Endometrial and Cervical Cancers

12th Annual Comprehensive Hematology/Oncology Review

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Disclosures

None

Endometrial Cancer

Uterine Cancer

Histologic Types

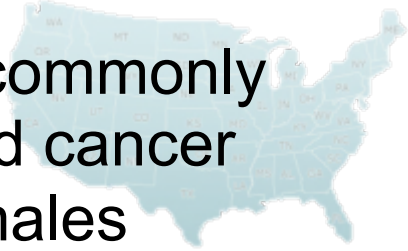
Adenocarcinoma:

- Endometrioid
- Mucinous
- Clear cell
- Serous
- Carcinosarcoma

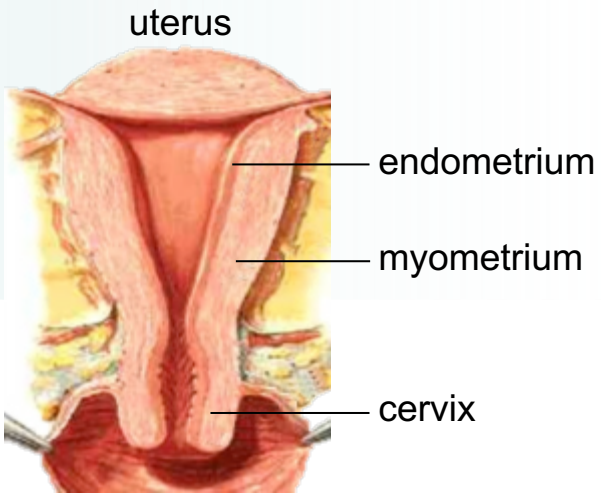
Sarcoma:

- Leiomyosarcoma
- Endometrial stromal sarcoma
- Adenosarcoma

Epidemiology



- 4th most commonly diagnosed cancer in US females
- **65,620 new cases** estimated in 2020 **(12,590 deaths)**



Endometrial Adenocarcinoma

Clinicopathologic Subtypes

Type I

Endometrioid Histology grade1-2 *(estrogen-related)*

- Risk factors include those leading to ↑ exposure to unopposed estrogen
- Often associated with PTEN mutations
- May demonstrate microsatellite instability

Type II

(non-estrogen related)

- Grade 3 endometrioid
- Non-endometrioid histologies:
  - Serous
  - Clear cell
  - Carcinosarcoma
- Associated with p53 mutations, chromosomal instability

Endometrial Cancer
Factors Increasing Risk

- Unopposed estrogen stimulation

	Risk
• **Obesity**	**3-10X**
• **Estrogen-only HRT**	**4-8X**
• **PCOS**	**2-6X**
• **Tamoxifen**	**2-3X**
• **Granulosa cell tumors**	**5X**
• **Nulliparity**	**2X**

- Increasing Age
- Diabetes
- Genetics (Lynch syndrome)

Endometrial Cancer

Tamoxifen

Tamoxifen = **SERM** (behaves as estrogen agonist at the endometrium)

- Associated with small but significantly ↑ risk of endometrioid adenocarcinoma and carcinosarcoma
- Causes cystic hypertrophy of endometrium
- **ALL** patients on tamoxifen should have annual pelvic exam and be asked about postmenopausal or irregular vaginal bleeding or discharge
- No benefit to use of U/S and endometrial biopsy for endometrial cancer screening

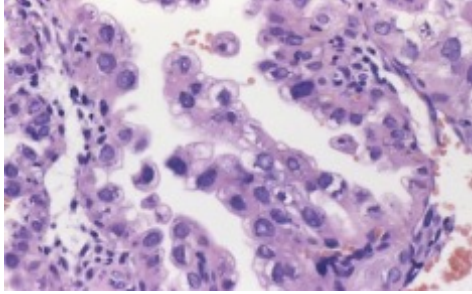
Curtis RE et al. *J Nat'l Cancer Inst* 2004.
ACOG Committee Opinion 336. ACOG June 2006.

Lynch syndrome

- ~3-5% of endometrial cancers
- Autosomal dominant mutation in mismatch repair genes – *MLH1, MSH2, MSH6, PMS2*
- 40–60% lifetime risk of endometrial cancer (*PMS2:* 15-25% risk)
  - Mean age at presentation: late 40s
  - Ovarian cancer ~12% lifetime risk (*PMS2:* 1-3% risk)
  - Screening optional: endometrial biopsy q1-2 years, U/S and CA 125 at clinician discretion
  - Offer risk-reducing hysterectomy and removal of tubes/ovaries

Lindor NM et al. *JAMA* 2006
NCCN Guidelines - Genetic/Familial High-Risk Assessment: Colorectal. Version 1.2021

Endometrial Cancer
Poor Prognosis Histologies



- **Clear cell and serous carcinomas**
  - Nearly 70% will have extrauterine disease at presentation
  - In SEER review, serous and clear cell carcinomas accounted for 10% and 3% of all endometrial carcinomas, but responsible for 39% and 8% of deaths, respectively

Hamilton CA et al. *Br J Cancer* 2006.

- **Carcinosarcoma**
  - Considered a high-grade carcinoma, with sarcomatous dedifferentiation
  - <5% of uterine cancers but poor prognosis
- **Squamous**
  - Rare but aggressive

Endometrial Cancer

Survival by Stage (FIGO 2009)

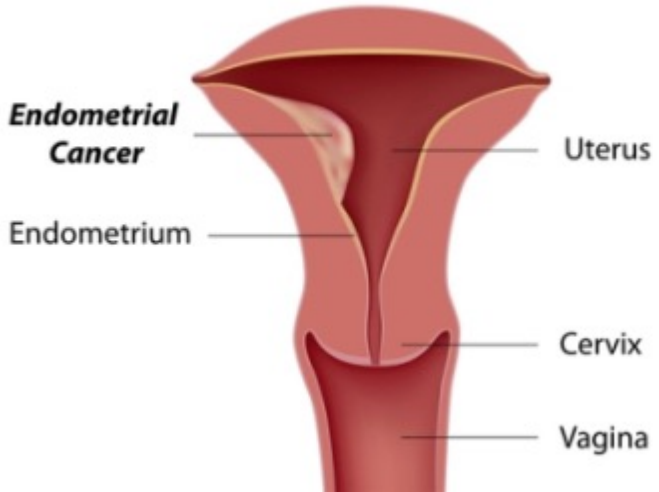
Stage	Survival	
IA	90%	<50% myometrial invasion
IB	81%	>50% myometrial invasion
II	81%	Cervical stroma involvement
IIIA	69%	Uterine serosa or adnexal involvement
IIIB	53%	Vaginal and/or parametrial involvement
IIIC1-2	51-58%	Pelvic, paraaortic lymph node involvement
IVA	22%	Bowel or bladder mucosa
IVB	21%	Distant metastasis (includes intra-abdominal disease, inguinal nodes)

Endometrial Cancer
Treatment

- Surgical staging
  - Total hysterectomy/removal of tubes and ovaries ± pelvic/periaortic lymphadenectomy or sentinel lymph node biopsy
  - Minimally invasive approach as effective as open surgery

Walker JL et al. *J Clin Oncol* 2012.

- Adjuvant radiation
  - If risk factors for recurrence present
- Chemotherapy
  - Advanced stages, high-risk histology



Endometrial Cancer
Fertility-Sparing

CANDIDATES:

- Grade 1 endometrioid histology on D&C
- Disease confined to endometrium on MRI (no myometrial invasion)
- No evidence of metastatic disease on imaging
- No contraindications to medical therapy or pregnancy

Endometrial Cancer
Fertility-Sparing

Management:

- Continuous progestin-based therapy
  - Megestrol, Medroxyprogesterone, or Levonorgestrel IUD
- Endometrial sampling every 3-6 months
  - If complete response: encourage conception. Hysterectomy after childbearing complete
  - 50-70% complete response. 20-35% relapse after initial CR

Gunderson CC et al. *Gynecol Oncol* 2012
Baker J et al. *Gynecol Oncol* 2012

Endometrial Cancer
Lymph node dissection

- Two large RCTs failed to show survival benefit
- Can identify those at high risk of recurrence and guide adjuvant therapy
- Who benefits most, and extent of LND highly debated
  - Sentinel lymph node dissection: a standard of care
  - “Mayo criteria”: Risk of LN involvement <2% if grade 1-2, <50% myometrial invasion, and tumor <2 cm

Panici PB et al. JNCI 2008
ASTEC study group. Lancet 2009
Mariani Aet al. Gyn Onc 2008.
Milam MR et al. *Obstet Gynecol* 2012.
Rossi EC et al Lancet Oncol 2017.

Endometrial Cancer
Postoperative Treatment

- Low Risk: Stage IA Grade 1-2, confined to endometrium
  - Observation
- Intermediate Risk: Stage IA (with myoinvasion), stage IB, stage II
  - Low-intermediate risk: observation
  - High-intermediate risk: brachytherapy or RT
- High Risk: Stage III-IV; high-risk histology (serous, clear cell, carcinosarcoma) any stage
  - Chemotherapy ± radiation

Endometrial Cancer
Case Studies

- 55 yo s/p laparoscopic hyst, BSO. No lymphadenectomy done
  - Grade 2
  - 1 cm tumor, no myometrial invasion
  - Peritoneal wash positive
- Management?

A. Observation, she is low-risk

B. Pelvic RT, because she did not receive lymph node dissection

C. Chemotherapy, because the peritoneal wash was positive

Endometrial Cancer
Case Studies

- 65 yo s/p laparoscopic hyst, BSO, sentinel node biopsy.
  - Grade 1
  - 70% myometrial invasion
  - Lymphovascular space invasion (LVSI) present
  - Sentinel nodes negative
- Management?

A. Observation; she is low-risk

B. Vaginal brachytherapy; she is high-intermediate risk

C. Pelvic RT; she is high-intermediate risk

Postoperative Treatment
High-intermediate Risk

- GOG 99
  - Risk factors: Outer third myometrial invasion, grade 2-3, LVSI
  - HIR group: age ≥70 + 1 risk factor, age 50-69 + 2 risk factors, age <50 + 3 risk factors
- PORTEC 1*
  - Risk factors: Age>60, ≥50% myometrial invasion, grade 3
  - HIR group: 2 risk factors

➢ Pelvic RT in HIR: reduced risk of locoregional recurrence (13-18%->5%), no overall survival benefit

Postoperative Treatment
High-intermediate Risk

- PORTEC 2: Non-inferiority trial of vaginal brachytherapy vs. pelvic RT in stage I with HIR, stage IIA*
  - Vaginal recurrence rate the same (1.6-1.8%), 5-yr locoregional relapse rate 5% vs 2% (not significant), less toxicity with brachytherapy

Nout RA et al. PORTEC-2 *Lancet* 2010.

- Conclusion: Vaginal brachytherapy is as effective as pelvic RT for preventing locoregional recurrence for:
  - Grade 1-2 ≥50%
  - Grade 3 <50%

Endometrial Cancer
Case Studies

- 65 yo s/p laparoscopic hyst, BSO, sentinel node biopsy.
  - Grade 1
  - 70% myometrial invasion
  - Lymphovascular space invasion (LVSI) present
  - Sentinel nodes negative
- Management?

A. Observation; she is low-risk

B. Vaginal brachytherapy; she is high-intermediate risk

C. Pelvic RT; she is high-intermediate risk

Endometrial Cancer
Case Studies

WARNING: CONTROVERSIAL CASE!

- 68 yo s/p laparoscopic hyst, BSO, sentinel node biopsy.
  - Grade 3, 85% myometrial invasion
  - Lymphovascular space invasion (LVSI) present
  - Sentinel nodes negative
- Management?

A. Vaginal brachytherapy

B. Pelvic RT

C. Chemotherapy + vaginal brachytherapy

D. B or C are reasonable

E. Chemotherapy + Pelvic RT

NCCN Guidelines
Surgically Staged – Stage I

FIGO Stage	Histologic Grade	Adjuvant Treatment
IA	G1, G2	Observation preferred or Vaginal brachytherapy if any risk factors[o,p]
	G3	Vaginal brachytherapy preferred or Consider observation if no myoinvasion and no lymphovascular space invasion[o]
IB[l]	G1, G2	Vaginal brachytherapy preferred or Consider observation if no risk factors[o]
	G3	RT (vaginal brachytherapy and/or EBRT) ± systemic therapy[q]

[q] risk factors that would lead to EBRT ± systemic therapy are: age, LVSI, and depth of myoinvasion. Risk factors are continuous variables. Risk of recurrence is higher with older age (especially >60 yrs), extensive LVSI, and deeper myoinvasion (>50%). Also, when there are more risk factors present, the risk of recurrence is higher.

Postoperative Treatment
High-intermediate Risk – Chemotherapy?

- GOG 249: Vaginal brachytherapy + carbo/taxol x3 vs. Pelvic RT in stage I with HIR*, stage II, stage I-II clear cell/serous
  - No difference in RFS or OS, no diff in subgroups

Randall ME et al. JCO 2019.

- PORTEC 3: Pelvic RT vs. cisRT + carbo/taxol x4 in stage I gr3 with deep myometrial invasion and/or LVSI, Stage II or III, serous or clear cell
  - Subgroup analysis: No difference in FFS or OS for stages I-II

deBoer SM et al. *Lancet Oncol* 2018.

Endometrial Cancer

Case Studies

WARNING: CONTROVERSIAL CASE!

- 68 yo s/p laparoscopic hyst, BSO, sentinel node biopsy.
  - Grade 3, 85% myometrial invasion
  - Lymphovascular space invasion (LVSI) present
  - Sentinel nodes negative
- Management?

A. Vaginal brachytherapy

B. Pelvic RT

C. Chemotherapy + vaginal brachytherapy

D. B or C are reasonable

(E. Chemotherapy + Pelvic RT)

Endometrial Cancer
Case Studies

- 63 yo s/p laparoscopic hyst, BSO, sentinel node biopsy.
  - Grade 2
  - 30% myometrial invasion
  - Left pelvic sentinel node positive
- Management?

  A. Pelvic RT

  B. Chemotherapy ± vaginal brachytherapy

  C. Chemotherapy + pelvic RT, because adding pelvic RT improves survival

Postoperative Treatment
Advanced Stage Disease

- Historical gold standard? Radiation
- **GOG 122**
  PFS and OS advantage with doxorubicin + cisplatin vs whole abdominal radiation
- **GOG 177** Randall ME et al. *J Clin Oncol* 2006.

  Addition of paclitaxel to AP improved survival
- **GOG 209** Fleming GF et al. *J Clin Oncol* 2004.

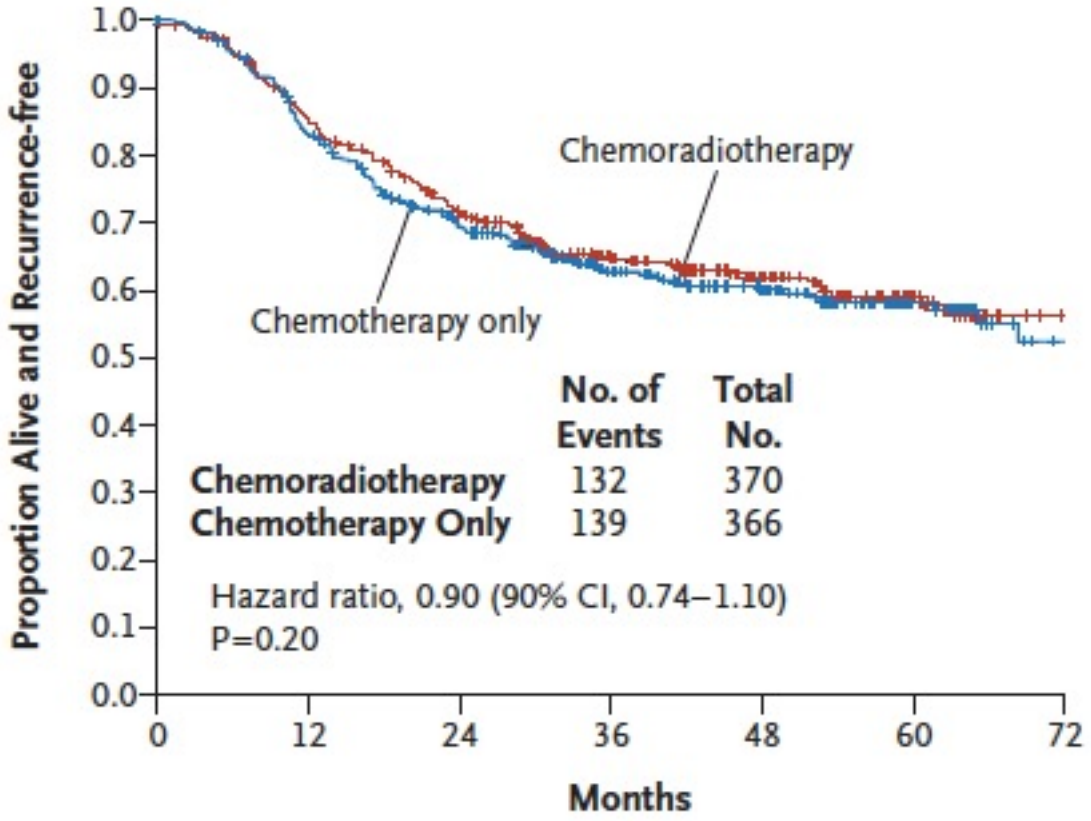
  Non-inferiority of carboplatin/paclitaxel to TAP
- **RTOG 9708** Miller D et al. *Gynecol Oncol* 2012.
  RT followed by chemotherapy associated with excellent survival rates in high-risk patients

  Greven K et al. Gynecol Oncol 2006.
- **New standard of care: chemo ± radiation**

Endometrial Cancer
Advanced Stage Disease

- **GOG 258:** Stage III, IV <2cm residual
  - Chemotherapy (Carbo/taxol x6)

  vs. ChemoRT (cisRT, then carbo/taxol x4)



Addition of RT to chemotherapy did not improve RFS

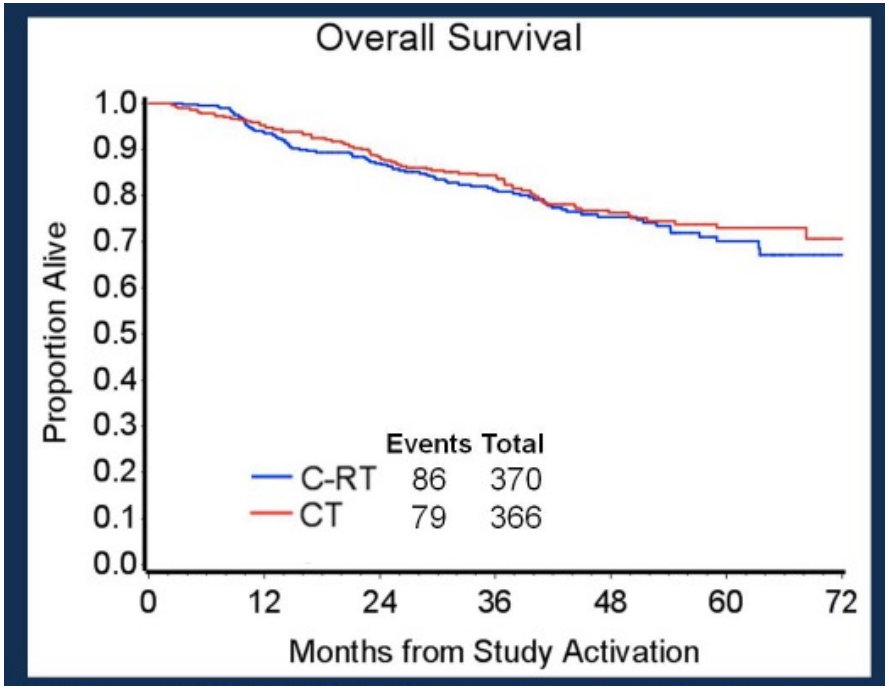
5-yr RFS:
Chemo - 58%
ChemoRT - 59%

Matei D et al. NEJM 2019.

Endometrial Cancer
Advanced Stage Disease

- **GOG 258:** Stage III, IV <2cm residual
  - Chemotherapy (Carbo/taxol x6)

  vs. ChemoRT (cisRT, then carbo/taxol x4)



5-yr OS estimates:
Chemo - 73%
ChemoRT - 70%

(Data not mature for final analysis)

Matei D et al. ASCO 2017.

Endometrial Cancer
Advanced Stage Disease

- **GOG 258:**

ChemoRT arm vs. chemotherapy:

- ↓ vaginal recurrence (2% vs 7%)
- ↓ pelvic and PA node recurrence (11% vs 20%)
- ↑ distant recurrence (27% vs 21%)

Matei D et al. NEJM 2019.

Endometrial Cancer
Advanced Stage Disease

- PORTEC 3: Pelvic RT vs. cisRT + carbo/taxol x4
  - Addition of chemo to RT improved 5-yr FFS 76% vs. 67%

Subgroup analysis:

Stage I-II – no diff in FFS

Stage III – chemoRT with improved FFS (69% vs 58%, p=0.031), no diff in OS (79% vs 70%, adjusted p=0.07)

-reinforces importance of chemo in stage IIII

deBoer SM et al. *Lancet Oncol* 2018.

Endometrial Cancer
Case Studies

- 63 yo s/p laparoscopic hyst, BSO, sentinel node biopsy.
  - Grade 2
  - 30% myometrial invasion
  - Left pelvic sentinel node positive
- Management?

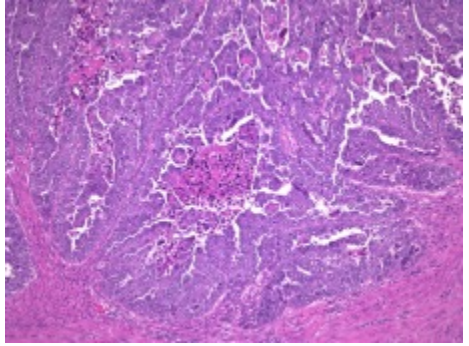
A. Pelvic RT

B. Chemotherapy ± vaginal brachytherapy

C. Chemotherapy + pelvic RT, because adding pelvic RT improves survival

Postoperative Treatment

Poor Prognosis Histology



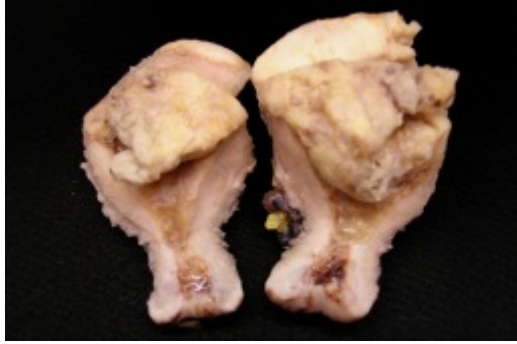
Serous Carcinoma and Clear Cell Carcinoma

- CA125 levels often reflect disease response to treatment
- Associated with high frequency of distant recurrence, even in early stage disease
- Retrospective data suggests benefit chemotherapy (platinum-taxane) in all stages
  - Exception: If disease limited to endometrial polyp, possibly if limited to endometrium

Boruta DM et al. *Gynecol Oncol* 2009.
Kelly MG et al. *Gynecol Oncol* 2005.

Postoperative Treatment

Poor Prognosis Histology



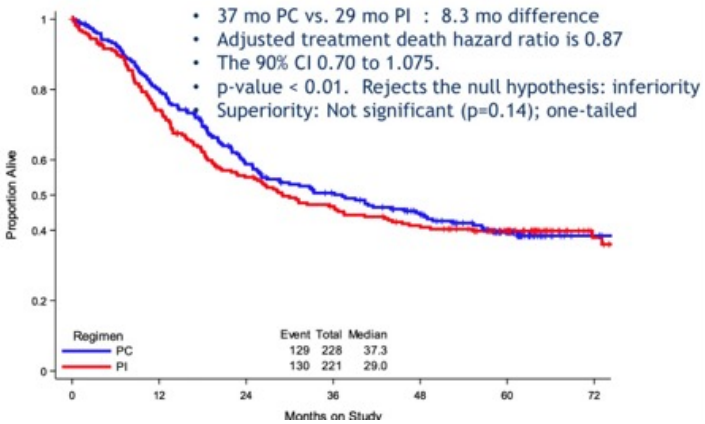
Carcinosarcoma

- Ifosfamide and paclitaxel previously associated with greatest survival benefit

Bansal N et al. *Obstet Gynecol* 2008.
Tanner EJ et al. *Gynecol Oncol* 2011.
Homesley HD et al. *J Clin Oncol* 2007.

- **GOG 261:** RCT comparing ifosfamide/paclitaxel to carboplatin and paclitaxel (OS primary endpoint)

Carbo/taxol non-inferior!



Powell et al. ASCO 2019.

Endometrial Cancer
Surveillance & Recurrence

- **Surveillance**
  - Physical exam, including pelvic, every 3-6 months for 2 years, then every 6-12 months
  - Pap test no longer recommended
  - Consider CA125, if elevated preoperatively
  - Counseling on lifestyle changes

- **Recurrence**
  - ↑ Recurrence risk with high-risk histology
  - Sites: Type 1—Local (pelvis/vagina) most common
    Type 2—Distant (outside pelvis)

Recurrent Endometrial Cancer
Treatment

- Consider radiation for local vaginal recurrence or isolated recurrence in nodal beds
- Surgical resection can be an option for *isolated* recurrences
- Hormonal therapy
  - Most effective in **low-grade** endometrioid cancers
  - Medroxyprogesterone/tamoxifen – RR 27%
  - Progestins – RR 15-20%
- Chemotherapy
  - For many, carboplatin/paclitaxel is 1st line
  - RR 50-60%

Carey MS et al. *Gynecol Oncol* 2006.

Recurrent Endometrial Cancer
Treatment

- Second-line chemotherapy (RR 10-25%): doxorubicin, taxanes (weekly), ifosfamide
- Biologics:
  - Bevacizumab
  - Pembrolizumab in MSI-high
- Two prospective studies (GOG 86P, ENDO-7) demonstrated PFS benefit of adding bevacizumab to chemotherapy
- Phase 2 study of everolimus and letrozole demonstrated clinical benefit rate of 40%
  - Notable lack of response in patients with serous tumors
- Pembrolizumab and Lenvatinib:

  Response rate 40-50%

Carey MS et al. *Gynecol Oncol* 2006.
Oza AM et al. *J Clin Oncol* 2011.
Aghajanian C et al. *J Clin Oncol* 2011.
Slomovitz BM et al. *J Clin Oncol* 2015.
Makker et. Lancet Oncol 2019.

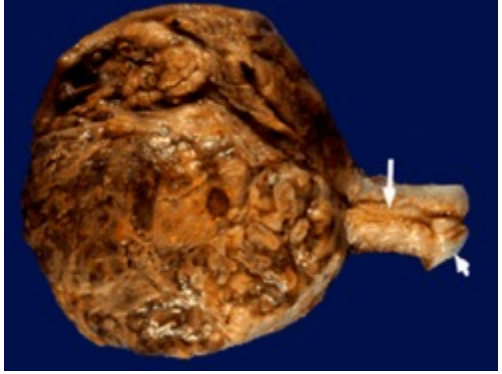
Recurrent Endometrial Cancer

Immune checkpoint inhibitors - ORR

	Avelumab[1]	Durvalumab[2]	Dostarlimab[3]	Pembrolizumab + lenvatinib[4]
MMRd	26.7% (7.8-55.1)	47%	44.7%	50% (6.8-93.2)
MMRp	6.25% (0.16-30.2)	3%	13.4%	39.6% (21.9 – 51.2)

1. Konstantinopoulos et al. JCO 2019 2. Antill et al. J Immunotherapy Cancer 3. Oaknin et al. ESMO 2020 4. Makker et al. Lancet Oncol. 2019 20(5): 711-718

Uterine Sarcomas
Background & Evaluation



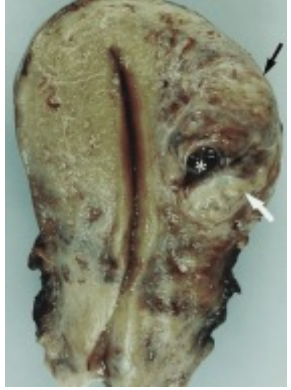
- Epidemiology
  - *Rare*—only 3% of all uterine malignancies
- Risk Factors
  - Prior pelvic radiation
  - ↑ Rate leiomyosarcomas in African Americans
- Surgery

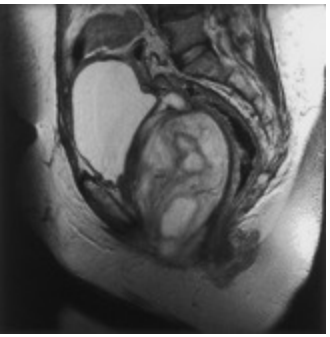
• Hysterectomy, ± removal of ovaries, ± lymphadenectomy
• Surgery one of few interventions with impact on uterine sarcomas

FIGO Staging
Leiomyosarcoma

- Stage I: Limited to uterus
  - IA: <5 cm
  - IB: >5 cm
- Stage II: Extends beyond uterus, within pelvis
  - IIA: Involves adnexa
  - IIB: Involves other pelvic tissues
- Stage III: Infiltrates abdominal tissues
  - IIIA: One site
  - IIIB: > 1 site
  - IIIC: Regional LN mets
- Stage IV: Bowel/bladder invasion or DM
  - IVA: Involvement of bladder/bowel mucosa
  - IVB: Distant mets

Uterine Sarcomas
Treatment





- **Leiomyosarcoma**
  - Gemcitabine/docetaxel active in advanced stages of disease, superior to historical treatments

    Hensley ML et al. *Gynecol Oncol* 2008.
  - No survival benefit of adjuvant RT in early stage

    Reed et al. Eur *J Ca* 2008.
  - No survival benefit of adjuvant chemotherapy in early stage disease

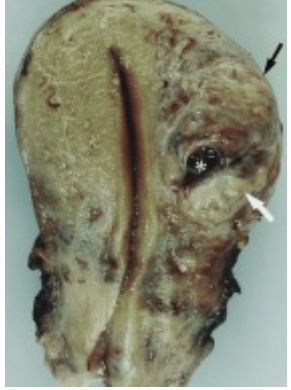
    GOG20: Doxorubicin vs obs Omura et al. *J Clin Oncol* 1985

    GOG277:

GOG 277	Gemcitabine/docetaxel x 4 Doxorubicin x 4	Observation

.Hensley ML et al. *J Clin Oncol* 2018.

Uterine Sarcomas
Treatment

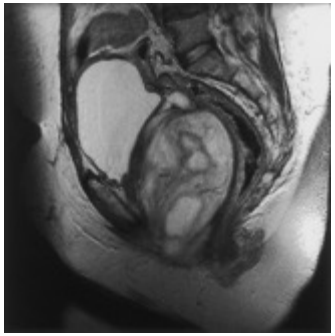


- **Leiomyosarcoma**
  - GeDDis: Gemcitabine/Docetaxel vs. Doxorubicin as first-line in advanced/metastatic – similar PFS/OS

    Seddon et al. *Lancet Oncol* 2017.

  - Doxorubicin + olaratumab: no better than doxorubicin alone

    Tap WD et al. *ASCO 2019*.

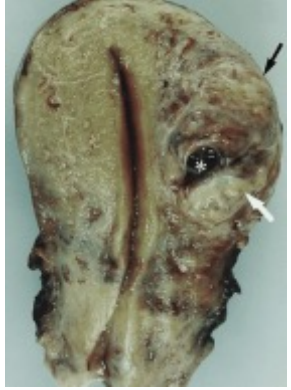


  - GOG 250 (phase III trial): no benefit to adding bevacizumab to gemcitabine/docetaxel

    Hensley ML et al. *J Clin Oncol* 2015.

  - Recurrent disease: pazopanib, trabectedin, ifosfamide, dacarbazine, eribulin. Consider hormonal blockade if ER/PR+, slow pace.

Uterine Sarcomas
Treatment



- **Low-grade Endometrial Stromal Sarcoma**
  - Hormonal therapy 1st line: Aromatase inhibitors, progestins, GnRH analogs, fulvestrant
- **High-grade Endometrial Stromal Sarcoma/ Undifferentiated Uterine Sarcoma**
  - Chemo often offered due to high risk of recurrence. Doxorubicin-based therapy first-line.
  - Consider radiation to reduce local recurrence

Cervical Cancer

Histologic Types

- Squamous cell ~70%
- Adenocarcinoma ~25%
- Adenosquamous
- Glassy cell
- Small cell

Epidemiology

- Peak age incidence 40–60 yo
- 2021:

US

14,480 new cases
4,290 deaths

Significantly ↓ incidence due to implementation of screening with Pap

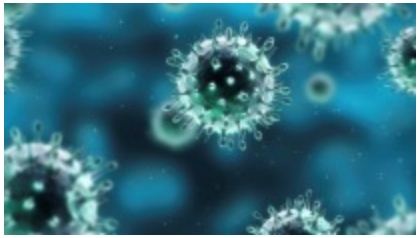
Worldwide

>85% of all cases of cervical cancer occur in low-resource countries

Global Cancer Facts & Figures 2021, American Cancer Society.
World Health Organization

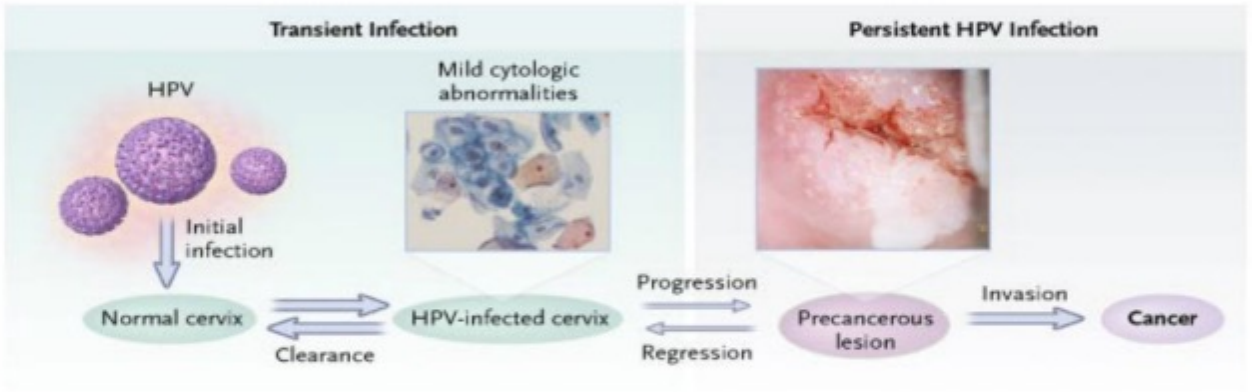
Cervical Cancer
Risk Factors

- Smoking
- Multiple sexual partners
- Sexually transmitted infection
- Immunosuppression
  - HIV/AIDS
  - Prior organ transplant recipient
- HPV infection



Cervical Cancer
Role of HPV

- Human papilloma virus incorporated into cellular genome; persistent infection can ➔ dysplasia
- HPV oncoproteins E6 and E7 lead to inactivation of p53 and Rb
- >20 high-risk types associated with anogenital cancers
  - Types 16 & 18: >70% of cervical cancers



Wright & Schiffman. *N Engl J Med* 2003.

Cervical Cancer

HPV Vaccine

Available

Gardasil: Quadrivalent *(types 6,11,16,18)*

Cervarix: Bivalent *(types 16,18)*

Gardasil 9: Nanovalent *(types 6, 11, 16, 18, 31, 33, 45, 52, 58)*

- Significantly ↓ incidence squamous and glandular dysplasia and carcinoma *in situ*

  FUTURE II Study Group. *N Engl J Med* 2007; Joura EA et al. *Lancet* 2007. Joura EA et al. N Engl J Med 2015.

- ACIP, ACS, ACOG, AAP: **ALL** girls and boys should be vaccinated against HPV at age 9–12 yrs

- Approved for all genders, ages 9-26, now expanded to include ages 27-45

Cervical Cancer
Screening

- Start at age 21
- Ages 21-29: Pap every 3 years
- Ages 30-65: Co-testing with Pap and HPV every 5 years OR primary HPV testing alone (OR Pap alone every 3 years)
- Age >65: No screening if normal prior screening
- Screen even if vaccinated
- No screening after hysterectomy with removal of cervix, unless prior CIN3/cancer

US Preventative Services Task Force (USPSTF) recommendations.

Cervical Cancer

Diagnosis and staging

- Diagnosis via biopsy
- Previously clinically staged – NEW staging FIGO 2018 allows imaging and pathology
  - Pelvic exam (speculum, bimanual, rectovaginal)
  - Biopsies, cervical cone/LEEP
  - Cystoscopy
  - Proctosigmoidoscopy
  - Intravenous pyelogram (IVP)
  - Chest x-ray
  - US, CT, MRI, PET scan now allowed
  - Pathology from lymph nodes, other surgical or biopsy specimens now allowed

Cervical Cancer

Staging - OLD

Stage	Spread
Stage I	**Confined to cervix (disregard corpus extension)**
IA	Diagnosed only by microscopy
IA1	≤3 mm depth and ≤7mm horizontal spread
IA2	>3 and ≤5 mm depth, and ≤7mm horizontal spread
IB	Clinically visible, or microscopic lesion greater than IA
IB1	≤4 cm tumor
IB2	>4 cm tumor
Stage II	**Beyond uterus, but no to pelvic sidewall or lower third of vagina**
IIA	Vaginal involvement (less than upper two-thirds)
IIA1	≤4 cm tumor
IIA2	>4 cm tumor
IIB	Parametrial invasion

Cervical Cancer

Staging - OLD

Stage	Spread
Stage III	**Extends to pelvic sidewall* and/or involves lower third of vagina**
IIIA	Involves lower third of vagina (no pelvic sidewall)
IIIB	Extends to pelvic sidewall, and/or causes hydronephrosis or non-functioning kidney
Stage IV	**Involves bowel or bladder mucosa, or extends beyond true pelvis**
IVA	Bowel or bladder mucosa (bullous edema not sufficient)
IVB	Distant metastases (extends beyond true pelvis)

Cervical Cancer

New Staging - 2018

Stage	Spread
Stage I	**Confined to cervix (disregard corpus extension)**
IA	Diagnosed only by microscopy, with maximum depth <5mm
IA1	<3 mm depth
IA2	≥3 mm and <5 mm depth
IB	Depth invasion ≥5 mm, confined to cervix
IB1	<2 cm in greatest dimension
IB2	≤2 cm and <4 cm
IB3	≥4 cm
Stage II	**Beyond uterus, but not to pelvic sidewall or lower third of vagina**
IIA	Vaginal involvement (less than upper two-thirds)
IIA1	<4 cm in greatest dimension
IIA2	≥4 cm
IIB	Parametrial invasion

Cervical Cancer

New Staging - 2018

Stage	Spread
Stage III	**Involves lower third of vagina and/or extends to pelvic sidewall* and/or involves pelvic or paraaortic lymph nodes**
IIIA	Involves lower third of vagina (no pelvic sidewall extension)
IIIB	Extends to pelvic sidewall*
IIIC	Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent
IIIC1	Pelvic lymph node metastasis only
IIIC2	Paraaortic lymph node metastasis
Stage IV	**Involves bowel or bladder mucosa, or extends beyond true pelvis**
IVA	Bowel or bladder mucosa (bullous edema not sufficient)
IVB	Distant metastases (extends beyond true pelvis)

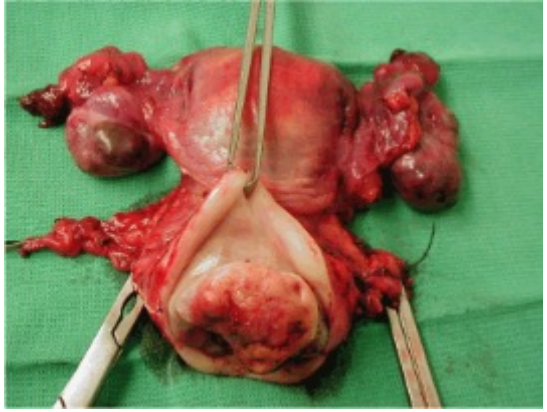
* or causes hydronephrosis or nonfunctioning kidney

Cervical Cancer

Management

Spread	Stage	Recommended therapy
Confined to cervix, microinvasive	IA1	Simple hysterectomy or cone
Confined to cervix, ≤4 cm	IA2-IB2	Surgery or Chemoradiation
Bulky cervix and/or locally advanced disease	IB3-IVA	Chemoradiation
Distant spread	IVB	Chemotherapy ± radiation

Cervical Cancer
Early-Stage Disease



- **Surgery**
  - Ex-lap, radical hysterectomy, pelvic lymphadenectomy or sentinel node biopsy
  - Favored approach for preservation of sexual function
  - Minimally invasive surgery is inferior to laparotomy for survival outcomes

Ramirez PT et al. NEJM 2018.

- **Radiation**
  - External beam radiation with chemosensitization, followed by brachytherapy

- Surgery vs RT: equivalent survival outcomes. Individuals who receive both have the most side effects

Landoni F. et al. Lancet 1997.

Cervical Cancer
Case Studies

- 52 yo with stage IB2 cervical SCC (3 cm tumor) s/p ex-lap, radical hyst, BSO, sentinel lymph node biopsy
  - Depth of cervical stromal invasion: 50%
  - LVSI present
  - Sentinel nodes negative
- Management?

A. Observation, she is low-risk

B. Pelvic RT, she is intermediate-risk

C. ChemoRT, she is high-risk

Cervical Cancer
Indications for Post-op Treatment

Intermediate-Risk

LVSI	Depth of cervical stromal invasion	Tumor size (clinical)
+	Deep third	Any
+	Middle third	≥2 cm
+	Superficial third	≥5 cm
-	Middle or deep	≥4 cm

With combination of risk factors, **pelvic radiation** ↓ risk of recurrence (28% ->15%)

Sedlis A. *Gynecol Oncol* 1999.

Cervical Cancer
Case Studies

- 52 yo with stage IB2 cervical SCC (3 cm tumor) s/p ex-lap, radical hyst, BSO, sentinel lymph node biopsy
  - Depth of cervical stromal invasion: 50%
  - LVSI present
  - Sentinel nodes negative
- Management?

A. Observation, she is low-risk

B. Pelvic RT, she is intermediate-risk

C. ChemoRT, she is high-risk

Cervical Cancer
Case Studies

- 65 yo with stage IB2 cervical adenocarcinoma (3.5 cm tumor) s/p ex-lap, radical hyst, BSO, bilateral pelvic and common iliac LND
  - Depth of cervical stromal invasion: 85%
  - LVSI present
  - One of 16 pelvic lymph nodes positive
- Management?

  A. Pelvic RT

  B. RT with cisplatin-based chemosensitization

  C. Chemotherapy

Cervical Cancer
Indications for Post-op Treatment

- **High-Risk**
  - Positive lymph nodes
  - Parametrial disease
  - Positive/close margins

Postop adjuvant treatment with **chemoradiation** to ↓ recurrence and improve overall survival

Peters WA. *JCO* 2000.

Cervical Cancer
Case Studies

- 65 yo with stage IB2 cervical adenocarcinoma (3.5 cm tumor) s/p ex-lap, radical hyst, BSO, bilateral pelvic and common iliac LND
  - Depth of cervical stromal invasion: 85%
  - LVSI present
  - One of 16 pelvic lymph nodes positive

➢ Management?

A. Pelvic RT

B. RT with cisplatin-based chemosensitization

C. Chemotherapy

Cervical Cancer

Locally Advanced Disease - Optimizing Chemoradiation

- Radiation historical treatment for cervical cancer
- 5 RCTs in 1990s showed significant survival benefit with chemotherapy and radiation for stage IB2-IVB diseases

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Strong consideration should be given to chemoradiation instead of RT alone

- Chemo regimens not consistent across studies
  - Weekly cisplatin (40 mg/m^2) most feasible, least toxicity
  - Cisplatin and 5-fluorouracil
  - Mitomycin

Recommendations

NCCN National Comprehensive Cancer Network

"concurrent cisplatin-containing chemotherapy"

Eifel PJ et al. *Semin Radiat Oncol* 2006.

Cervical Cancer

Locally Advanced Disease - Optimizing Chemoradiation

- Radiation with concurrent chemotherapy, followed by brachytherapy
  - Radiation dose goal: 80–85 Gy
- International Phase III trial in advanced disease:

Weekly Cisplatin & Gemcitabine Concurrent EBRT/Brachytherapy Adjuvant Cis/Gem q 21d x 2 cycles	Weekly Cisplatin Concurrent EBRT/Brachytherapy

- Gemcitabine + cisplatin arm associated with significant improvement in PFS/OS
- ↑ Toxicity in cis/gem arm, concern regarding the monitoring for side effects
- Unclear if benefit due to concurrent or post-radiation chemotherapy

Duenas Gonzalez A et al. *J Clin Oncol* 2011.

Cervical Cancer
Locally Advanced Disease - Adjuvant Chemotherapy?

- OUTBACK trial/GOG 274 – international randomized phase 3 trial
  - Stage IB2- IVA (FIGO 2008 staging) or stage IB1 and node positive receiving chemoRT with curative intent

Cisplatin-based ChemoRT	Cisplatin-based ChemoRT Carboplatin/paclitaxel x 4 cycles

  - No difference in PFS/OS
  - Similar patterns of disease recurrence

Mileshkin et al. ASCO 2021

Cervical Cancer

Locally Advanced Disease – Alternatives to Chemoradiation?

- Neoadjuvant chemotherapy followed by radical surgery instead?

  Inferior to chemoRT

  - Phase III RCT in stage IB2-IIB cervical cancer:

    -ChemoRT vs. Neoadj Carbo/taxol x3 followed by radical hysterectomy (+- post-op RT or chemoRT if indicated)

    -ChemoRT with superior 5-yr DFS 77% vs. 69%

    Gupta S et al. *J Clin Oncol* 2018.

  - EORTC GCG 55994:

    -Similar finding, ChemoRT superior to neoadj chemotherapy followed by surgery (5-yr PFS 66% vs 57%)

    ASCO 2019.

Cervical Cancer
Surveillance

- NCCN Recommendations:

  Pelvic exam every 3-6 months for complete responders

  - Consider imaging, as clinically indicated
  - Although Pap tests routinely used, may not be accurate in detecting recurrence

- Future use PET/CT scan: Assessment of metabolic response
  - A post-treatment PET/CT performed at 3-6 months after chemoradiation can be used to identify early persistence/recurrence

NCCN Clinical Practice Guidelines. Cervical Cancer. Version I. 2012.
Kidd EA et al. *Int J Radiat Oncol Biol Phys* 2012.

Recurrent Cervical Cancer
Rate & Patterns

- Majority occur within 2 years of primary treatment
- Recurrence sites:

  Local: Vaginal cuff, cervix, ovaries

  Distant: Lungs, paraaortic/supraclavicular lymph nodes, abdominal cavity most common
- Poor prognosis with recurrence
  - Review of 3 prospective clinical trials showed OS of 6-13 months
  - Importance of focusing on QOL and incorporating palliative care

Elit L et al. *Gynecol Oncol* 2009.
Chase DM et al. *Gynecol Oncol* 2012.

Metastatic/Recurrent Cervical Cancer
Treatment Options—Chemotherapy

- **GOG 204**: Comparison of 4 cisplatin-based doublets for recurrent cervical cancer favored cis/taxol

Monk BJ et al. *J Clin Oncol* 2009.

- **GOG 240:**
  Comparison of chemotherapy ± bevacizumab
  - No difference between chemo arms
  - Arms containing bev with significant improvement in PFS, OS, ORR

Tewari K et al. *NEJM*. 2014.

- **JCOG 0505**
  - Randomized phase III trial of cis/T vs carbo/T
  - Similar OS – carbo/taxol not inferior
  - However, if no prior cis, OS shorter with carbo/T

Kitagawa R et al. *J Clin Oncol* 2015.

Recurrent Cervical Cancer
Treatment Options

- **Chemotherapy – Second-line options:**
  - Abraxane, Paclitaxel, Ifosfamide, Topotecan, Carboplatin, Pemetrexed, Vinorelbine, Irinotecan
  - Response rates 15-29%
- **Radiation**
  - Consider if no prior RT or have recurrence outside irradiated field
- **Surgery**
  - Patients with central (i.e., pelvic/vaginal) recurrence: potential candidates for pelvic exenteration

Benn T et al. *Gynecol Oncol* 2011.

Recurrent Cervical Cancer
Immunotherapy

- Strong rationale for immunotherapy in HPV-related cancers
  Liao JB. *Gynecol Oncol* 2016
- Adoptive T-cell therapy
  - Phase 2 trial: 18 patients receiving Tumor-infiltrating Lymphocyte therapy - 5/18 (28%) had objective tumor responses
    Stevanovic S et al. *Clin Cancer Research* 2019.
- Immune checkpoint inhibitors
  - Pembrolizumab – now FDA-approved (if PD-L1+)
    - Keynote-158 (cohort E): Overall response rate 14.3%
    - Keynote-028: ORR 12.5%
  - Nivolumab
    -Checkmate-358 (cervix cancer cohort n=19, PDL1+ not required): ORR 26%

Metastatic/Recurrent Cervical Cancer
Immunotherapy

- **KEYNOTE-826: phase 3 RCT in persistent/recurrent/metastatic cervical cancer**
  - Platinum-based chemotherapy ± bevacizumab vs. Pembrolizumab + platinum-based chemotherapy ± bevacizumab
    - 6/22/21: Merck announced addition of pembrolizumab resulted in increased OS and PFS at interim analysis

https://bit.ly/3gM2rVy

QUESTIONS

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