Endometrial and Cervical Cancers

11th Annual Comprehensive Hematology/Oncology Review

Kathryn Pennington, MD
Assistant Professor
Division of Gynecologic Oncology
University of Washington Medical Center
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Disclosures

None

Endometrial Cancer

Uterine Cancer

Histologic Types

Adenocarcinoma:

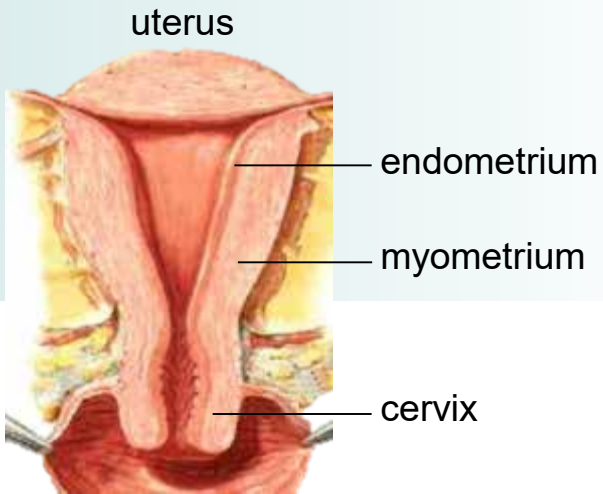
- Endometrioid
- Mucinous
- Clear cell
- Serous
- Carcinosarcoma

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
- 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.

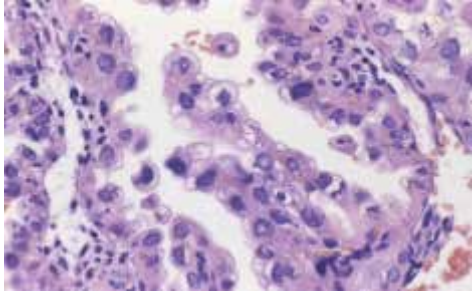
Lynch syndrome

- ~3–5% of endometrial cancers
- Due to autosomal dominant mutation in mismatch repair genes – *MLH1, MSH2, MSH6, PMS2*
- 40–60% lifetime risk of endometrial cancer
  - Mean age at presentation: 40s
  - Ovarian cancer ~12% lifetime risk*
  - Screening with endometrial biopsy, possibly with U/S and CA 125, can be considered
  - Consider prophylactic hysterectomy and removal of tubes/ovaries

Lindor NM et al. *JAMA* 2006.

Endometrial Cancer

Poor Prognosis Histologies



- **Clear cell and serous carcinomas**
  - Nearly 70% will have extrauterine disease at presentation
  - In recent 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)

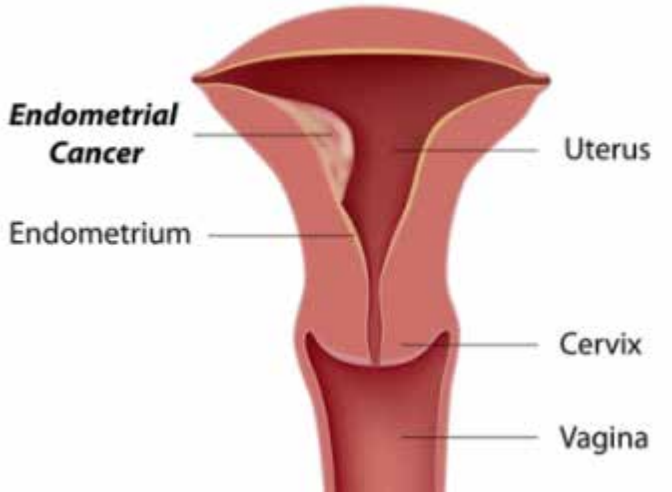
Stage	Survival	
IA	90%	<50% myometrial invasion
IB	81%	>50% myometrial invasion
II	81%	Cervical stroma involvement
IIIA	69%	Uterine serosa or adnexal involvement
IIIB	53%	Vaginal and/or parametrial involvement
IIIC1-2	51-58%	Pelvic, paraaortic lymph node involvement
IVA	22%	Bowel or bladder mucosa
IVB	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
  - "Mayo criteria": Risk of LN involvement <2% if grade 1-2, <50% myometrial invasion, and tumor <2 cm
  - Sentinel lymph node dissection another standard of care

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: 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

- GOG99
  - 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

Postoperative Treatment

High-intermediate Risk – Chemotherapy?

- GOG 249: Pelvic RT vs. vaginal brachytherapy + carbo/taxol x3 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)

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.

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.

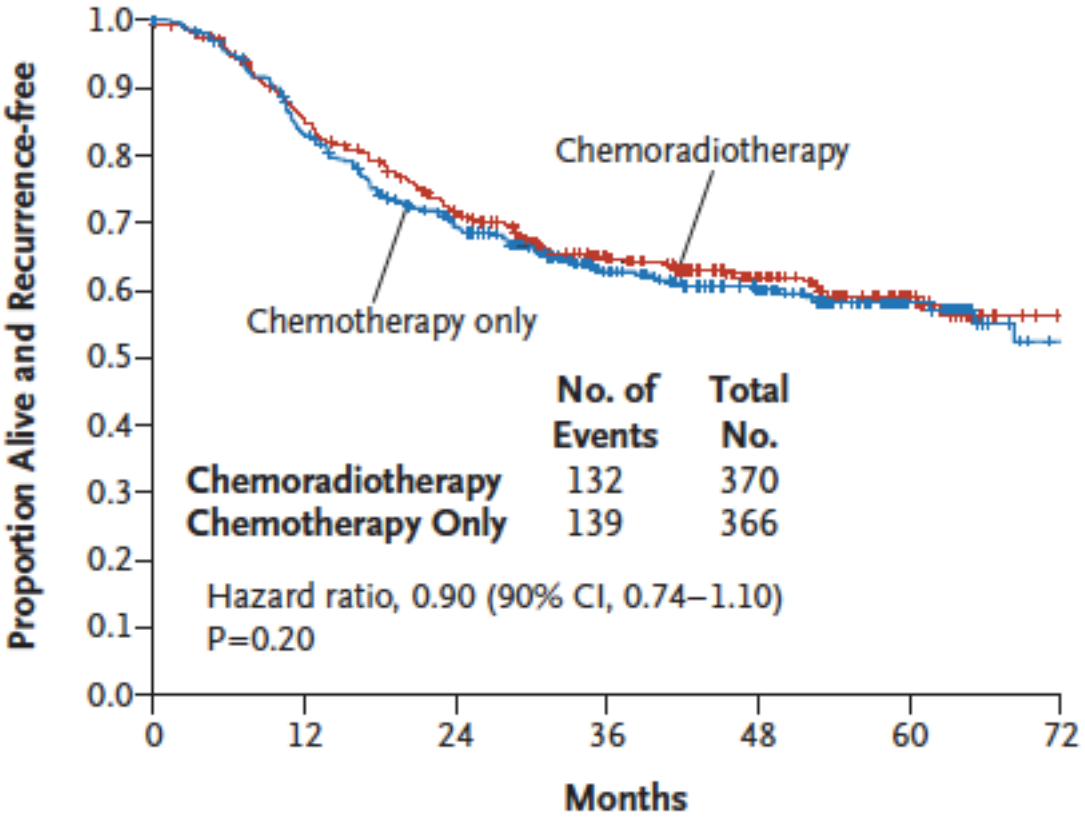
  Non-inferiority of carboplatin/paclitaxel to TAP
- **RTOG 9708** Miller D et al. *Gynecol Oncol* 2012.
  RT followed by chemotherapy associated with excellent survival rates in high-risk patients

  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

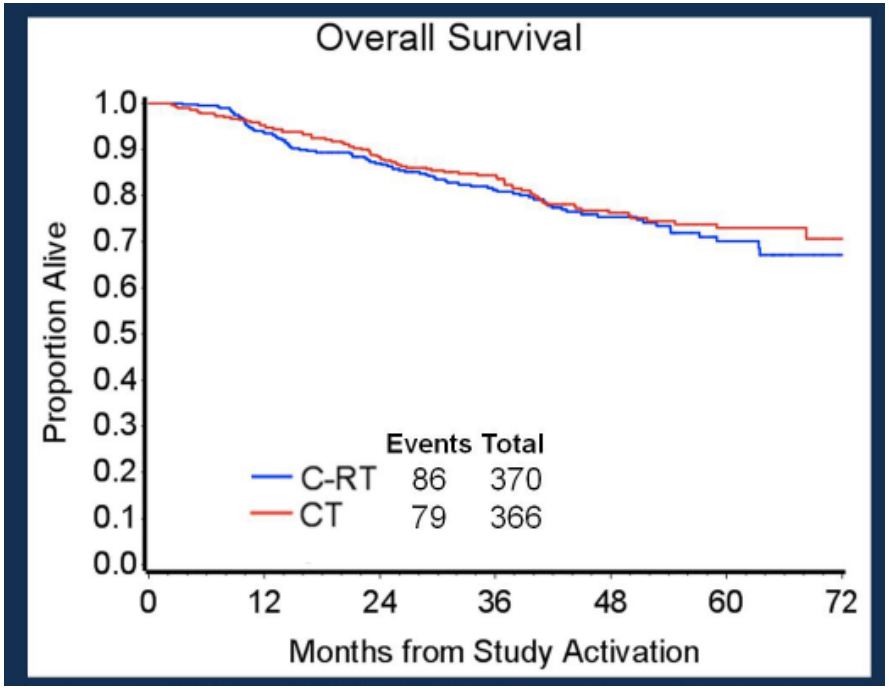
<u>5-yr RFS:</u>
Chemo - 58%
ChemoRT - 59%

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)



<u>5-yr OS estimates:</u>
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%

<u>Subgroup analysis:</u>

Stage I-II – no diff in FFS

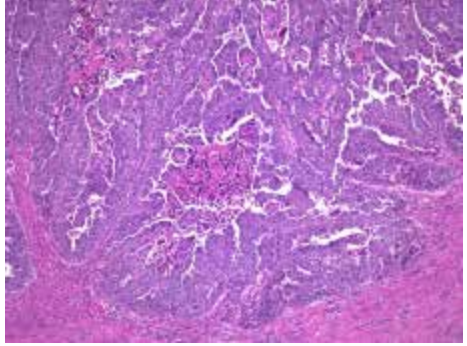
Stage III – chemoRT with improved FFS (69% vs 58%, p=0.031), no diff in OS (79% vs 70%, adjusted p=0.07)

-reinforces importance of chemo in stage IIII

deBoer SM et al. *Lancet Oncol* 2018.

Postoperative Treatment

Poor Prognosis Histology



Serous Carcinoma and Clear Cell Carcinoma

- Comprehensive surgical staging, including upper abdominal evaluation
- 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.

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

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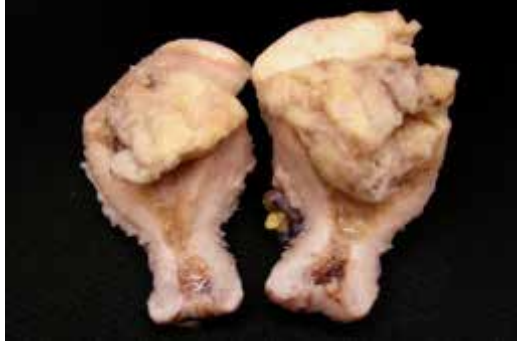
Postoperative Treatment

Poor Prognosis Histology



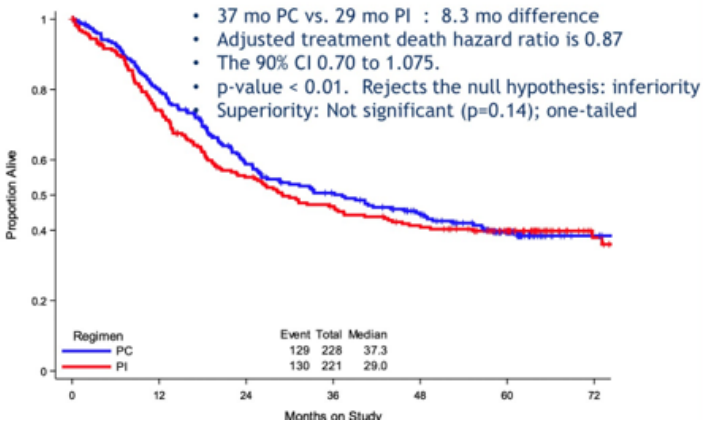
Carcinosarcoma

- 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.

Uterine Adenocarcinoma
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 Uterine Adenocarcinoma
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 Uterine Adenocarcinoma
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%

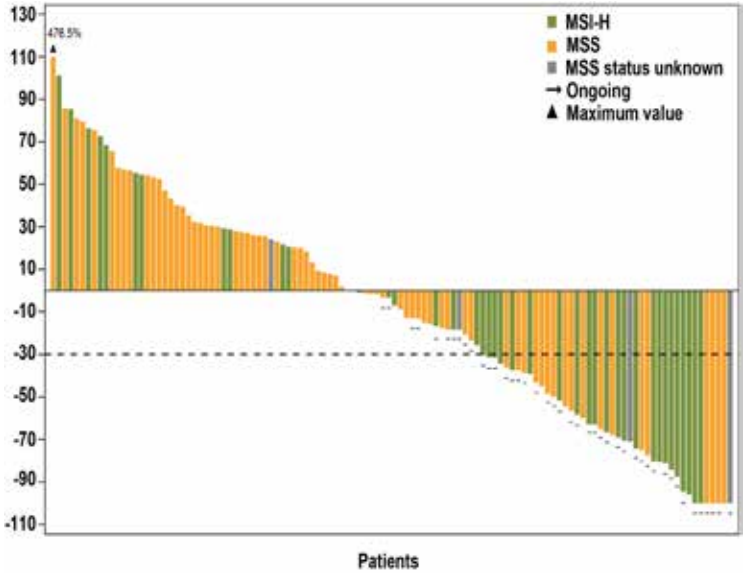
Carey MS et al. *Gynecol Oncol* 2006.
Oza AM et al. *J Clin Oncol* 2011.
Aghajanian C et al. *J Clin Oncol* 2011.
Slomovitz BM et al. *J Clin Oncol* 2015.
Makker et. Lancet Oncol 2019.

Recurrent Uterine Adenocarcinoma

Immune checkpoint inhibitors - ORR

	Avelumab[1]	Durvalumab[2]	Dostarlimab[3]	Durvalumab*[4]	Durvalumab + Tremelimumab*[4]	Pembrolizumab + lenvatinib*[5]
MMRd	26.7% (7.8-55.1)	43%	49%	NA	NA	50% (6.8-93.2)
MMRp	6.25% (0.16-30.2)	3%	20%	15%	11%	39.6% (21.9 – 51.2)

1. Konstantinopoulos et al. ASCO 2019 Abs 5502 2. Antill et al. ASCO 2019 Abs 5501 3. Oaknin et al. SGO 2019 4. Rubinstein et al. ASCO 2019 Abs 5582 5. Makker et al. Lancet Oncol. 2019 20(5): 711-718



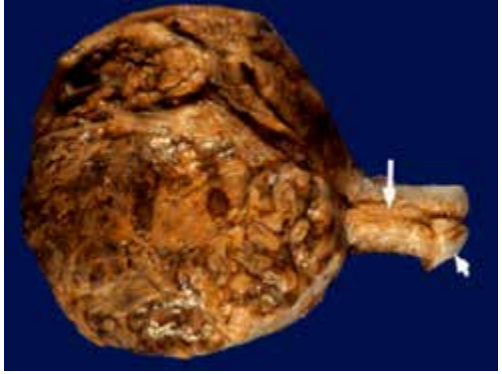
Dostarlimab: clinically meaningful responses regardless of MSI status

- >50% reduction in total tumor burden in 85% of MSI-H and 69% of MSS responders
- ~50% of responders remained on therapy >1 yr

Avelumab predictors of response:

- responses seen regardless of PD-L1 status
- tumor mutational burden and TILs did not predict response

Uterine Sarcomas
Background & Evaluation



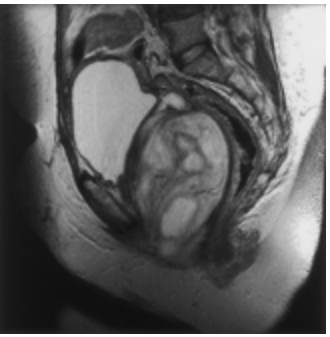
- Epidemiology
  - *Rare*—only 3% of all uterine malignancies
- Risk Factors
  - Prior pelvic radiation
  - ↑ Rate leiomyosarcomas in African Americans
- Surgery

• 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.

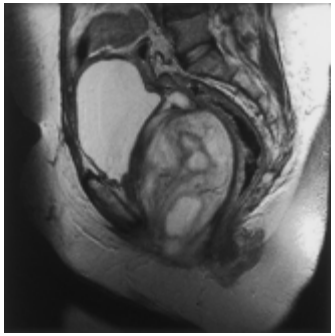
Uterine Sarcomas
Treatment

- **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
- 2020:

US

13,800 new cases
4,290 deaths

Significantly ↓ incidence due to implementation of screening with Pap

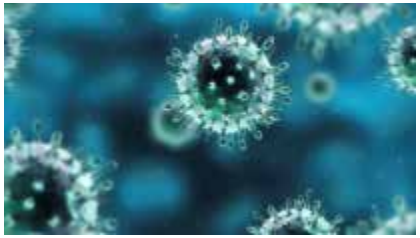
Worldwide

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

Global Cancer Facts & Figures, 4th ed. American Cancer Society.

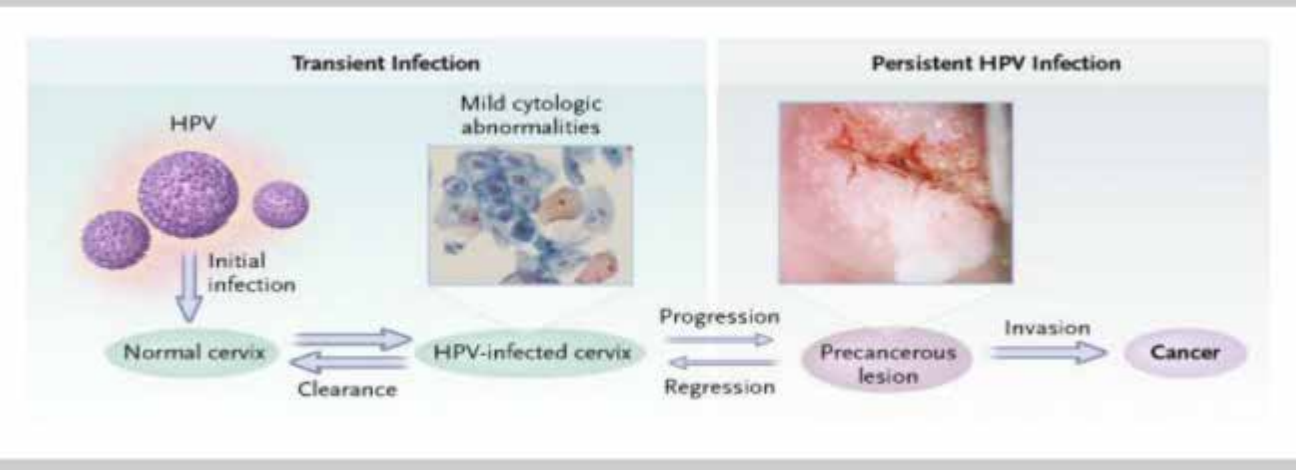
Cervical Cancer
Risk Factors

- 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 (new: HPV testing alone every 5 years also acceptable by USPSTF)
- Age >65: No screening if normal prior screening
- Screen even if vaccinated
- No screening after hysterectomy with removal of cervix, unless prior CIN3/cancer

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)

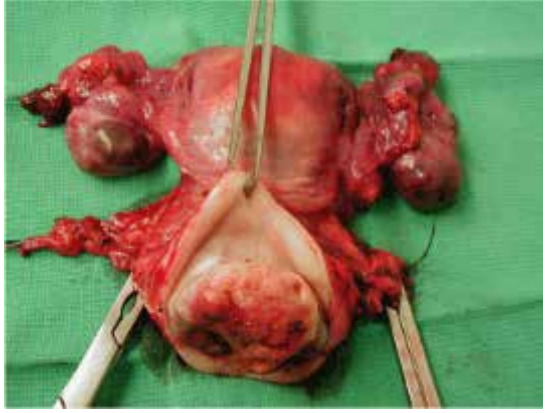
* or causes hydronephrosis or nonfunctioning kidney

Cervical Cancer

Management

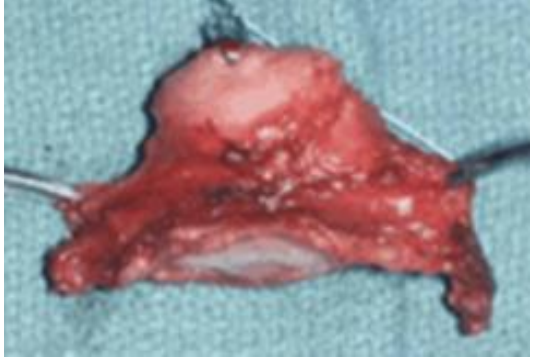
Spread	Stage	Recommended therapy
Confined to cervix, microinvasive	IA1	Simple hysterectomy or cone
Confined to cervix, ≤4 cm	IA2-IB2	Surgery or Chemoradiation
Bulky cervix and/or locally advanced disease	IB3-IVA	Chemoradiation
Distant spread	IVB	Chemotherapy ± radiation

Cervical Cancer
Early Stage Disease



- **Surgical**
  - Ex-lap, radical hysterectomy with pelvic lymphadenectomy
  - Favored approach for preservation of sexual function
- ~~(Minimally invasive approach feasible with excellent short-term outcomes)~~ Ramirez PT et al. NEJM 2018.
- **Non-Surgical**
  - External beam radiation with chemosensitization, followed by brachytherapy

Cervical Cancer
Fertility-Sparing



- Radical trachelectomy with lymphadenectomy
- Criteria:
  - Reproductive age / Desires to preserve fertility
  - Squamous cell or adenocarcinoma (no high-risk histologies)
  - Stage IA1 with LVSI, IA2, or IB1
  - Tumor size ≤2 cm* with limited endocervical extension (assessed by colpo, MRI)
  - No evidence of lymph node metastasis
  - LVSI is a risk factor for nodal recurrence, but not a strict contraindication

Kim CH et al. *Gynecol Oncol* 2012.
Diaz JP et al. *Gynecol Oncol* 2008.

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%
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  - 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:

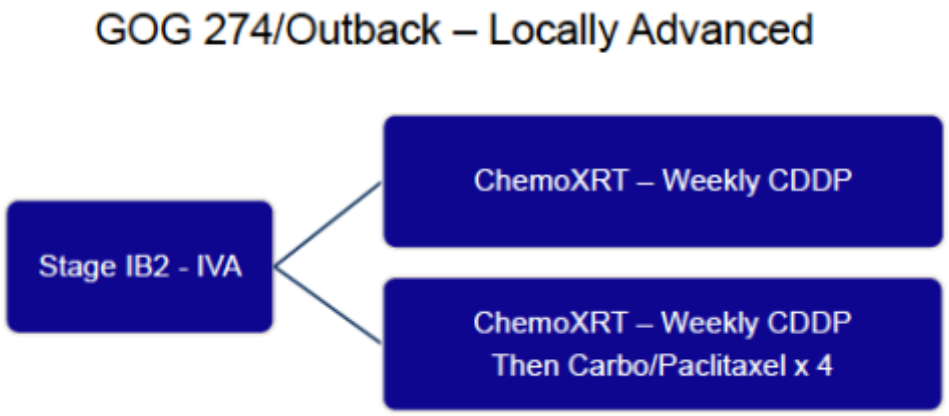
Weekly Cisplatin & Gemcitabine Concurrent EBRT/Brachytherapy Adjuvant Cis/Gem q 21d x 2 cycles	Weekly Cisplatin Concurrent EBRT/Brachytherapy

- 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
Ongoing Controversies

- Assessing the specific benefit of chemotherapy after primary chemoradiation



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:

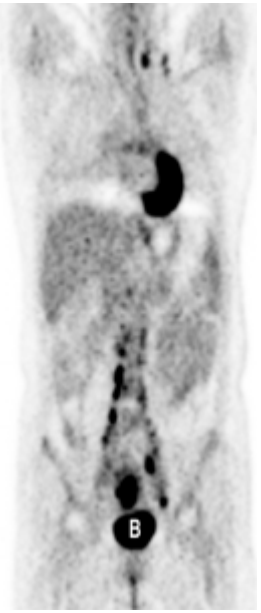
    -Similar finding, ChemoRT superior to neoadj chemotherapy followed by surgery (5-yr PFS 66% vs 57%)

    ASCO 2019.

Cervical Cancer
Nodal Status

- Lymph node involvement important prognostic indicator
  - 5-yr DSS 50–60% with pelvic lymph node involvement, 20–40% with paraaortic lymph nodes
- **Diagnostic Techniques**
  PET/CT:
  - Best sensitivity/specificity for nodal involvement

  MRI:
  - Less sensitivity for nodes
  - ↑ accuracy for determining local invasion/spread



- Consider lymph node dissection in setting of PET/CT showing bulky nodes, or (+) pelvic LN but negative PALN

Gien & Covens. *J Surg Oncol* 2009.
Uzan C et al Oncologist 2011
Ramirez PT et al. Cancer 2011

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?
  - NCI trial of 9 patients receiving T-cells harvested & expanded from tumor showed 3/9 had objective tumor responses

    Stevanovic S et al. *J Clin Oncol* 2015.

- 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%

QUESTIONS

katypenn@uw.edu