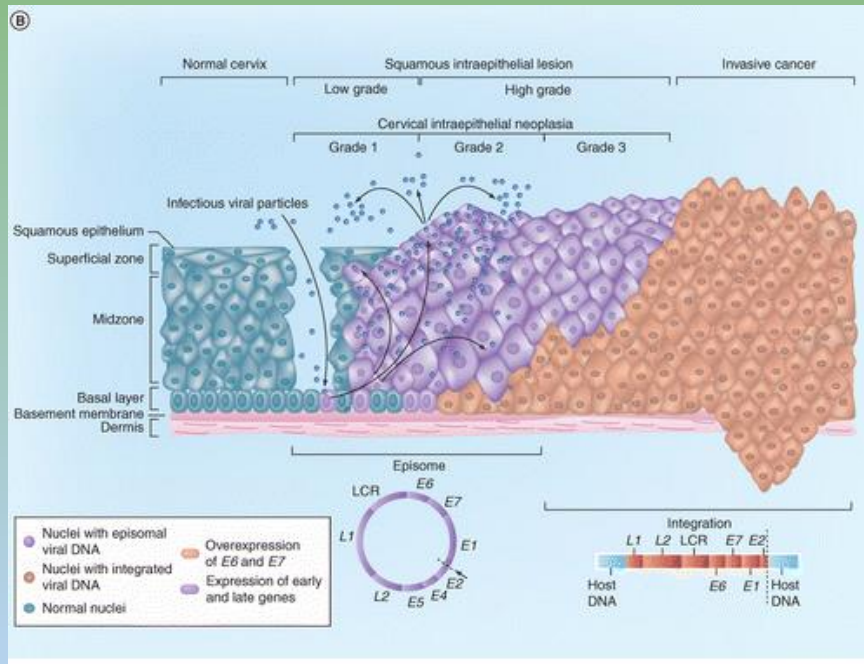
- HPV also implicated in vaginal, vulvar, anal, head and neck cancers
- Majority of women exposed to HPV, most will clear infection within 2 years
- If unable to clear the infection, progression to CIN will occur
  - Approximately 10 years from transmission to precancerous lesions.

# HPV and Cancer

- 4 steps
- 1) Infection of metaplastic epithelium
- 2) Viral persistence
  - HPV type is strongest factor; HPV 16.
- 3) Progression to pre-cancer (CIN 3)
  - HPV is necessary precursor
  - CIN3 has same aneuploidy DNA content and genetic instability as invasive cancer
  - Associated risk factors: tobacco use, host immunosuppression, multiparity, age at 1<sup>st</sup> full term pregnancy, use of oral contraception
- 4) Invasion

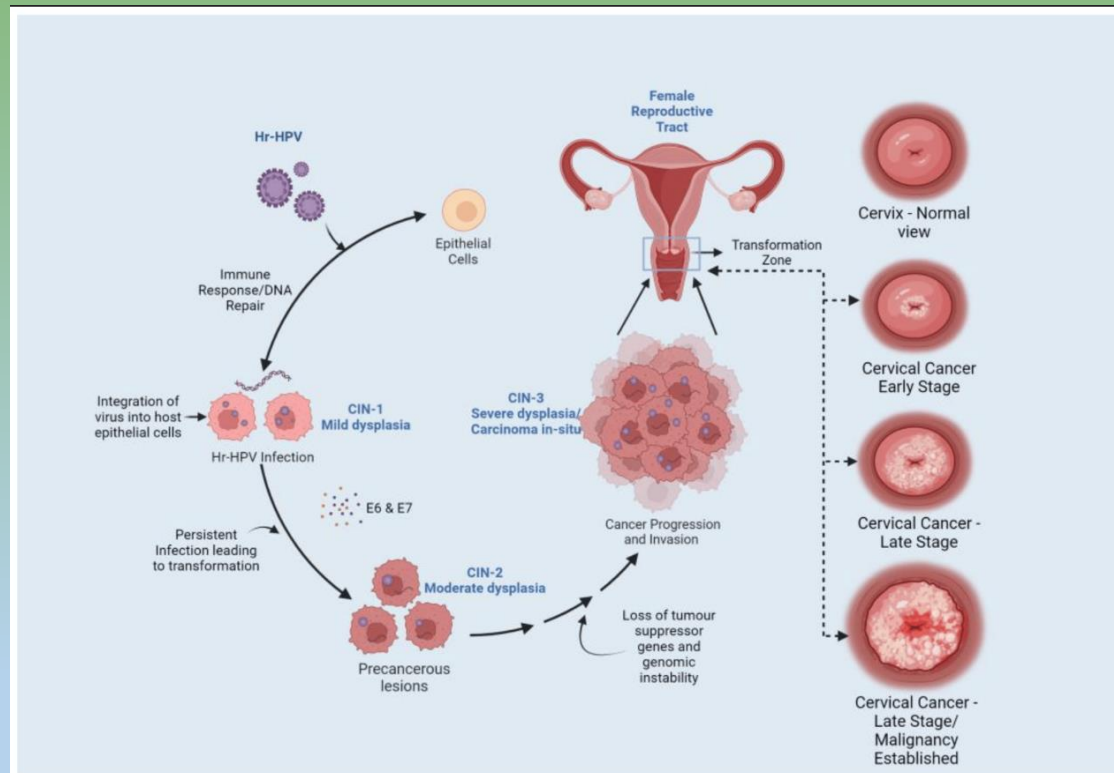


# HPV and Cancer



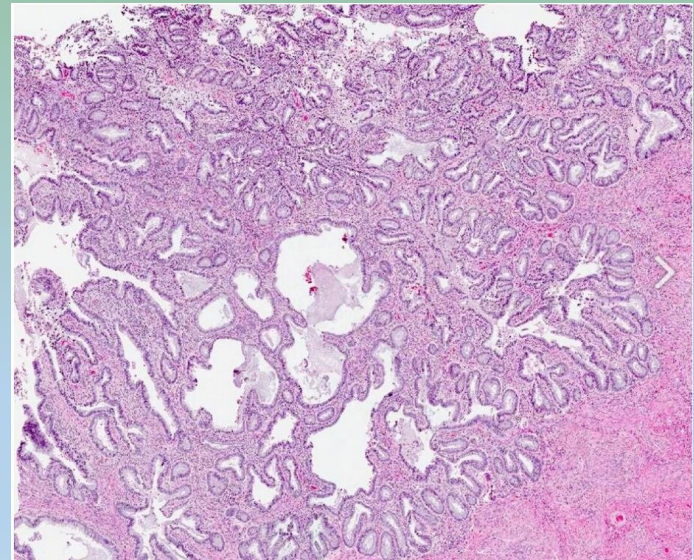
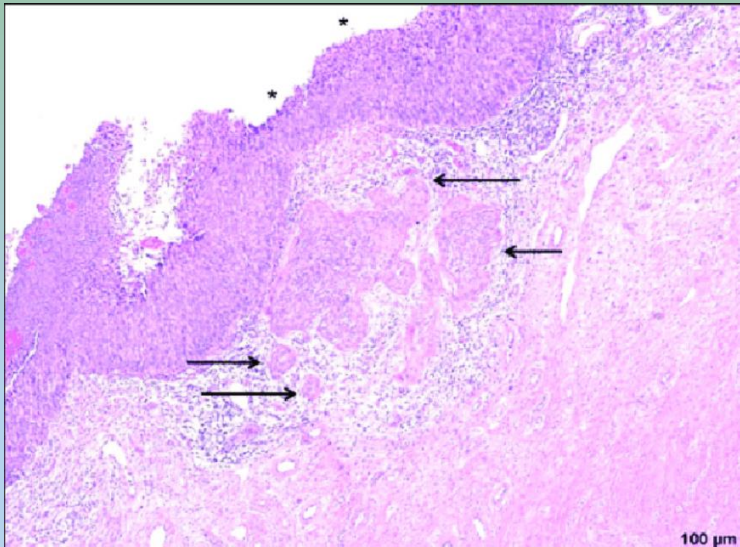
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# HPV and Cancer



# Cervix Cancer Histology

- Squamous Cell Carcinoma (80%)
- Adenocarcinoma (20%)
- Incidence increasing, especially in younger patients



# Screening

- Decreased incidence and mortality in the developed world due to primary prevention with HPV vaccination and secondary prevention with screening.
- Screening detects precursor lesions (CIN) which can allow for treatment and prevent development of invasive cancer
- Screening must achieve balance
  - Benefits of early detection (decrease in incidence and mortality)
  - Risks of false positive and unnecessary procedures
- Still debates about who should be screened, screening intervals, best testing methods

# Screening

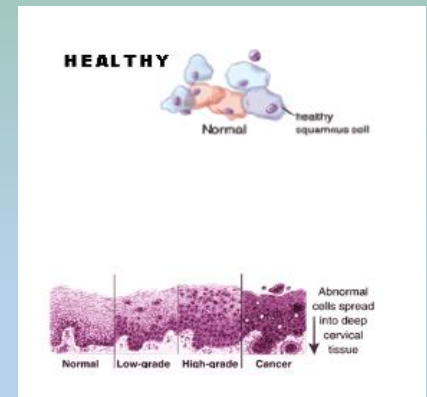
- **Benefits**

- Mortality reduction

- In US, cervix cancer mortality has decreased since the 1970s
    - *Incidence has decreased by 70%*

- Cervical disease detection and incidence

- Decreasing incidence of cervix cancer
    - Associated with higher cure rates of invasive cervix cancer



# Screening

- **Pap alone**

- Cytology every 3 years looking for cell abnormalities

- **Primary HPV testing**

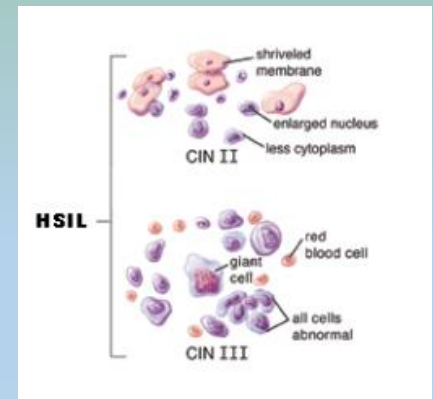
- Test for HPV without cytology every 5 years. (Australia, Netherlands, UK)
  - May ultimately be paired with self-sampling devices

- **Co-testing**

- Pap and HPV testing performed every 5 years.

- **Reflex HPV testing**

- HPV testing performed on abnormal Paps only.



# Screening

- **Age <21:** no screening advised, regardless of age of initiation of sexual activity
  - **Harm>benefit** due to low incidence and high rate of spontaneous immunologic clearance of virus
- **Age 21-29:** can start at age 21 with Pap alone every 3 years (USPSTF guidelines) or age 25 with primary HPV testing every 5 yrs (ACS guidelines)
- **Age 30-65:** Primary HPV testing every 5 years v Co-testing every 5 years v Pap alone every 3 years.
- **Age >65:** can consider stopping screening if adequate screening over lifetime.

Moscicki AB et al., Regression of low grade squamous intra-epithelial lesions in young women. Lancet 2004;364:1678.

Curry SJ. Screening for cervical cancer: United States Preventative Services Task Force recommendations statement. JAMA 2018;320:674.

Fontham ETH, et al., Cervical cancer screening for individuals at average risk:2020 guideline update from the American Cancer Society. CA Cancer J Clin 2020.

# Vaccination

- Gardasil 9 targets HPV types 6,11,16,18,31,33,45,52,58
- Protects females and males from oropharyngeal, vulvar, vaginal cervical, penile and anal cancers
  - 9 valent also protects against genital warts
  - HPV burden of disease is lower in males, vaccinating males provides population benefit from herd immunity
- **Individuals <26 yrs**
  - 11-12 years old, can start as early as age 9.
  - <15 yrs get 2 dose series 6 mo apart. >15 yrs get 3 dose series 0, 1, 6 months.
- **Individuals >26 yrs**, some exceptions...(health care workers, no prior vaccination with no prior sexual experience, etc)
- Not a treatment for HPV infection, existing genital warts or AIN present.
  - Does not impact cervical cancer screening recommendations

# Cervical Cancer Diagnosis

- **Symptoms**

- Asymptomatic until advanced, especially in non-sexually active women
- Vaginal bleeding, post-coital bleeding
- Large tumors → watery vaginal discharge, pelvic pain or pressure, passing urine or stool from vagina (fistula)

- **Signs**

- Speculum: cervix mass, although if in the endocervix, may appear grossly normal
  - Vaginal mass
- Enlarged liver, palpable supraclavicular nodes or groin nodes

# Cervical Cancer Diagnosis

- **Cytology**

- Pap may show malignant cells in background of blood, inflammatory cells, and necrotic cells
- May have a false negative rate of 50% in women with invasive cancer

- **Biopsy**

- Any visible mass or lesion should be biopsied. If an endocervical curettage (ECC) can be performed, may rule out adenocarcinoma.
- If no visible lesion, may need colposcopy or cold knife cone biopsy of cervix
  - Adenocarcinoma may be in the canal and not visible

# Cervical Cancer Diagnosis

- **Classically Clinically Staged**

- Most global patients are treated with radiation therapy
- Exam under anesthesia, physical exam, cystoscopy, proctoscopy, chest x-ray

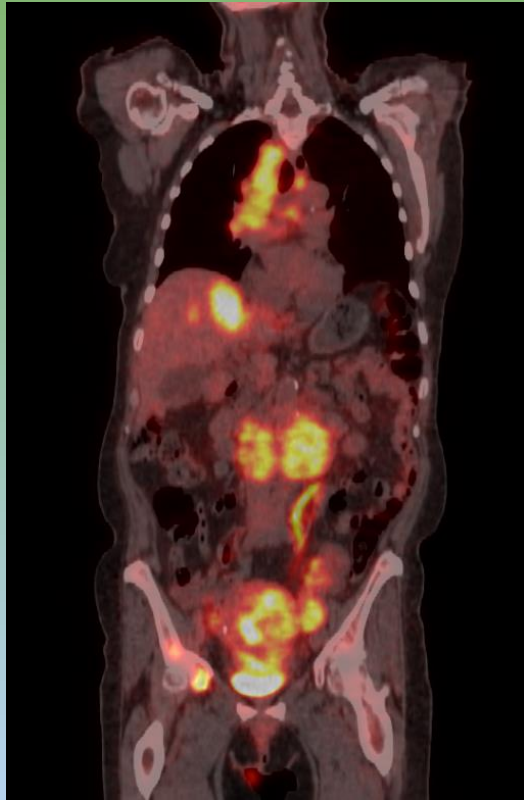
- **Imaging**

- **PET/CT**

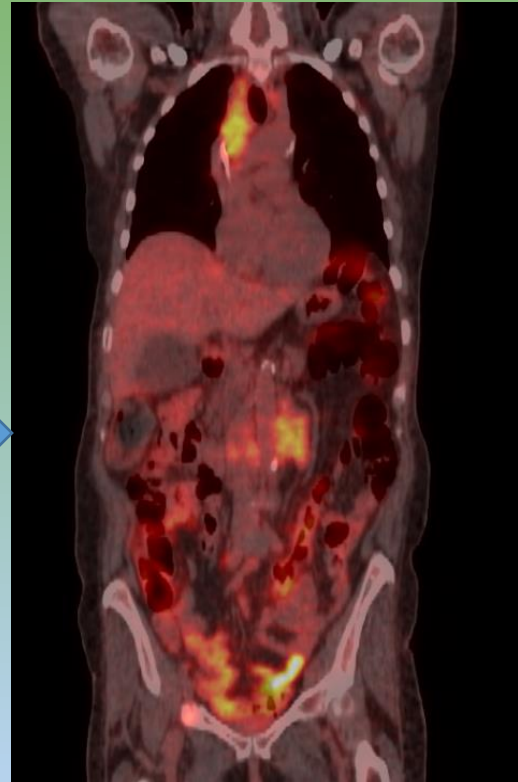
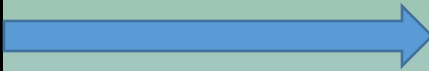
- For evaluation of distant metastasis, lymph node involvement, etc.
- Uses radionuclide-labeled analogue of glucose to identify sites of increased glycolysis
  - Sensitivity of 96% and Specificity of 95%.

- **MRI**

- For local evaluation of pelvis, lymph nodes, uterus, cervix, vagina and parametria
- Helps to determine tumor size, depth of invasion, vaginal involvement, uterine involvement, parametrial involvement, lymph node involvement
  - Accuracy of 90% for stage of disease vs 65% for CT scan.



Stage IV cervix cancer at presentation



After 6 cycles of chemotherapy/immunotherapy

# Cervix Cancer Treatment (Early Stage)

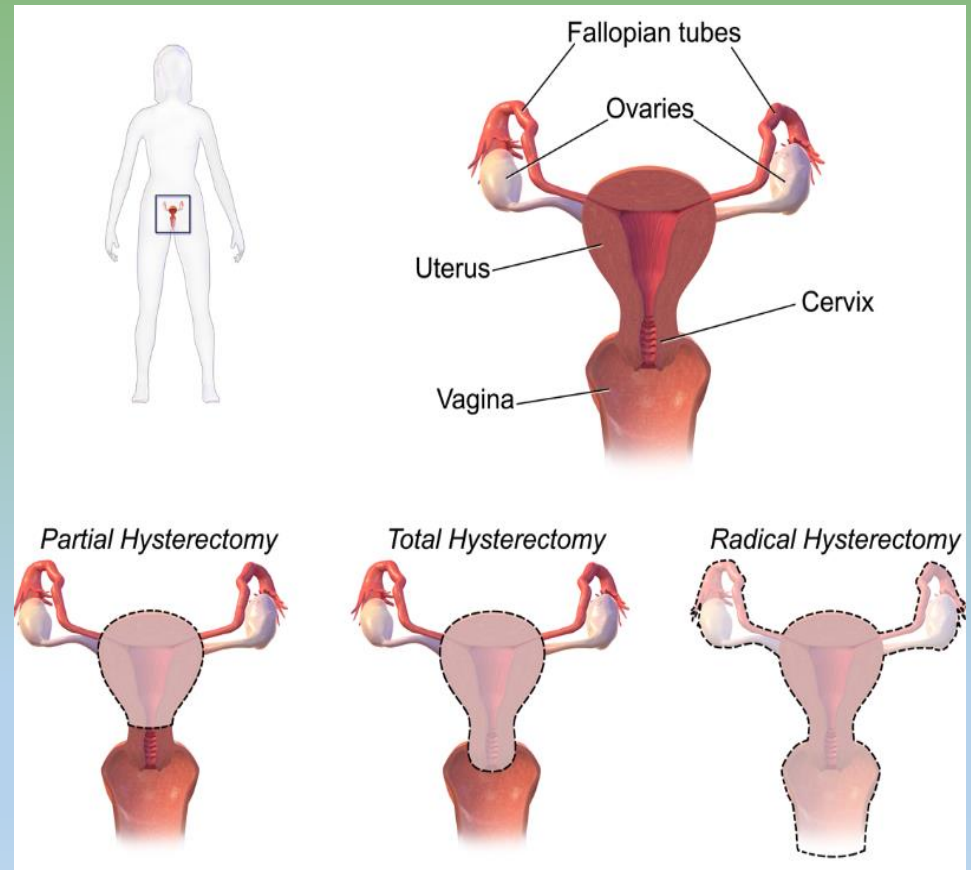
- Essential to ascertain which patients will benefit from surgery and which patients will benefit from primary radiation therapy
- Patients managed with radical surgery subsequently needing post treatment radiation therapy have greater morbidity and long term complications
- Surgery with hysterectomy (Stage IA) or radical hysterectomy (Stage IB1).
  - Some will perform radical hysterectomy on Stage IB2 and IIA1 (tumor 4cm or less)
- Concurrent chemotherapy/radiation therapy for Stage IB3 (tumor >4cm) to IVA disease
  - Supported by 5 RCTs.

ACOG practice bulletin. Diagnosis and treatment of cervical carcinomas. Number 35, May 2002. American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 2002;78:79-91

Gaffney DK et al., ACR Appropriateness Criteria® on Advanced Cervical Cancer Expert Panel on Radiation Oncology-Gynecology. Int J Radiat Oncol Biol Phys 2011;81:609-614.

# Early Stage Cervix: Surgery

- Hysterectomy
  - Uterus, fallopian tubes, ovaries, cervix, fascia of the cervix removed
- Radical Hysterectomy
  - Uterine vessels ligated at origin from the hypogastric vessels
  - Uterosacral and cardinal ligaments are resected at attachments to sacrum and pelvic side wall
  - Upper ½ of vagina resected.



# Early Stage Cervix: Surgery

- **Radical hysterectomy**
- Minimally invasive approach...unpleasant surprise!
  - Movement had been towards laparoscopic/robotic surgery due to known benefits of MIS: shorter hospital stay, less wound infection or breakdown, decreased postoperative pain, etc
  - Meta-analysis of 26 studies had suggested comparable outcomes to open surgery.
- Recent Phase 3 LACC RCT showed MIS radical hysterectomy led to lower rates of Disease Free Survival (DFS) and Overall Survival (OS).
  - 3yr DFS 91.2% v 97.1%      3yr OS 93.8% v 99.0%
  - 2 epidemiologic studies have concurred with 5yr OS for MIS 81.3% v 90.8%.
- Most physicians have returned to laparotomy

Shazly SA et al., Robotic radical hysterectomy in early stage cervical cancer: A systematic review and meta-analysis. *Gynecol Oncol* 2015;138:457-471.

Ramirez PT, et al., Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. *N Eng J Med* 2018 Nov 15;379(20):1895-1904.

Margul DJ et al., Outcomes and costs of open, robotic, and laparoscopic radical hysterectomy for stage IB1 cervical cancer. *J Clin Oncol* 2018;36:5502

# High Risk Cervix: Chemo/RT

- Treatment of choice for stage IB3, II, III, IVA disease
- Adding concurrent chemotherapy to radiation → 30-50% decrease in risk of death vs radiation alone
  - Long term follow up of 3 RCTs found improved PFS and OS compared to radiation alone.
- Chemo/RT can serve as post op treatment also for patient's with positive lymph nodes, positive surgical margins, positive parametria, or "high risk" disease.
  - Adding concurrent chemotherapy (Cisplatin) improves OS.
  - No survival benefit for neoadjuvant chemotherapy (chemo → surgery)
    - Did decrease need for radiation therapy due to decreased tumor size and mets.

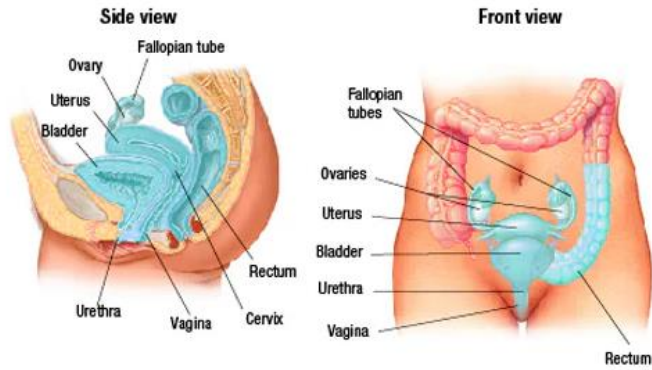
Eifel PJ, et al., Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG)90-01. J Clin Oncol 2004;22:872-880.

Peters WA et al., Concurrent chemotherapy and pelvic radiation therapy compared to pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999;340:1137-1143.

# Cervix Cancer: Advanced/Recurrent

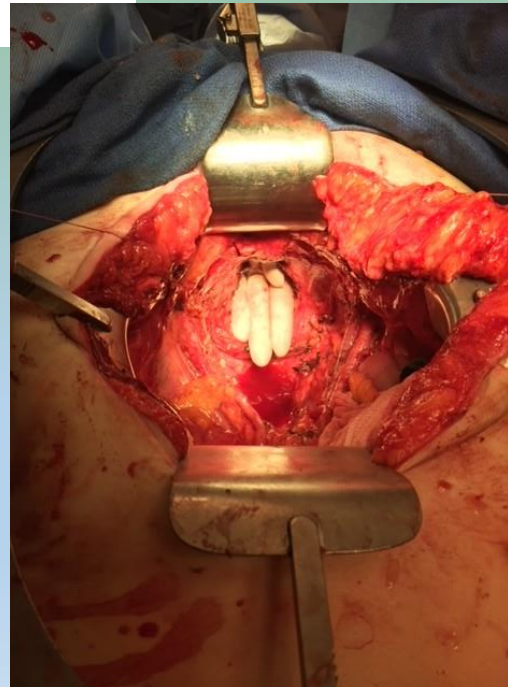
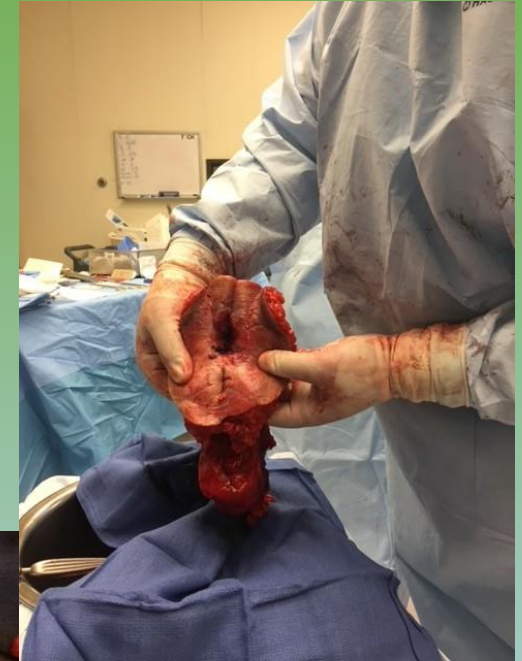
- Generally not curable.
  - Patients with prior radiation have limited options for additional RT
  - Some pts with locoregional recurrence can be cured with pelvic exenteration (50% cure rate in properly selected patients)
    - 15-34% had major post-op complications
- Sites of metastatic disease: Pelvic nodes (75%), para-aortic nodes (62%), lung (33-38%), liver (33%), peritoneum (5-27%), intestines (12%), skin (10%)
- Chemotherapy is modality of choice, platinum/taxane combination
  - Two new additions have improved outcomes
    - Bevacizumab
    - Checkpoint inhibitors

2c. Total pelvic exenteration surgery (organs removed in blue)



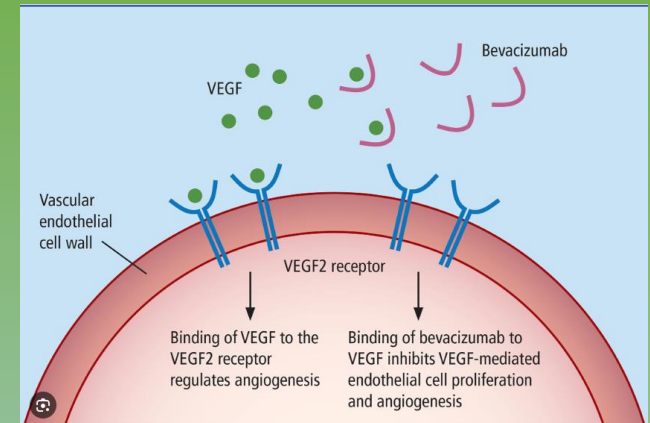
## Resection in total exenteration

Illustration of resection in total exenteration, including removal of all pelvic organs, requiring a permanent bag for urine and another bag for stool.



# Bevacizumab

- Biologic agent. Angiogenesis inhibitor
- FDA approved for treatment of cervix cancer
- GOG 240: Cisplatin/Taxol/Bevacizumab new standard of care.
  - 452 metastatic cancer pts; platinum/taxane +/- bevacizumab
  - Significant improvement in Overall Response Rate (ORR) 49% v 36%
  - Significant improvement in median PFS (8.2 mo v 6 mo)
  - Significant improvement in median OS (16.8 mo v 13.3 mo)
  - Patients who received Bevacizumab had increased side effects including hypertension (25%), GI fistulas (3%), GU fistulas, neutropenia, VTE.
  - No difference in quality of life between groups.

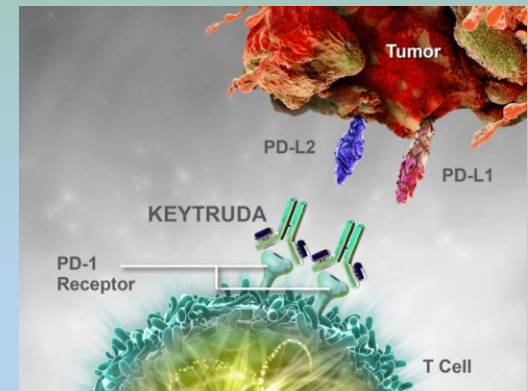


Tewari KS, et al., Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med 2014; 370:734.

Tewari KS, et al., Bevacizumab for advanced cervical cancer: final overall survival and adverse events analysis of a randomized, controlled, open-label, phase 3 trial (GOG 240) Lancet 2017;390:1654.

# Checkpoint Inhibitors

- Cancers expressing programmed cell death ligand 1 (PD-L1) with a combined positive score (CPS)>1 benefit from addition of pembrolizumab to chemo+Bevacizumab
- Checkpoint inhibitors
- Phase 3 study chemo+Bev+placebo vs chemo+Bev+pembrolizumab
  - 617 patients
  - Increased ORR 66% v 51%
  - Increased median PFS (10.4mo vs 8.2mo)
  - Increased median OS (26mo v 17mo) if CPS>1
  - Increased median OS (30mo v 17mo) if CPS>10



Colombo N, et al., Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. N Engl J Med 2021;385:1856

Mon BJ et al., First line Pembrolizumab+Chemotherapy Versus Placebo +Chemotherapy for Persistent, Recurrent, or Metastatic Cervical Cancer: Final Overall Survival Results of KEYNOTE-826. J Clin Oncol 2023;41:5505.

# Conclusions

- In the US we are seeing improvements in screening, vaccination and prevention that are making a difference for individuals and populations
  - Still much work to be done, especially in minority and low income populations
- Globally, however, cervix cancer remains a significant problem with no short term solution in sight.
  - Vaccination will make the greatest impact, but new screening and prevention strategies are needed
- Locally advanced and advanced malignancy seems to be a much more frequent first presentation
  - New drugs and treatments appear to be making a difference but can carry great expense.

- ▶ **Submit questions via chat box**
- ▶ **Click “Unmute” on bottom left of screen or dial \*6 to unmute if you’re on the phone**



# Thank you!



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