Endometrial Carcinoma

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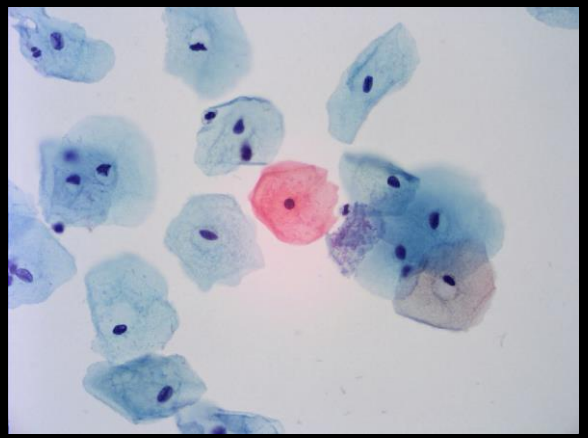
Postmenopausal bleeding

- ~5% of outpatient gynecology visits
- ~5-10% of women will have endometrial cancer (1%-25% depending on risk factors)
  - Nulliparous women >70yo -> 87% risk CAH or EnCa
  - Obesity, DM, tamoxifen
  - Full H&P should be performed etiology
- Can start with EMB or TVUS
- Remember cervical cytology



Postmenopausal Bleeding.

TABLE 49.4 CAUSES OF POSTMENOPAUSAL UTERINE BLEEDING

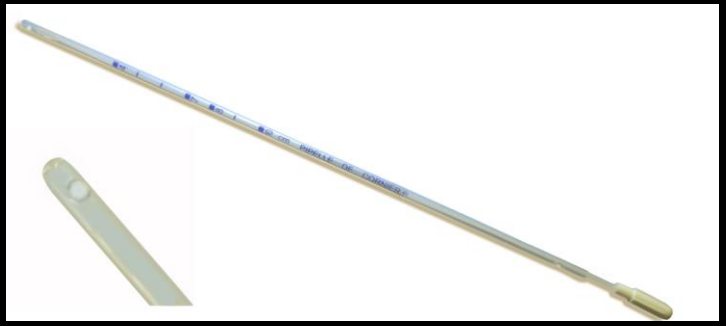
Cause	Frequency (%)
Atrophy of the endometrium	60–80
Hormone therapy	15–25
Endometrial cancer	10–15
Endometrial polyps	2–12
Endometrial hyperplasia	5–10

Abnormal Bleeding

- **ENDOMETRIAL BIOPSY!** "*Biopsy first, think later*"

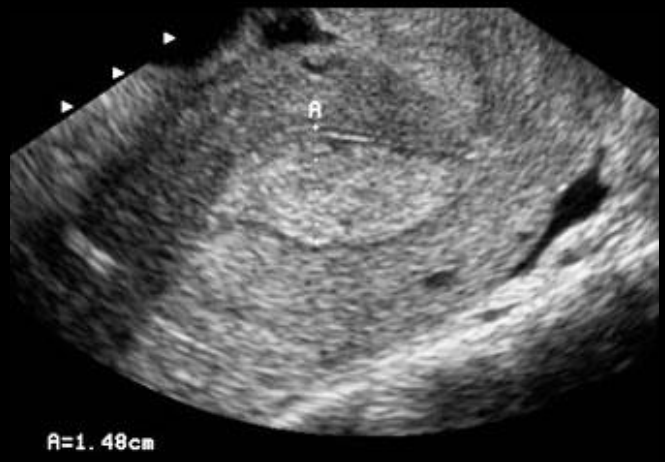
- Post-menopausal women: Indications for EMB:
  - Any PMB
  - PMB and TVUS criteria
  - Asymptomatic post-menopausal woman with incidental endometrial thickening or fluid *no PMB in 5-20% cases EnCa, however endometrial thickness on TVUS is less predictive in asymptomatic women
- Pre-menopausal women: Indications for EMB:
  - Over 45 – first line diagnostic for heavy, frequent AUB
  - <45yo: Unopposed estrogen (obesity (BMI≥30), PCOS), persistent AUB, failed medical management, other genetic risk
  - Cervical cytology: AGC-endometrial, AGC and age ≥35, endometrial cells and age ≥40 and other risk

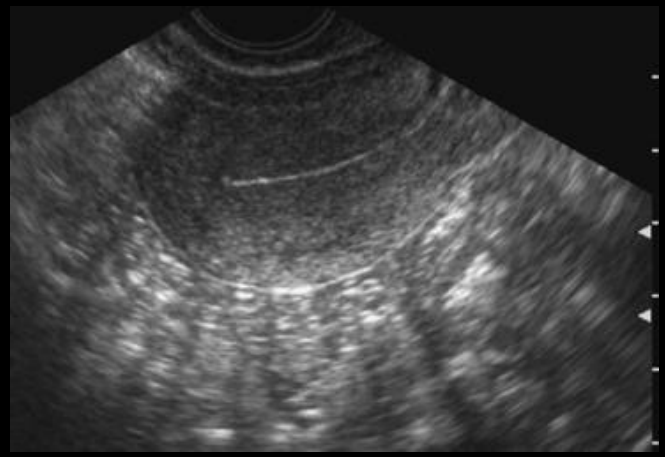
- Following up negative EMB with D&C
  - EMB may miss small lesions – consider if persistent bleeding, concerning risk factors
  - Nondiagnostic or failed EMB
  - Unable to complete office biopsy



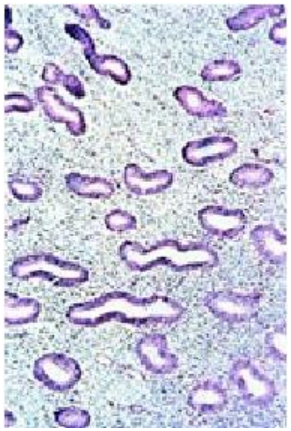
U/S findings

- Pelvic Ultrasound
  - Need for EMB if:
    - Endometrial lining >4mm
    - Heterogeneity of lining
    - Inadequate visualization
    - Persistent PMB – think type II endometrial cancer!
  - NO clear cutoff for premenopausal thickened lining
    - TVUS on day 4-6 of cycle
  - Not gold standard:
    - ≤5mm: risk EnCa reduced to 2.5%
    - >5mm: risk raised to 31% in one meta-analysis with 14% risk in population (Tabor 2002)

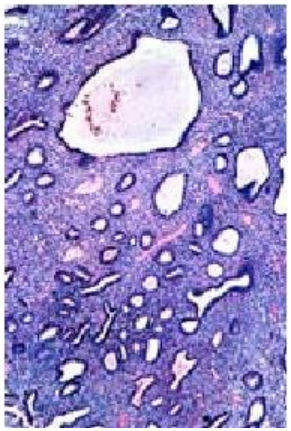




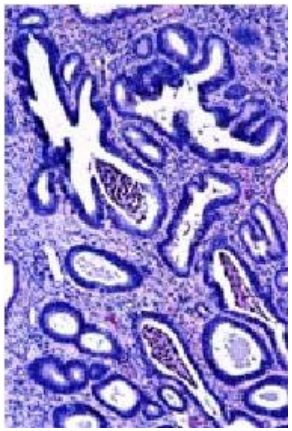
Endometrial Hyperplasia



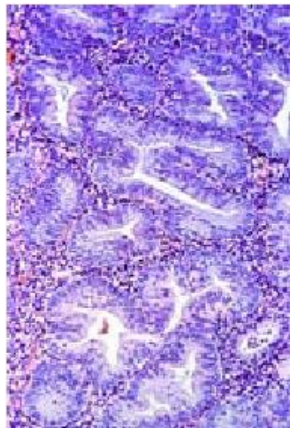
Proliferative Endometrium



Simple Hyperplasia



Complex Hyperplasia



Complex Atypical Hyperplasia

- One study found 42% rate of EmCa on hysterectomy with CAH on EMB

Trimble CL, Kauderer J, Zaino R, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer 2006;106:812–819

Endometrial Hyperplasia

TABLE 49.1 WORLD HEALTH ORGANIZATION'S CLASSIFICATION OF ENDOMETRIAL HYPERPLASIA

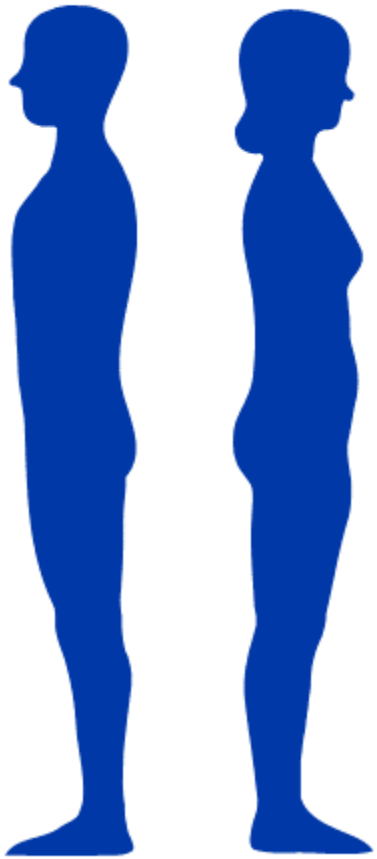
Types	Risk of Progressing to Cancer (%)
Simple hyperplasia without atypia	1
Complex hyperplasia without atypia	3
Simple hyperplasia with atypia	8
Complex hyperplasia with atypia	29

Endometrial Hyperplasia

- Management with progesterone
  - Oral
  - Mirena IUD
- Usually treat complex hyperplasia and monitor simple hyperplasia
- May treat complex hyperplasia with hormones if patient desires fertility or she is a poor surgical candidate

Estimated New Cancer Cases* in the US in 2019

Males 870,970	
Prostate	20%
Lung & bronchus	13%
Colon & rectum	9%
Urinary bladder	7%
Melanoma of skin	7%
Kidney & renal pelvis	5%
Non-Hodgkin lymphoma	5%
Oral cavity & pharynx	4%
Leukemia	4%
Pancreas	3%
All other sites	22%

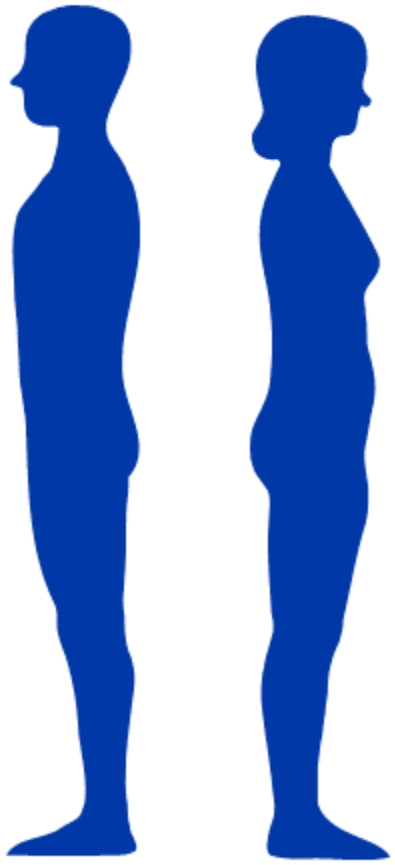


Females 891,480	
30%	Breast
13%	Lung & bronchus
7%	Colon & rectum
7%	Uterine corpus
5%	Melanoma of skin
4%	Thyroid
4%	Non-Hodgkin lymphoma
3%	Kidney & renal pelvis
3%	Pancreas
3%	Leukemia
21%	All other sites

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

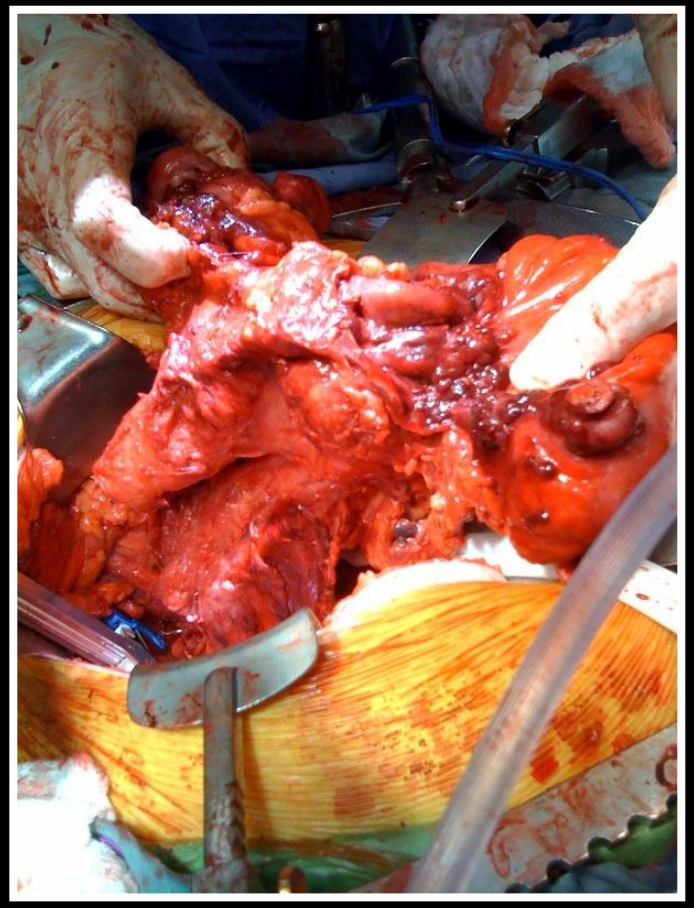
Estimated Cancer Deaths in the US in 2019

Males 321,670		Females 285,210	
Lung & bronchus	24%	23%	Lung & bronchus
Prostate	10%	15%	Breast
Colon & rectum	9%	8%	Colon & rectum
Pancreas	7%	8%	Pancreas
Liver & intrahepatic bile duct	7%	5%	Ovary
Leukemia	4%	4%	Uterine corpus
Esophagus	4%	4%	Liver & intrahepatic bile duct
Urinary bladder	4%	3%	Leukemia
Non-Hodgkin lymphoma	4%	3%	Non-Hodgkin lymphoma
Brain & other nervous system	3%	3%	Brain & other nervous system
All other sites	25%	24%	All other sites



Endometrial Cancer: Background

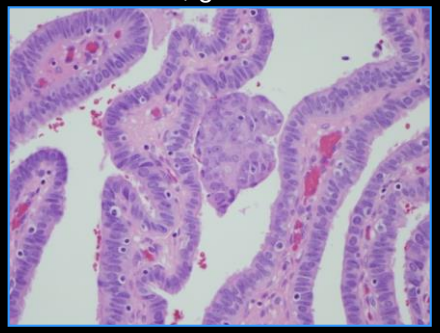
- Majority of disease is early stage and curable with surgery
- For advanced stage disease, adjuvant modalities are limited
- Understanding the risk factors will be crucial



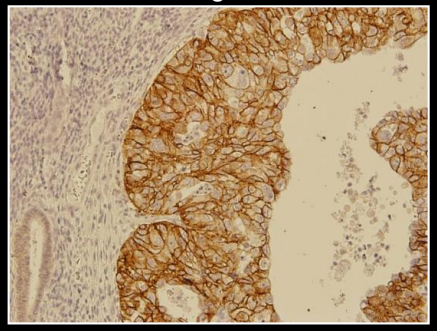
The Clinical Divide of Endometrial Cancer

Endometrial cancer encompasses a broad spectrum of histology that associates with clinical behavior

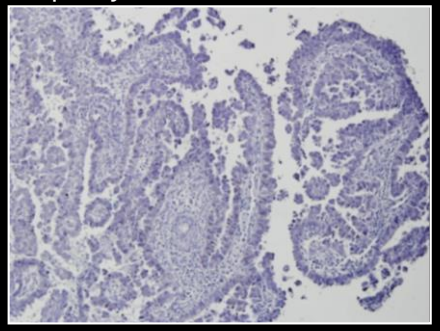
Endometrioid, grade 1



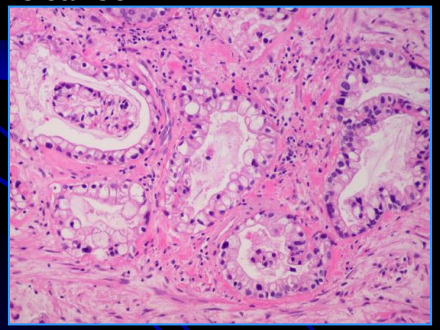
Endometrioid, grade 3



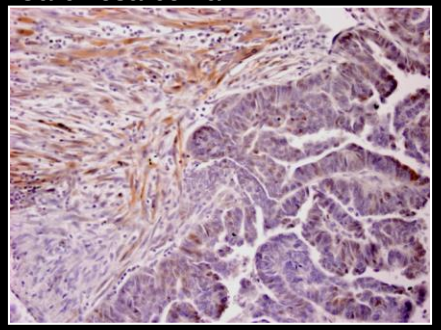
Papillary Serous



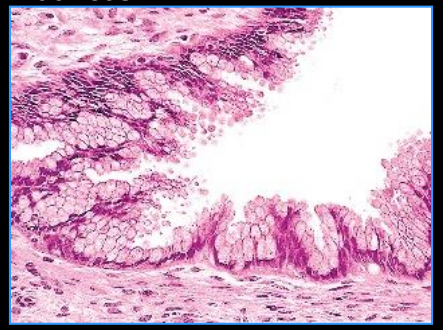
Clear Cell



Carcinosarcoma



Mucinous



GRADE

FIGO grading:

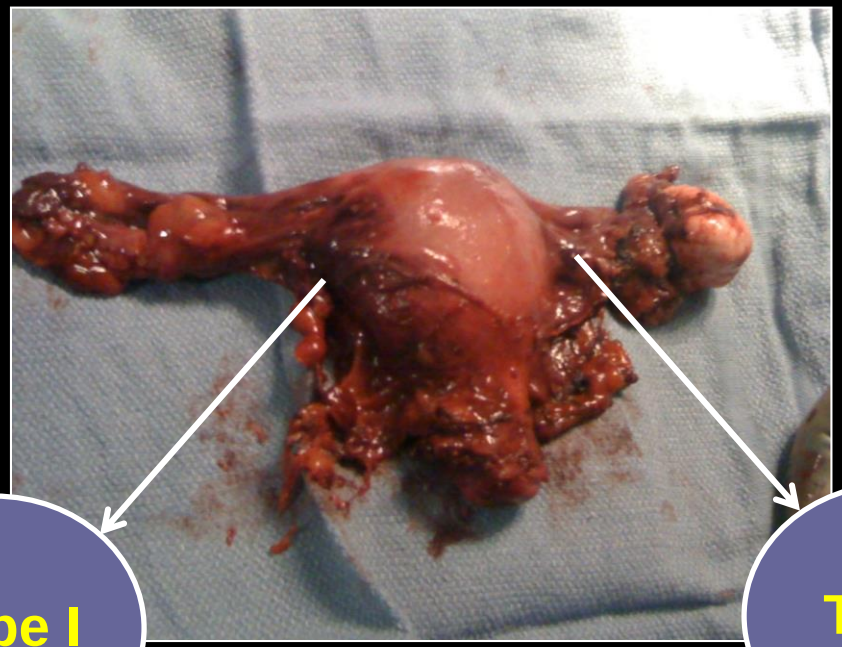
DEGREE OF DIFFERENTIATION

G1: 5% or less solid growth pattern
G2: 6% to 50% solid growth pattern
G3: More than 50% solid growth pattern

NOTES

Nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade 1 or grade 2 tumor by 1.
In serous adenocarcinomas, clear cell adenocarcinomas, and squamous cell carcinomas, nuclear grading takes precedence.
Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.

The Clinical Divide of Endometrial Cancer



Type I

Type II

Types of Endometrial Cancer

Type I (85%)

- Hyperplasia
- Hyperestrogen
- Well differentiated
- Endometrioid, Gr 1
- Steroid receptor (+)
- PTEN/MSI (55%)
- Good prognosis

Type II (8-10%)

- No hyperplasia
- No hyperestrogen
- Poorly differentiated
- Serous/clear cell
- p53 overexpression (80%)
- Poorer prognosis

The Clinical Divide of Endometrial Cancer

Feature	Type I	Type II
Pattern of recurrence	Local	Distant
Stage at presentation	I (73%) II (11%) III (13%) IV (3%)	I (54%) II (8%) III (22%) IV (16%)
Survival by stage	I (85-90%) II (70%) III (40-50%) IV (15-20%)	I (50-80%) II (50%) III (20%) IV (5-10%)

Adapted from Boruta DM et al. Gynecol Oncol 2009;115:142-53.;

Risk of Endometrial Cancer

- Iatrogenic
  - Unopposed Estrogen — 6-8x RR
  - Tamoxifen — 3x RR
- Physiologic
  - Obesity — up to 10x at 50 lbs over IBW
  - Diabetes — 2-3x RR
- Genetic
  - HNPCC Mutation — up to 60%
  - BRCA — ?? (up to 3% UPSC)
  - PTEN/ Cowden's — ?? (10%)

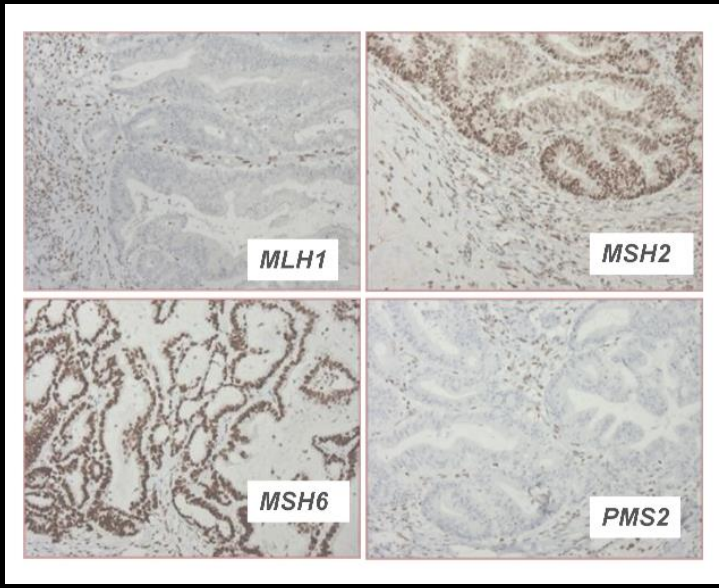
Tamoxifen and Endometrial Cancer

- Endometrial proliferation, polyps, hyperplasia
- Endometrial carcinoma: Risk of EmCa 2-3x general population
  - Age ≥50yo
  - Dose and time dependent
  - High dose tamoxifen (40mg/d) associated with high grade tumors
- Uterine sarcomas

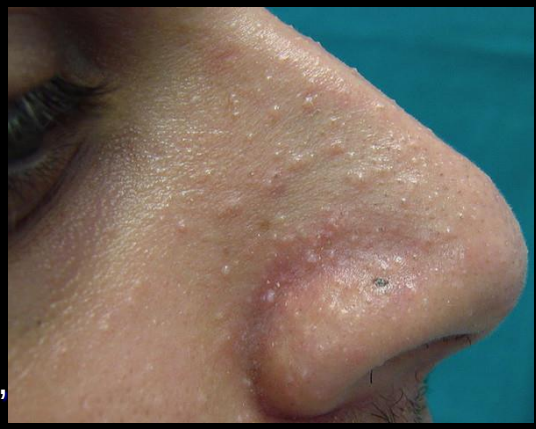
- No increased surveillance, but all concerns in post-menopausal women should be evaluated

Hereditary Endometrial Cancer

- Lynch syndrome / Hereditary Nonpolyposis Colorectal Cancer
  - Autosomal dominant mismatch repair gene mutation: MLH1, MSH2, MSH6, PMS2 or EPCAM (leads to hypermethylation of MSH2)
  - Up to 60% lifetime risk EnCa (varies by mutation 27 (MLH1)-71%(MSH6))
    - Also 3-20% lifetime risk ovarian cancer
  - Universal screening of EnCa by IHC for mismatch repair proteins
    - *Many MMR deficient tumors are sporatic: ~20% EnCa MSI but ~5% Lynch
  - Offer prophylactic surgery after completion of childbearing
  - Other tumors: colorectal, gastric, small intestine, GU, skin, pancreas
  - Screening: annual EMB and TVUS age 30-35 until surgery

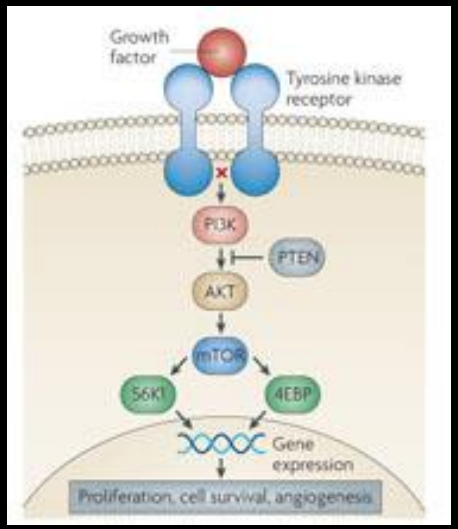


Hereditary Endometrial Cancer



- Cowden syndrome
  - Autosomal dominant *PTEN* mutation (tumor suppressor)
  - 5-28% lifetime risk
  - Other tumors: mucocutaneous hamartomas (non-cancerous), breast cancer (25-85%), thyroid (non-cancerous), GI, neuro
  - Screening: consider annual EMB and TVUS starting age 30-35

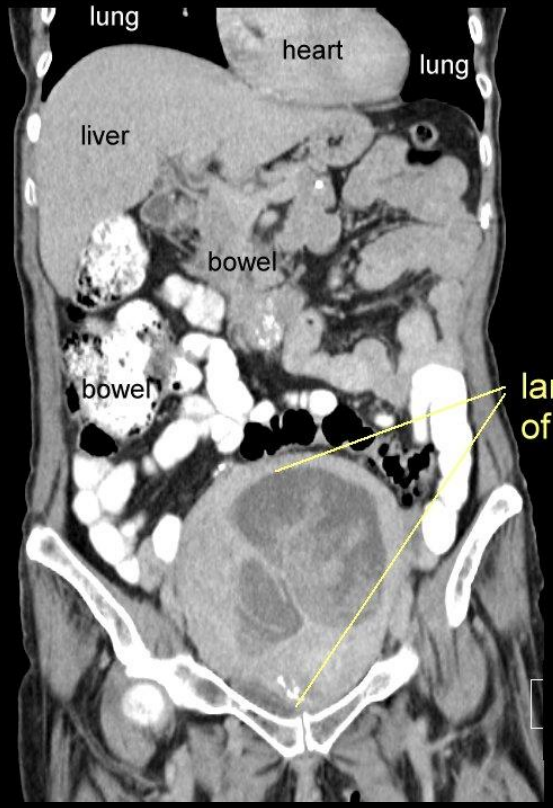
- BRCA: elevated risk USC?
  - Study of >1000 women: 5 cases USC vs. 0.33 expected
    - 3 of 5 had used tamoxifen; 4 BRCA1, 1 BRCA2
    - 2.6% risk USC by age 70
  - No current recommendation for concomitant hysterectomy without other indication



Shu JCO 2015

Endometrial Cancer – Pre-operative Evaluation

- Grade 1 endometrioid:
  - No imaging required
  - Standard pre-operative assessment
- High-grade / non-endometrioid histologies
  - CT vs. PET/CT scan
  - Standard pre-operative assessment
- Referral to Gyn Onc improves survival
- LAP2: Laparoscopy non-inferior to laparotomy



Chan, Sherman et al. Influence of Gynecologic Oncologists on the Survival of Patients with Endometrial cancer. J ClinOnc 2011

Surgical Therapy

Carcinoma of the corpus uteri (FIGO 2008)

Stage I*	Tumour confined to the corpus uteri.
IA*	No or less than half myometrial invasion.
IB*	More than half myometrial invasion.
Stage II*	Tumour invades cervical stroma, but does not extend beyond the uterus.**
Stage III*	Local and/or regional spread of the tumour.
IIIA*	Tumor invades the serosa of the corpus uteri and/or adnexae#.
IIIB*	Vaginal and/or parametrial involvement#.
IIIC*	Metastases to pelvic and/or para-aortic lymph nodes#.
• $IIIC_1$*	• Positive pelvic nodes
• $IIIC_2$*	• Positive paraortic lymphnodes with or without positive pelvic lymphnodes.
Stage IV*	Tumor invades bladder and/or bowel mucosa, and/or distant metastases.
IVA*	Tumor invasion of bladder and/or bowel mucosa.
IVB*	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes.

* Either G1, G2 or G3.

** Endocervical glandular involvement only should be considered as Stage I and no more as Stage II.

Positive cytology has to be reported separately without changing the stage.

Surgical Management

- Hysterectomy, bilateral salpingo-oophorectomy, pelvic washings, pelvic and paraaortic lymphadenectomy
  - Lymph node dissection
    - Sentinel Lymph node dissection
    - Mayo Critera
      - Grade 1 < 50% invasion on frozen, no cervix invasion, ≤2cm
      - Grade 2 and no/ minimal invasion, No cervix invasion, ≤2cm
        - Tumors >2cm have a 17% risk of nodal mets
- Omentectomy and biopsies added if type II cancer
  - Can have mets in up to 25% of UPSC with no invasion
  - Extrauterine extension in 65-85% of UPSC: nodes in 40%, Omentum 20%

Surgical Stage is THE most important predictor of Survival

	% in stage	5 yr OS
Stage I	70%	75%
Stage II	18%	60%
Stage III	8%	30%
Stage IV	4%	10%

Why Sentinel Lymph Node Mapping?

- Decreases Morbidity
  - Incidence of lymphedema following LND for endometrial cancer is high (GOG 244) – 10%+ increase in limb volume: 34%
  - 10%+ increase and impaired PRO: 20%
- Surgical Complications
- Surgical duration

Sentinel Lymph Node Mapping Reduces Rate of Lymphedema

- Patient-reported lower-extremity lymphedema(LEL) with SLN (180), LND (352), or no LN assessment (67):
- Self-reported LEL rates:
  - SLN:27%
  - LND:41%

M Leitao, Gyn Oncol, 2020

Sentinel Lymph Node Mapping

- Inject Indocyanine green to the cervix at 3 and 9 o’clock positions

Figure 1: Common cervical injection sites for mapping uterine cancer†

Figure 2: Most common location of SLNs (blue, arrow) following a umbilical ligament

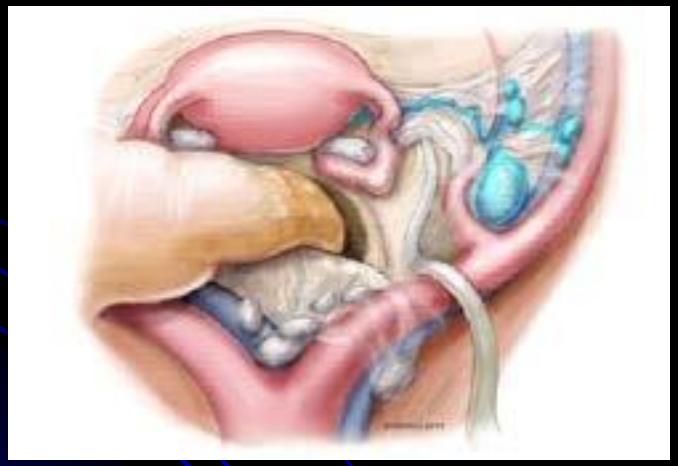
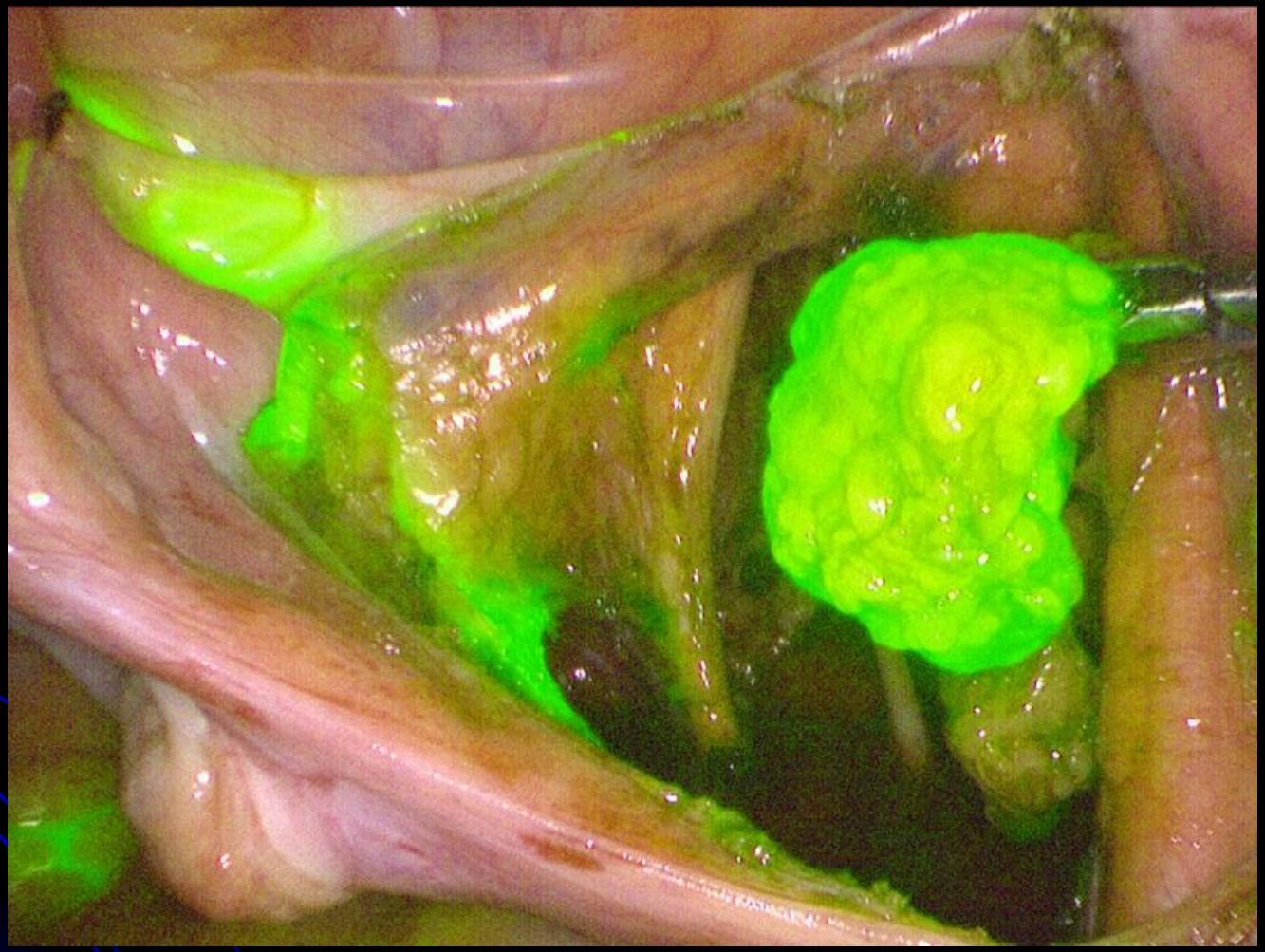


Figure 3: Less common location of SLNs (green, arrow) usual but following the mesoureter cephalad to common iliac and presacral region†

NCCN Guidelines, 2019



FIRES Trial

- 385 patients with endometrial cancer underwent SLN mapping with ICG followed by pelvic (340) and/or para-aortic (196) LND
- Low grade: 72%, high grade: 28%
- Mapping: bilateral (52%), unilateral (34%), neither (14%)
- Para-aortic SLN: 23% (isolated < 1%)
- LNs removed: SLNs – 2, total – 19
- **Lymph node metastasis: 11%**
- **False negative SLN (3%)**

E Rossi, Lancet Oncol; 2017

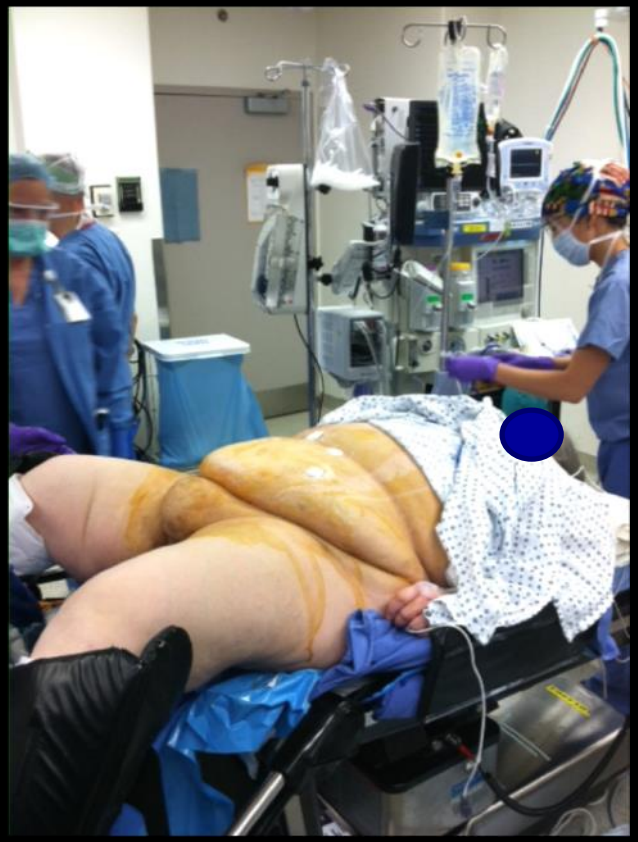
Surgical Cytoreduction in Stage IV Disease

- The amount of residual disease after surgery, performance status and age are independent predictors of survival.
- Stage IV endometrial cancer
  - OS 14.4 months with 3.9% alive at 5 years
    - Optimal cytoreduction median OS= 26 months
    - Suboptimal cytoreduction med OS= 9 months

Bristow et al, GynOnc, 2000
Chi et al, GynOnc,1997

What about non-surgical management?

- Non-surgical candidates:
  - Elderly
  - Obese
  - Comorbidities
- Fertility sparing
  - Reports of diagnosis of endometrial cancer in <45yo vary from 5-30%
  - Most patients diagnosed with endometrial cancer also have risk factors associated with subfertility
- Advanced disease / Palliative care



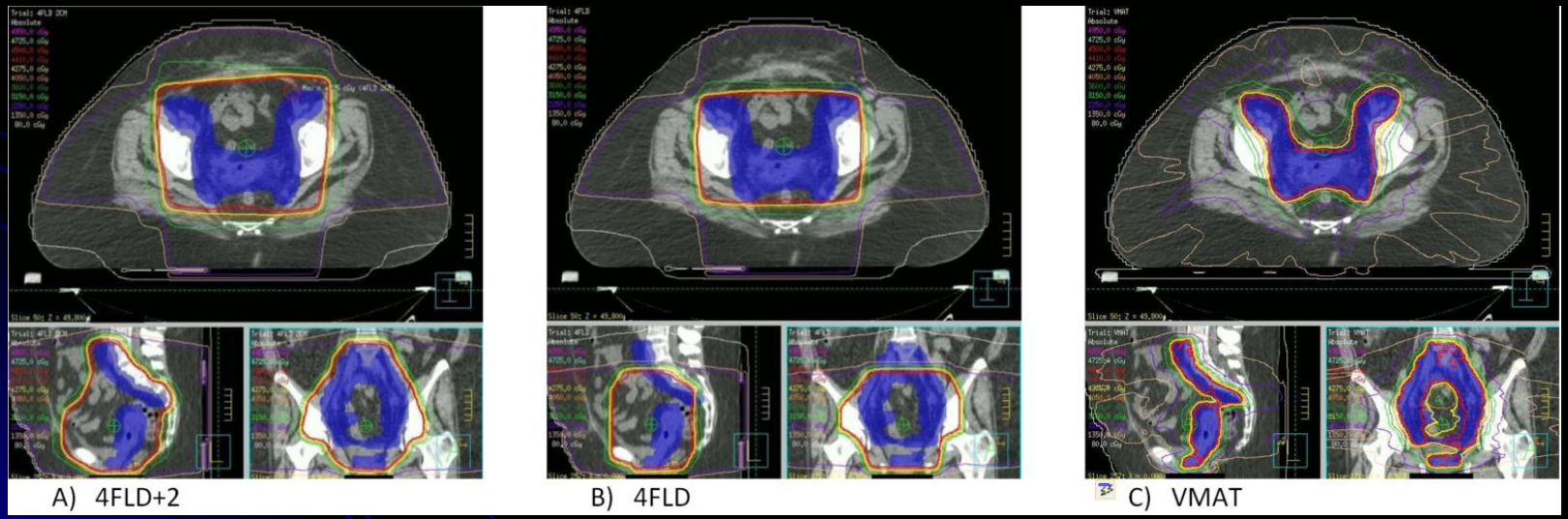
What are the non-surgical options?

- Radiation
  - Good for bleeding and pain control
  - +/- chemotherapy
- Progesterone therapy
  - Systemic: Megestrol, Medroxyprogesterone
  - Local: Levonorgestral intrauterine system

- Fertility-sparing candidates:
  - Low-grade endometrioid only
  - Need D&C, not just EMB
  - Pelvic MRI: assess myometrial invasion
  - EMB q3mo to assess response

Adjuvant Therapies

Endometrial Cancer Treatment:



A) 4FLD+2 B) 4FLD C) VMAT

Risk Stratification

Table 1
Comparison of high-intermediate risk groups in stage I endometrial cancer as defined by PORTEC-1 and GOG 99.

	PORTEC-1	GOG 99
Age	>60	See below
Grade	3	2–3
Myometrial invasion	>50% (outer 1/2)	>66% (outer 1/3)
Lymphovascular space invasion	N/A	Present
High intermediate risk group	2 of 3 above risk factors	Any age, all 3 above risk factors Age > 50, 2 above risk factors Age > 70, 1 above risk factor

Adjuvant Therapy in Endometrial Carcinoma

- Evolving for advanced disease
  - Hormonal therapy
  - Chemotherapy
  - Radiation +/- systemic therapy
- Early stage, Type I endometrial cancers
  - High-intermediate risk: WPXRT vs brachytherapy
- Early stage, Type II endometrial cancers
  - Trend to chemotherapy + brachytherapy or WPXRT

Table 5
Author estimates of vaginal recurrence with and without vaginal brachytherapy based on risk group.

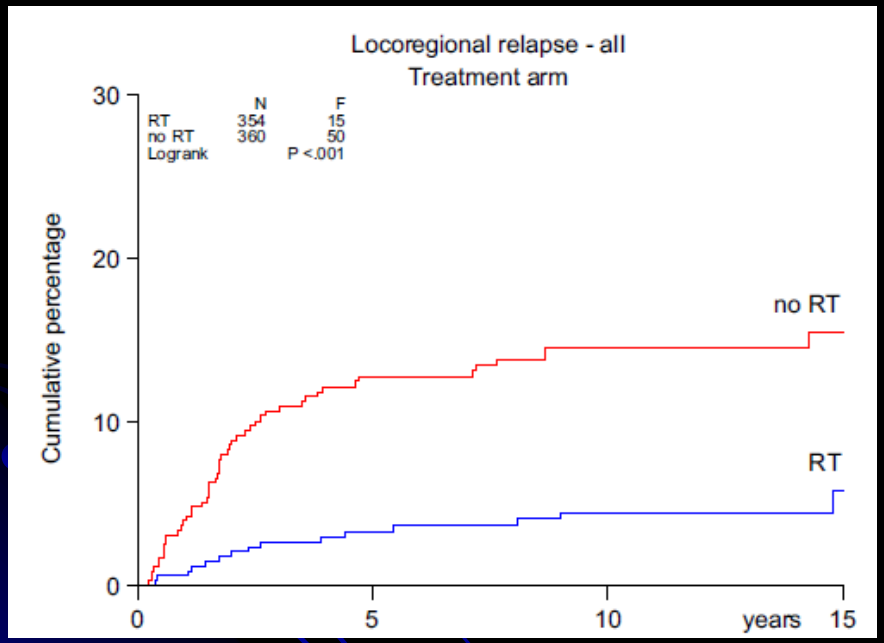
Primary Risk Factors	Age >60, LVSI, and/or large tumor size	Risk Group	Observation	VBT	Authors' recommendation
Non-invasive, Gr 1–2	–	Low	0–2% [5,67]	0–1%	Observation
Non-invasive Gr 1–2	+	Low	0–2% [5,67]	0–1%	Observation
<1/2 MMI Gr 1–2	–	Low-int	3–4% [3,4,7,22]	0–2% [22,30]	Observation OR Referral to radiation oncology
<1/2 MMI, Gr 1–2 OR non-invasive Gr 3	+ +/–	Low-int	5–6% [3,4,7]	0–2% [22,30]	Referral to radiation oncology
>1/2 MMI, Gr 1–2 OR <1/2 MMI, Gr 3	– –	Int	8–10% [3,4,7]	0–3% [18,29]	VBT
>1/2 MMI, Gr 1–2 OR <1/2 MMI, Gr 3	+ +	High-int	13–19% [3,4,7]	2–3% [28,29]	VBT, but consider EBRT based on risk factors & nodal dissection

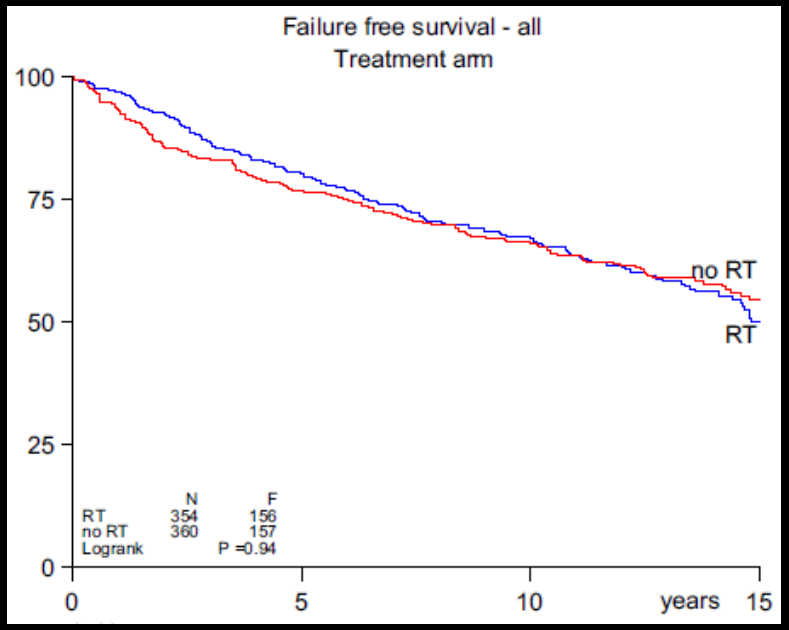
Adjuvant Radiation

- Radiation reduces recurrence in pelvis→ local modality, local control
  - balance cost/toxicity against risk
- Radiation does not lead to improved survival
- Have we studied XRT in the best populations yet
  - "too low risk" evaluated
  - selection, selection, selection → H-IR population
- Is whole pelvis the best radiation→ VCB??

Endometrial Cancer Treatment

Post operative radiation therapy leads to decreased recurrence without clear improvement in survival in high risk endometrial cancer





Scholten AN et al IJROBP 2005
Creutzberg CL et al IJROBP 2011
Nout RA et al Lancet 2010

GOG-99

- Survival from Endometrial Cancer was higher than expected *(50% of deaths due to other disease)*
- Defined High Intermediate Risk Group
  - Risk factors
    - Grade 2/3
    - LVSI
    - Outer 1/3 myometrial Involvement
  - High Intermediate Risk (25% recurrence rate)
    - > 50 yo with 2 risk factor
    - > 70 yo with 1 risk factors
    - Recommended WPRT in this group due to risk of recurrence (although NO significant difference in Survival)

Keys HM, Gynecol Oncol 92:744, 2004

PORTEC Trial

- Results
  - Patient characteristics
    - IB – 39%
    - G1-2 – 90%
  - less pelvic failures with RT (14% vs. 4%, p < 0.001)
  - no difference in overall survival at 5 years

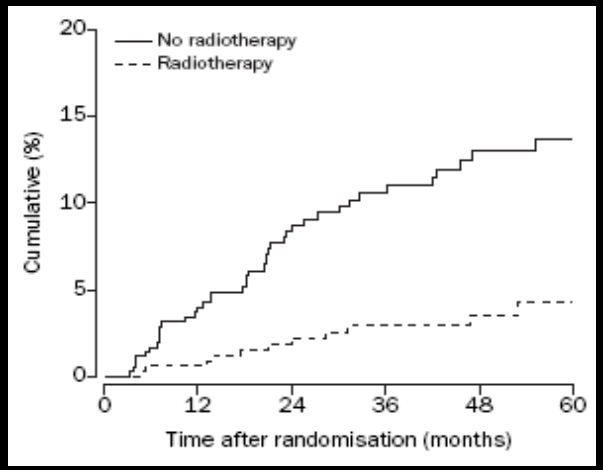


Figure 2: **Probability of locoregional (vaginal or pelvic) relapse for patients assigned to postoperative radiotherapy or no further treatment**

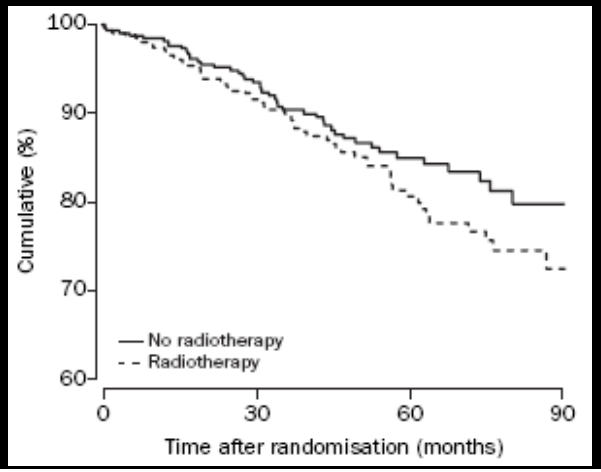


Figure 3: **Probability of survival for patients assigned to postoperative radiotherapy or no further treatment**

Creutzberg et al. Lancet. 2000 Apr 22;355(9213):1404-11

PORTEC 2 trial design

TAH/ BSO no LND

Eligibility:

High intermediate risk group

-Age>60+ IC G1-2 or IB G3

-Stage IIa (<50% myoinvasion)

N=427 pts

	G1	G2	G3
IA			
IB			■
IC	■	■	
IIA	■	■	

EBRT
46 Gy in 23 fractions
N=214

Brachytherapy
21 Gy in 3 HDR fractions
or 30 Gy LDR, to 0.5 cm depth
N=213

Primary endpoint: rate of vaginal relapse
Secondary endpoints: OS, QOL

Median F/U 36 months

R. Nout, ASCO, 2008

PORTEC 2 Results

Outcome	EBRT	Brachytherapy	
Vaginal relapse	1.9%	0.9%	*p = 0.97*
Locoregional relapse	2.5%	4%	*p = 0.15*
Distant relapse	5.7%	6.3%	*p = 0.37*
Pelvic relapse	0.6%	3.5%	***p = 0.03****
No deaths	20 pts	20 pts	
DFS-3Y:	89%	89%	
OS -3Y:	90%	90%	

QOL	EBRT	Brachytherapy	
Diarrhea	~30%	~10%	*p = 0.001*
Impairment in daily activities	~30%	~13%	*p = 0.03*
Decreased social functioning	~20%	~10%	*P=0.001*
G1-2 GI toxicity:	54%	13%	*p = 0.001*
G1-2 GU toxicity:	27%	22%	*p=0.1*
Skin toxicity:	20%	2%	*p = 0.001*

R. Nout, ASCO, 2008

PORTEC 2

- Summery:
  - Brachytherapy as effective as EBRT for high intermediate risk early stage EC.
  - Brachytherapy less toxic compared to EBRT
  - QOL significantly better with brachytherapy.

Advanced Stage Disease

Control with radiation alone in stage III

Recurrences (%)

	Pelvic	Abdom	Distant	Survival
Grigsby	23	10	23	56
Greven	21	14	27	64
Genest	11	16	28	70
Aalders	29	3	36	30

* Is radiation enough???

Endometrial Cancer Treatment: Chemotherapy

- Platinum compounds:
  - Form DNA crosslinks
  - Emetogenic, Neurotoxicity, Hypersensitivity
  - **Cisplatin**: the original
    - Ototoxicity, Renal toxicity
  - **Carboplatin**: newer, adopted for less non-hematologic side effects
    - Bone marrow suppression
- Taxanes:
  - Made from the Yew tree
  - Disrupt microtubule function
  - Neurotoxicity, Allergy, Alopecia
  - **Paclitaxel**
  - **Docetaxel**
    - Less neurotoxicity

Standard IV therapy:

Carboplatin AUC 5-7.5,
Paclitaxel 135-175mg/m^2
q3wk x 6 cycles

What about Combining Radiation and Chemotherapy?

PORTEC-3

- Stage IA G3 LVSI, IB G3
- Stage II
- Stage III

EBRT

Cisplatin (D#1 and #29) with concurrent EBRT—4 cycles carboplatin and paclitaxel

PORTEC 3 Conclusions

- Chemotherapy plus radiation does not improved OS but did improve PFS
- Stage III improve 5 year FFS (HR 0.66) and trended toward improved OS

PORTEC(s)

- PORTEC (2000)
  - Stage IB 2-3, IC G1-2
  - Observation vs WPRT
  - RT improves local regional control but not OS
- PORTEC 2 (2010)
  - Age >60, IBG3, IC G1-2, IIA (any age, exclude G3 and outer half invasionl
  - EBRT vs VCB
  - VCB is non inferior to EBRT in HIR group with less toxic effects.

Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer-GOG 258

Stage III or IVA endometrial cancer

Cisplatin/EBRT
Carbo/taxol x 4 cycles

vs

Carbo/taxol q 21 days
6 cycles

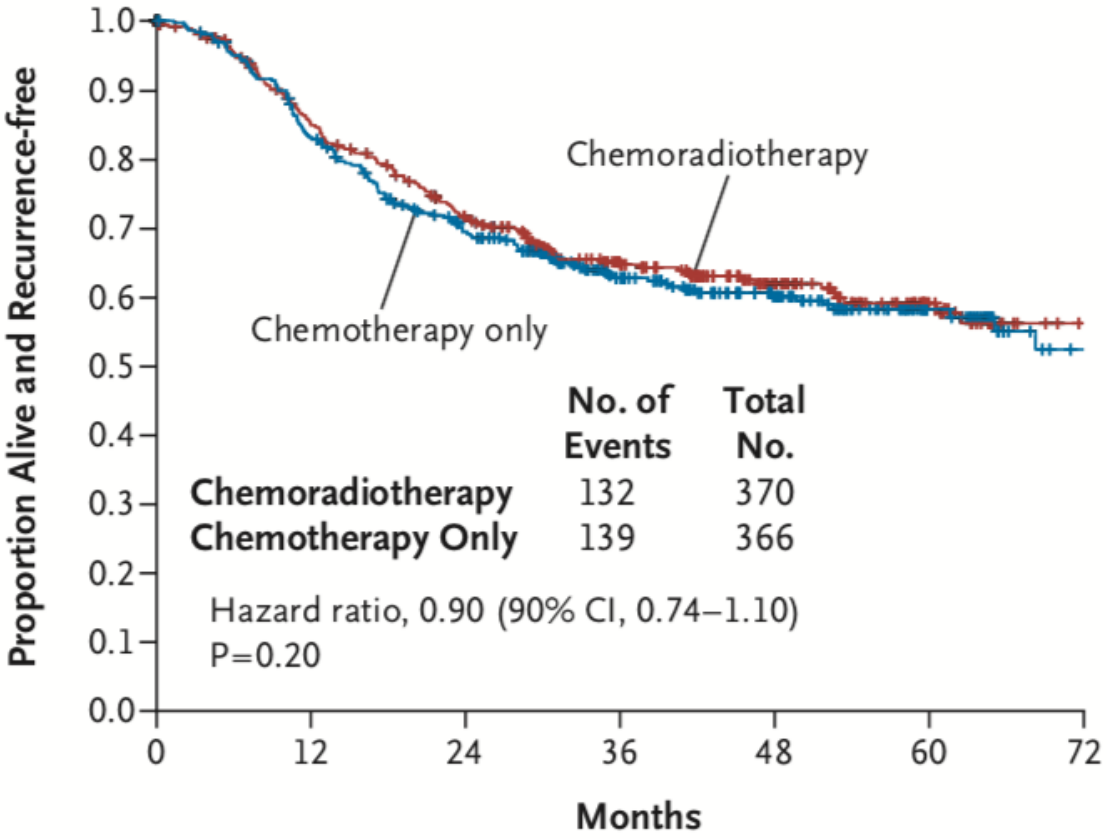
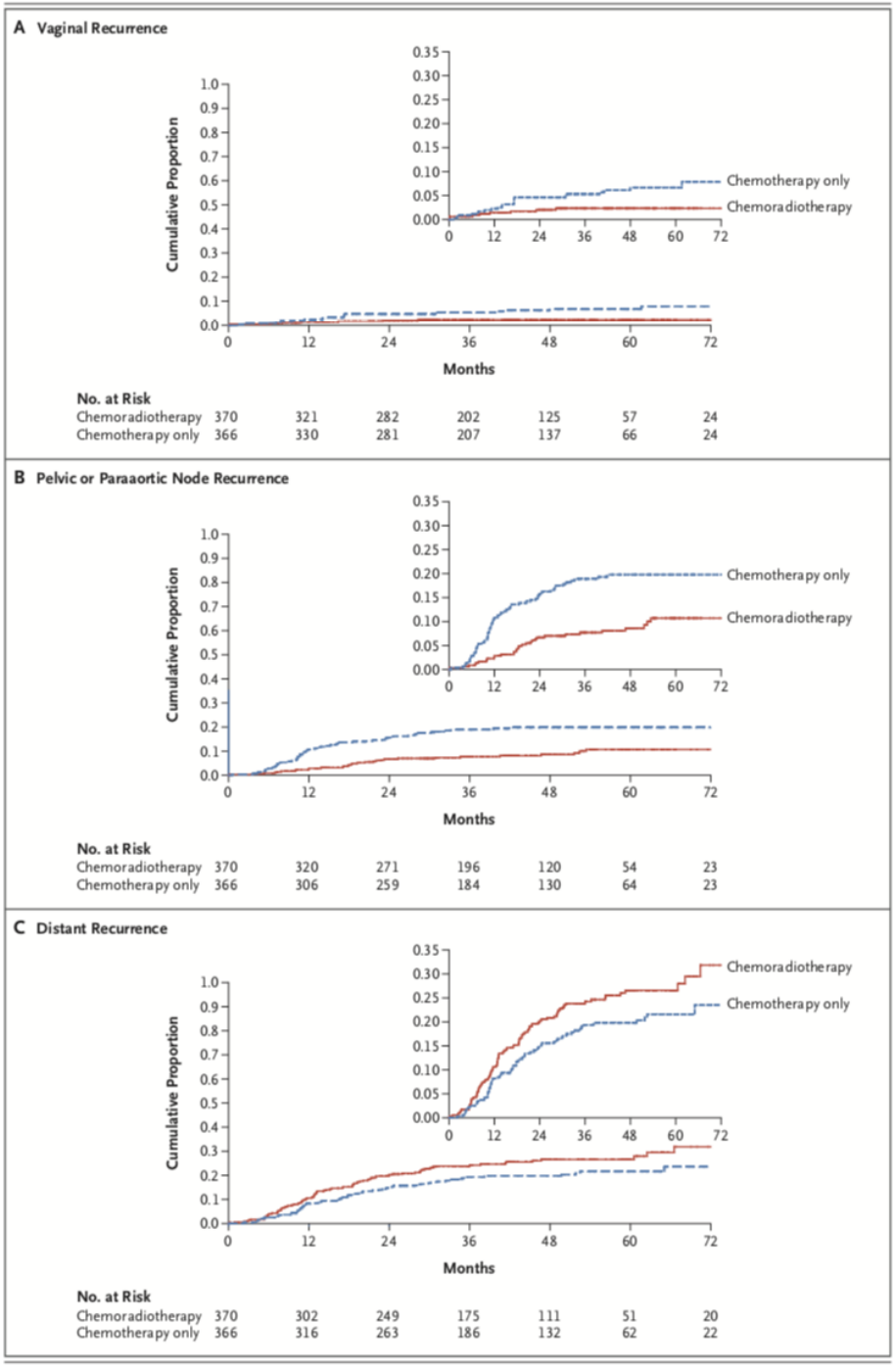


Figure 1. Relapse-free Survival.

Tick marks indicate censored data.


A Vaginal Recurrence
Cumulative Proportion
Months
Chemotherapy only
Chemoradiotherapy
No. at Risk
Chemoradiotherapy 370 321 282 202 125 57 24
Chemotherapy only 366 330 281 207 137 66 24
B Pelvic or Paraaortic Node Recurrence
Cumulative Proportion
Months
Chemotherapy only
Chemoradiotherapy
No. at Risk
Chemoradiotherapy 370 320 271 196 120 54 23
Chemotherapy only 366 306 259 184 130 64 23
C Distant Recurrence
Cumulative Proportion
Months
Chemoradiotherapy
Chemotherapy only
No. at Risk
Chemoradiotherapy 370 302 249 175 111 51 20
Chemotherapy only 366 316 263 186 132 62 22

Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer-GOG 258

- Chemoradiation did not improve RFS (HR 0.9, 95% CI 0.74-1.1)
- More acute toxicities in chemoradiation group
- Distant recurrences more common in chemoradiation group

Matei, NEJM 2019

So how do I decide?

Adjuvant Treatment for Locally Advanced Disease

- Stage II-radiation alone
- Stage IIIc-PORTEC-3 regimen or chemotherapy alone
- Stage IV-chemotherapy alone

Adjuvant Therapy

UPSC

UPSC

- 50 patients with UPSC
- The problem:
  - Extrauterine disease
    - 72% overall
    - nodal mets in up to 50% with inner 1/2 myometrial involvement
      - depth of invasion not an accurate predictor of extrauterine disease
    - LVSI associated with very high risk of extrauterine disease

Goff BA, Gynecol Oncol 54(3):264, 1994

Recurrence in Early Stage Serous Endometrial Cancers

Table 2
Recurrence in women with surgical stage I UPSC according to substage and adjuvant therapy.

Final stage	Overall RR *N* responders/*N* total (%)	Observation only RR *N* responders/*N* total (%)	Adjuvant XRT RR *N* responders/*N* total (%)	Adjuvant CT ± XRT RR *N* responders/*N* total (%)
IA	24/177 (13.6)	14/115 (12.2)	10/40 (25)	3/56 (5.4)
No residual disease	0/13 (0)	0/10 (0)	0/1 (0)	0/2 (0)
Polyp only disease	1/19 (5.3)	1/9 (11.1)	0/3 (0)	0/7 (0)
Polyp only or no residual	1/31 (3.2)	1/19 (5.3)	0/4 (0)	0/9 (0)
Other IA	11/67 (16.4)	2/27 (14.8)	4/12 (33.3)	2/28 (7.1)
IB	10/64 (15.6)	7/25 (28)	3/26 (11.5)	5/66 (7.6)
IC	9/30 (30)	3/6 (50)	5/16 (31.3)	4/24 (16.7)
IB and IC combined	59/212 (27.8)	25/67 (37.3)	26/71 (36.6)	12/107 (11.2)
All stage I combined	78/389 (20)	41/190 (21.6)	23/106 (21.7)	18/165 (10.9)

Data from [41,52,87,93,96–98,100–104]. UPSC = uterine papillary serous carcinoma, RR = recurrence rate, XRT = radiotherapy, CT = chemotherapy.

Boruta, 2011

Follow up

- More than 80% of recurrences occur in the *first 3 years* after treatment
- 60-95% will present with symptoms
  - Surveillance mainly history, exams, possibly CXR and pap smears
    - CA125 if high risk of regional or distant failure
    - CT scans based only on symptoms/ clinical findings
- Isolated vaginal cuff recurrences are treatable
  - Surgery, radiation, +/- chemotherapy
  - Salvage Rates: 40-80% with RT; 20% with Exent
- Few women with distant recurrences will achieve long-term survival
  - Single agent chemotherapy response rates: 14-36%

Gallion et al, J Clin Oncol, 2003

Advanced/Recurrent Serous Endometrial Cancer

- Phase II trial-Paclitaxel and Carboplatin +/- trasuzumab
  - Primary Stage III/IV or Recurrent HER2/neu-positive uterine serous carcinoma
    - Median PFS 12.6 months in Herceptin arm vs 8 months in paclitaxel/carboplatin
      - Primary advanced PFS 17.9 months vs 9.3 months
      - Recurrent disease PFS 9.2 months vs 6 months
- Fader, et. Al, JCO, 2019

Progestins: Defining success

- Receptor positive status: How defined?
- Prior radiation?
  - Recurrence within or outside radiation field?
- Prior chemotherapy?

IDEAL CANDIDATE:
Grade 1 tumor
No prior RT
No prior Chemo

RECEPTER CONTENT	PROGESTIN RESPONSE
Positive	80%
Negative	5%

ER/PR rule of thumb: **G1: 80% +, G2 60% +, G3 40% +**

Recurrent Endometrial Cancer

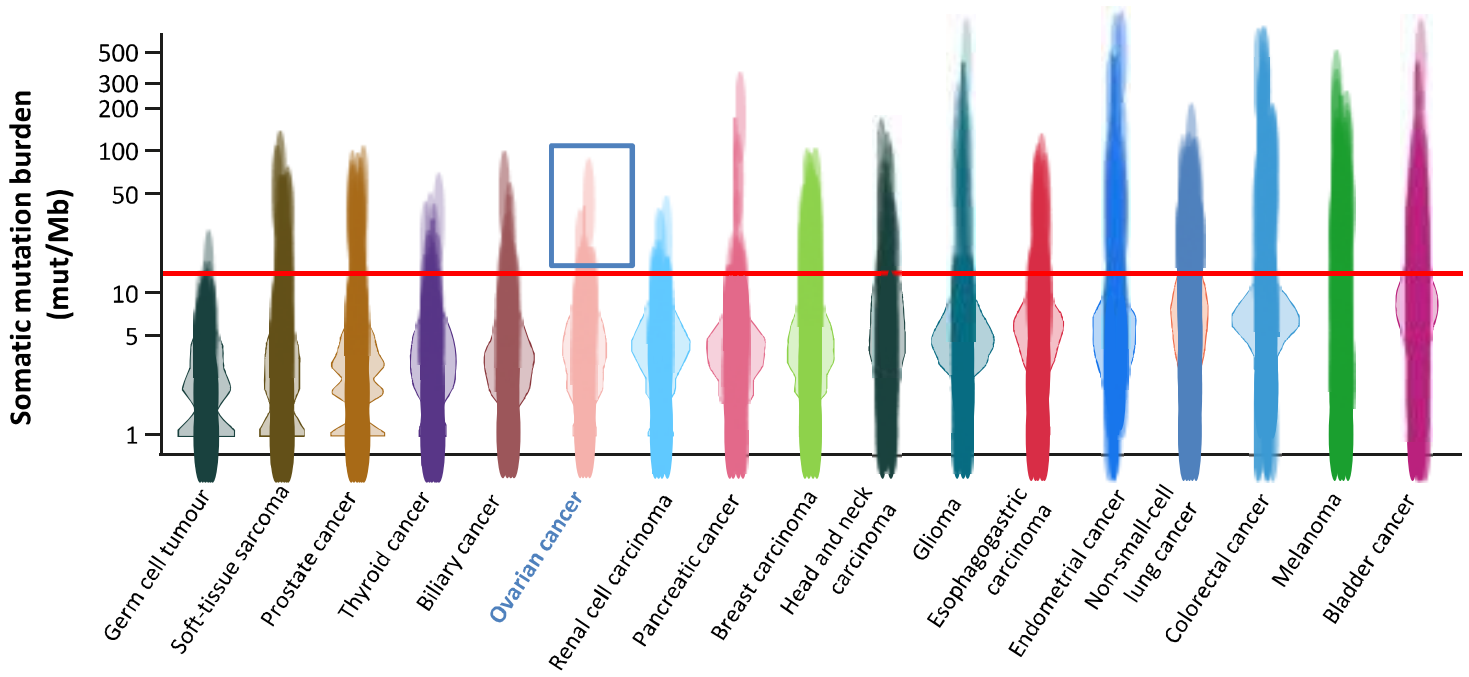
- Everolimus and letrozole
  - Phase II Study
  - mTOR inhibition overcomes endocrine resistance
    - 38 patients
    - RR 32%
  - Least response in serous endometrial cancers

Slomovitz, JCO, 2015

Checkpoint Inhibitors

- Pembrolizumab
  - FDA approval in May 2017 as the first tissue agnostic treatment
  - Solid tumors with MMR deficiency or MSI-H

Mutational Load



Red line indicates the threshold for samples with a high mutational burden (13.8 mutations/Mb)

Mb, megabase

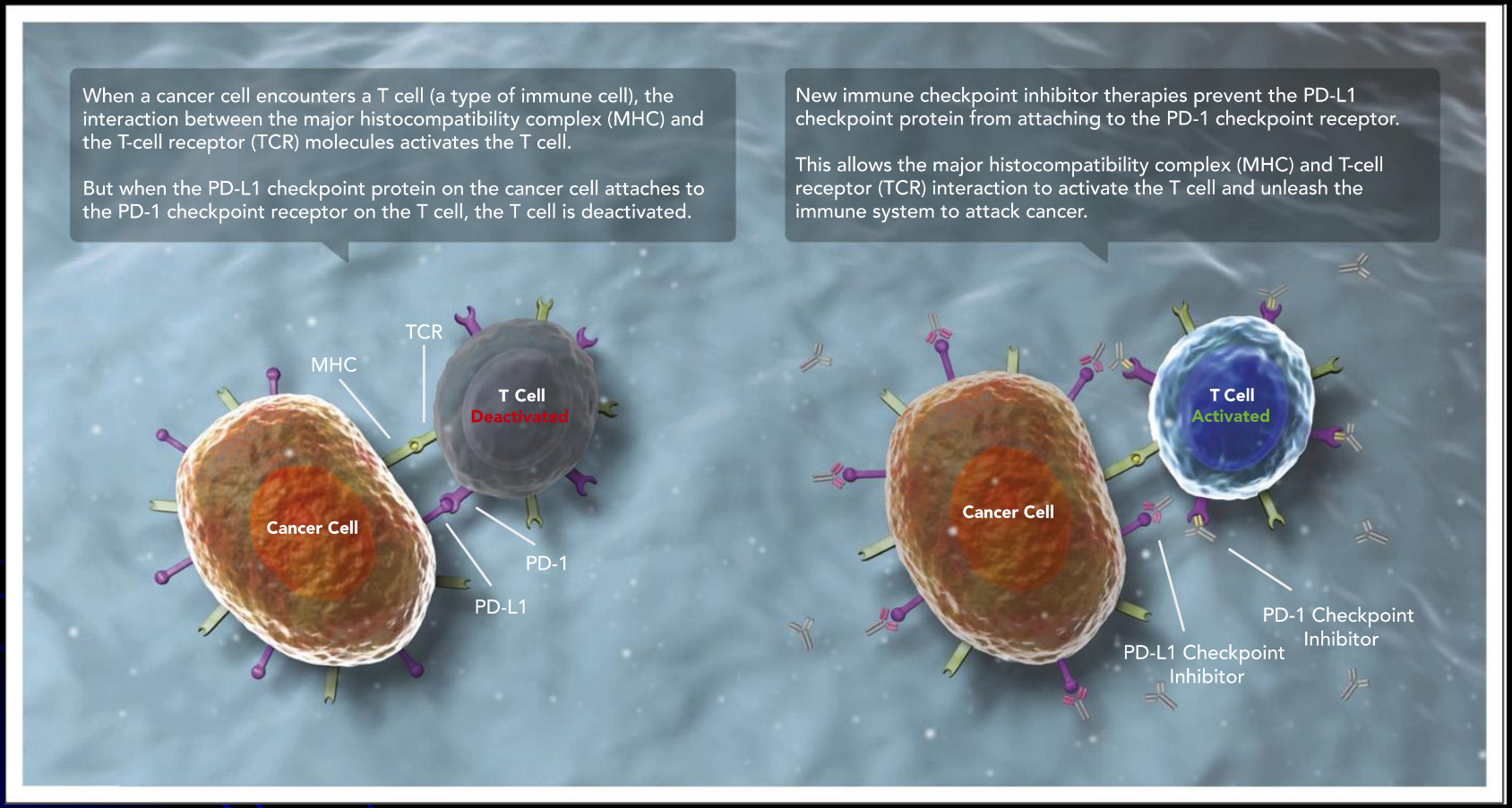


Fig 2. Immune [illegible] programmed death [illegible]

ASCO clinical advances 2017

Recurrent Endometrial Cancer

- Pembroluzimab/Lenvatinib-Approved September 2019
  - For patients who are not candidates for curative surgery or radiation and who have disease that is not microsatellite instability–high (MSI-H) or mismatch repair deficient (dMMR).
  - single-arm, multicenter, open-label, multi-cohort phase Ib/II Study 111/KEYNOTE-146 trial (NCT02501096), which evaluated 108 patients
    - ORR 38.3% in non-MSI/dMMR tumors-CR 10.6%, PR 27.7%
    - 69% had DOR of at least 6 months
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