Evidence Based Radiation Oncology Fact Sheets
Uterine Cancer 2023

Andrew Zhang, MD
andrewzhangmd.com

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Overview:

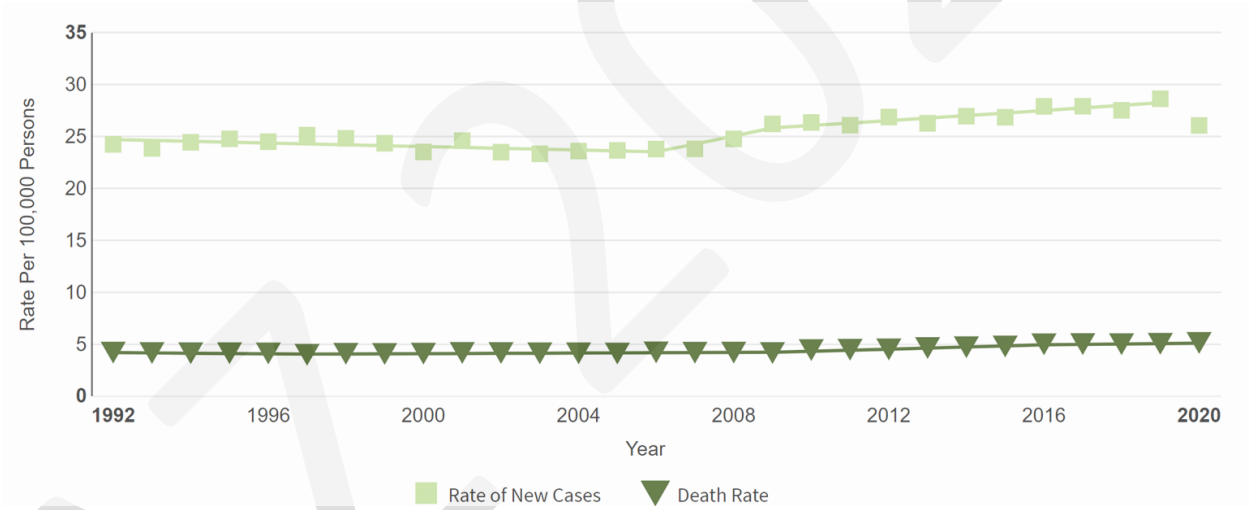
	New Cases 2019	Deaths 2019
Breast Cancer (Female)	268,600	41,760
Lung and Bronchus Cancer	228,150	142,670
Prostate Cancer	174,650	31,620
Colorectal Cancer	145,600	51,020
Melanoma of the Skin	96,480	7,230
Bladder Cancer	80,470	17,670
Non-Hodgkin Lymphoma	74,200	19,970
Kidney and Renal Pelvis Cancer	73,820	14,770
Uterine Cancer	61,880	12,160
Leukemia	61,780	22,840
	1,762,450	606,880

Estimated New Cases in 2023	66,200
% of All New Cancer Cases	3.4%
Estimated Deaths in 2023	13,030
% of All Cancer Deaths	2.1%

5-Year Relative Survival

81.0%

2013–2019



Epidemiology:

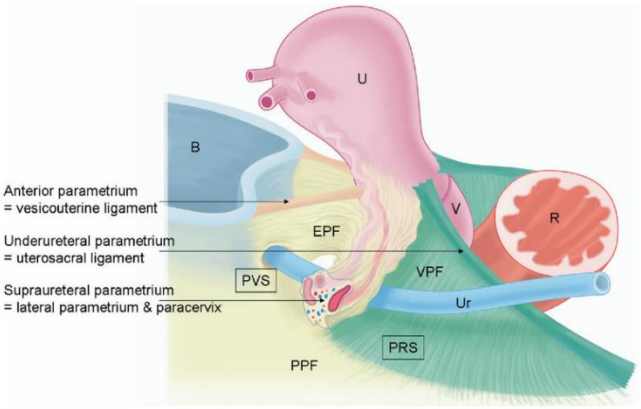
- Most frequent gynecologic malignancy in U.S.
- 2.8% lifetime risk for women
- Most common in postmenopausal women
- Avg age of diagnosis: 61
- Incidence is increasing 1.1% per year (increasing age of population & obesity)

Risk Factors:

- Increasing Age
- Unopposed estrogen exposure
  - Physiologic: obesity, nulliparity, early menarche, late menopause
  - Pathologic: DM, PCOS
  - Exogenous: HRT/Tamoxifen in post-menopausal women
  - **VS. PROTECTIVE: Exercise, pregnancy/breast feeding, OCPs, weight loss.**
- Hyperplasia with atypia
- HNPCC / Lynch syndrome (mutations in *MLH1 or MSH2 or MSH6)*:
  - Type II pts have a 30-70% lifetime risk of endometrial cancer **vs. 3% general risk**
  - Median age ~15-20 years earlier
  - Screen with annual endometrial sampling and TVUS starting at age 30-35
- Cowden's Syndrome (mutations in PTEN tumor suppressor gene)
  - 13 to 19% lifetime risk

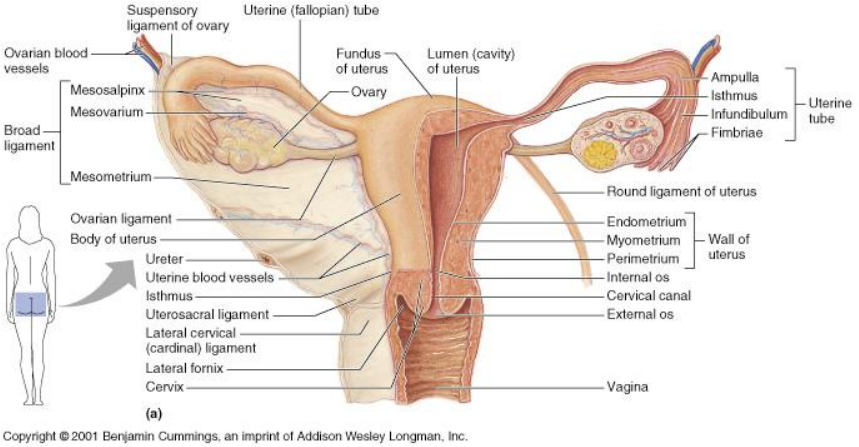
Anatomy

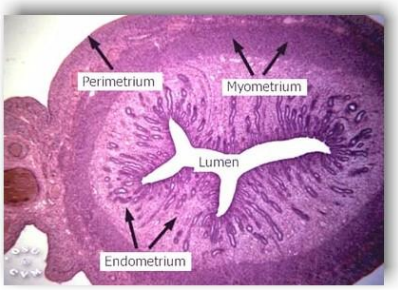
FIGURE
Representation of different parts of parametrium



Lateral parametrium and paracervix are supraureteral cellulofatty tissue, whereas posterior parametrium is an infraureteral dense connective tissue. *B*, bladder; *EPF*, extraserosal pelvic fascia; *PPF*, parietal pelvic fascia; *PRS*, pararectal space; *PVS*, paravesical space; *R*, rectum; *U*, uterus; *Ur*, ureter; *V*, vagina; *VPF*, visceral pelvic fascia.

Touboul. The lateral infraureteral parametrium. Am J Obstet Gynecol 2008.





- Uterine corpus: Upper 2/3 of uterus above internal cervical os (COMPOSED: uterine body and fundus…both separated by tubouterine opening)
- Cervix and lower uterine segment: Lower 1/3 of uterus.
- 3 major ligaments to support uterus
  - Broad ligament, uterosacral ligament, and transverse (aka Mackendrodt's or Cardinal).

Pathology

Type I	Type II	Familial
70-80%	20%	Lynch II
↑ Estrogen related	Unrelated	HNPCC
Precursor: Hyperplasia	Intraepithelial carcinoma (atrophic endometrium)	
Young	Old	
Endometroid	**Non-endometroid**	
Stage 1	=(	
Grade 1 or 2	=(	
Prognosis: Good	**=(**	

- Histology is very generally divided into epithelial tumors (90-95%) vs. mesenchymal tumors (5-10%).
  - Epithelial tumors: **Endometroid (85%)**, Adenosquamous (4%), Papillary Serious (4%), Clear Cell (2%), Mucinous (2%), NOS (3%).
  - Mesenchymal: Carcinosarcoma (60%), Leiomyosarcoma (30%), Endometrial Stromal Sarcoma (10%), Adenosarcoma (< 1%).
- **All "Non-endometroid" *generally* is considered to be…**
  - **Aggressive** clinical course, Poorer prognosis.
  - ALSO MELF (microcystic, elongated, and fragmented) = worse pathology and may necessitate nodal staging

- **Grade is very important**. G1, G2, and G3 have ≤ 5% , 6-50%, > 50% nonsquamous or solid growth patterns. OR they are Non-endometroid.

PRINCIPLES OF PATHOLOGY[a,1,2,3]

Procedure:
- **TH/BSO: Total hysterectomy + bilateral salpingo-oophorectomy**
- **RH: Radical hysterectomy**

Pathologic assessment for carcinoma (including carcinoma, carcinosarcoma, and neuroendocrine carcinoma):
- **Uterus**
  - **Hysterectomy type**
  - **Specimen integrity (intact, opened, morcellated, other)**
  - **Tumor site (endometrium, lower uterine segment, polyp)**
  - **Tumor size**
  - **Histologic type**
  - **Histologic grade (if applicable)**
  - **Myometrial invasion (depth of invasion in mm/myometrial thickness in mm)**
  - **Cervical stromal involvement[b]**
  - **LVSI[c]**
- **Other tissue/organ involvement (fallopian tubes, ovaries, vagina, parametrium, peritoneum, omentum, other)**
- **Peritoneal/ascitic fluid cytology[d]**
- **Lymph nodes (when resected)**
  - **Sentinel lymph nodes (SLNs) should undergo ultrastaging for detection of low-volume metastasis.[e]**
  - **Isolated tumor cells are staged N0(i+) and should not upstage patients, but should be considered in the discussion of adjuvant therapy.**
  - **Level of nodal involvement (ie, pelvic, common iliac, para-aortic)**
  - **Number of lymph nodes with isolated tumor cells, micrometastasis, macrometastasis**
  - **Thorough gross evaluation of the SLN tissue specimen is recommended to ensure that lymph node tissue is included. This could be performed either by the surgeon (depending on experience/comfort level with gross evaluation) or by seeking an intraoperative pathology consultation.**
- **Morphologic evaluation of endometrial carcinoma to determine histologic type—especially in high-grade cancers—is challenging and issues exist regarding diagnostic reproducibility.[4,5]**
- **HER2 immunohistochemistry (IHC) testing (with reflex to HER2 fluorescence in situ hybridization [FISH] for equivocal IHC) is recommended for all serous and carcinosarcoma tumors.[6-9] Consider HER2 testing for p53 abnormal carcinomas regardless of histology.**
- **Estrogen receptor (ER) and progesterone receptor (PR) testing is recommended in the settings of stage III, stage IV, and recurrent disease.**

Presentation:

- Abnormal uterine bleeding (~90%)
    - Postmenopausal bleeding
        - Even one drop of blood in a postmenopausal woman on HRT is worrisome
        - 15% of postmenopausal bleed is due to endometrial cancer.
- Most commonly due to atrophy.
    - Abnormal perimenopausal bleeding
- Abnormal vaginal discharge (watery)
- Abnormal Pap smear (rare presentation)
    - 1183 PAP cytology cases… (739 normal endometrial cells, 423 atypical endometrial cells)
    - "Significant endometrial lesions" were found on….
        - 2.7% of cases with NORMAL endometrial cells,
        - 18.4% of cases with atypical cells,
        - 100% of cases with endometrial cancer cells.

Workup

- History (risk, Gyn history) & Physical (bimanual pelvic).
- Routine CBC / CMP + LFT
- Routine CXR (patient probably will be taken to surgery)…..
- Transvaginal U/S
    - normal endometrial thickness ("stripe") is 4-5 mm
    - average thickness is 20 mm for endometrial ca
- **CT ab/pelvis if Clinical Macroscopic Stage II**
- **Diagnosis required!** (see next slide!)

- CT chest (CXR non-diagnostic)
- Ca-125 (suspected advanced disease)
- PET/CT (suspected advanced disease)
- MRI (medically inoperable: depth and brachy planning)
    - Best modality for assessing myometrial invasion and cervical involvement.
    - Provide no additional info if surgery is planned anyway

- Endometrial biopsy (Gold standard)
    - Office procedure
    - Well tolerated
    - Low cost
    - 90-98% sensitivity
    - 85% specificity
- If above non-diagnostic → formal D&C
    - Endocervix curettage first
    - Avoid uterine contamination
    - +/- hysteroscopy
    - Higher yield, but also higher complications

Figure 1: Common cervical injection sites for mapping uterine cancer[1]

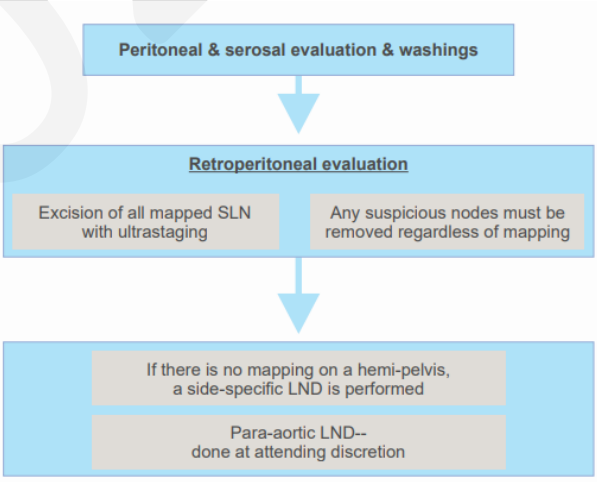


Figure 2: Most common location of SLNs (blue, arrow) following a cervical injection[†]

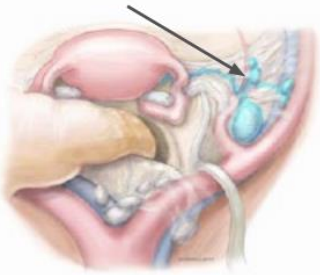
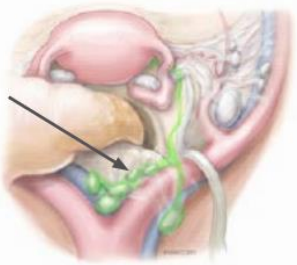


Figure 3: Less common location of SLNs (green, arrow) usually seen when lymphatic trunks are not crossing over the umbilical ligament but following the mesoureter cephalad to common iliac and presacral region[†]

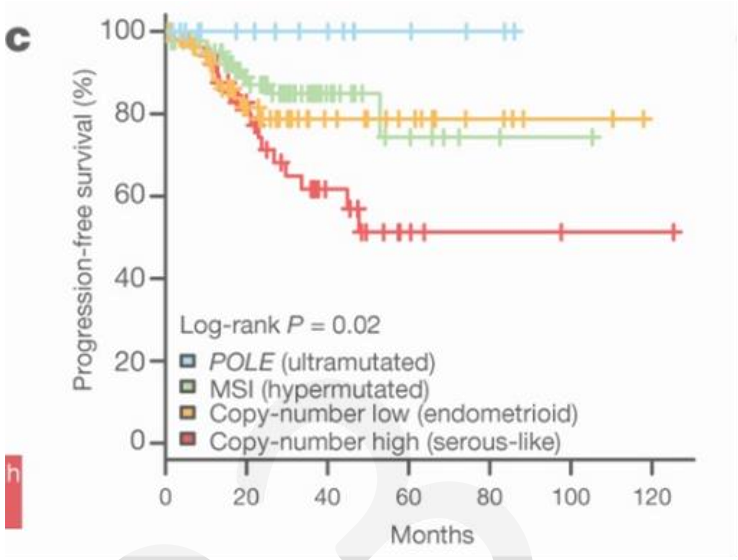


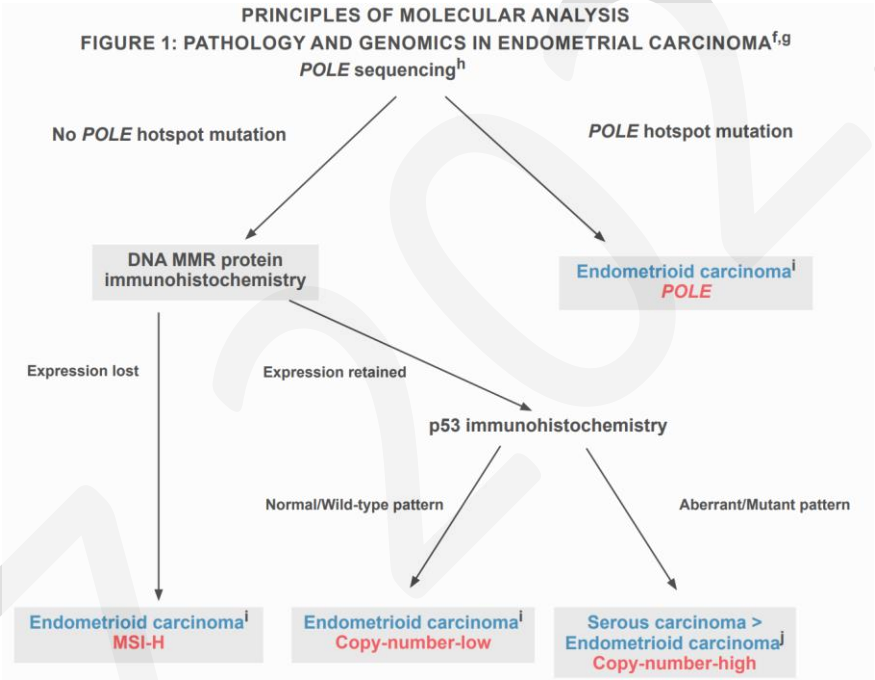
- **Note: IF PAP SEROUS → CONSIDER OMENTAL BIOPSY.**

Molecular Markers

The Cancer Genome Atlas Project, Nature 2013

- POLE:
  - 6.4% of low grade
  - 17.4% of high grade
- Hypermutated/MSI
  - 28.6% low grade
  - 54.3% high grade
- Copy number LOW (endometrioid)
  - 60% low grade
  - 8.7% high grade
  - 2.3% serous
  - 25% mixed histology
- Cop number HIGH (serous like)
  - Serous
  - 90% p53 mutations





PRINCIPLES OF MOLECULAR ANALYSIS

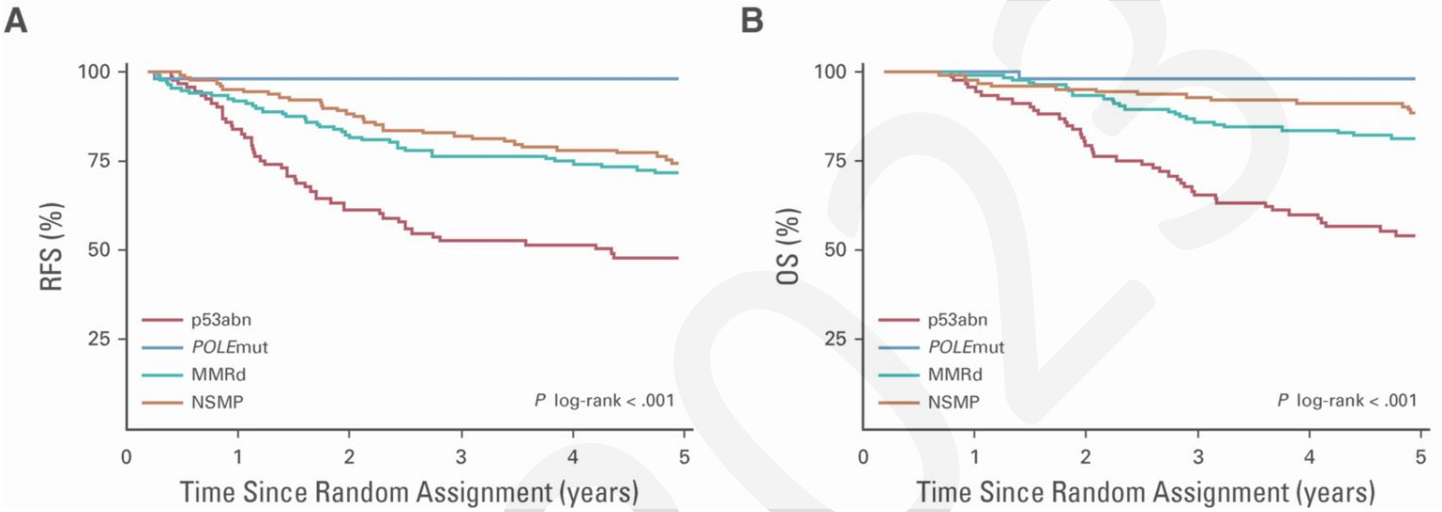
- Molecular analysis of endometrial carcinoma has identified four clinically significant molecular subgroups associated with differing clinical prognoses: *POLE* mutations, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), no specific molecular profile (NSMP), and p53 abnormal.[10,11]
- Retrospective analyses indicate that these four molecular subgroups may respond to therapy differently and therefore may require escalation or de-escalation of therapy compared to previous guidelines. Prospective randomized trials are ongoing to determine the role of a molecular profile–guided treatment strategy in the management of high-intermediate-risk and high-risk endometrial carcinomas
- Ancillary studies for *POLE* mutations (hotspot mutations in the exonuclease domain), IHC staining for mismatch repair (MMR) or MSI testing, and p53 IHC are strongly encouraged to complement morphologic assessment regardless of histologic tumor type.[12]
  See Figure 1: Pathology and Genomics in Endometrial Carcinoma (ENDO-A 3 of 4).
- Comprehensive molecular profiling is strongly encouraged via an FDA-approved assay, or a validated test performed in a clinical laboratory improvement amendment (CLIA)-certified laboratory, in the initial evaluation of uterine neoplasms.
- For tumors that are POLE-mutated, MSI-H, or copy number high, clinical trial enrollment is strongly encouraged.
- Molecular testing may be performed on the initial biopsy or D&C material or the final hysterectomy specimen.
- Universal testing of endometrial carcinomas for MMR proteins is recommended.
  - MSI testing is recommended if results are equivocal.
  - MLH1 loss should be further evaluated for promoter methylation to assess for an epigenetic mechanism.
  - Genetic counseling, molecular analysis, and testing for all other MMR abnormalities is recommended.
  - For those who have a strong family history of endometrial and/or colorectal cancer, genetic counseling and testing are recommended regardless of MMR or MLH1 promoter methylation results [see Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer Syndrome) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal].
- Consider *NTRK* gene fusion testing for metastatic or recurrent endometrial carcinoma.
- Consider tumor mutational burden (TMB) testing through an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory.[13]

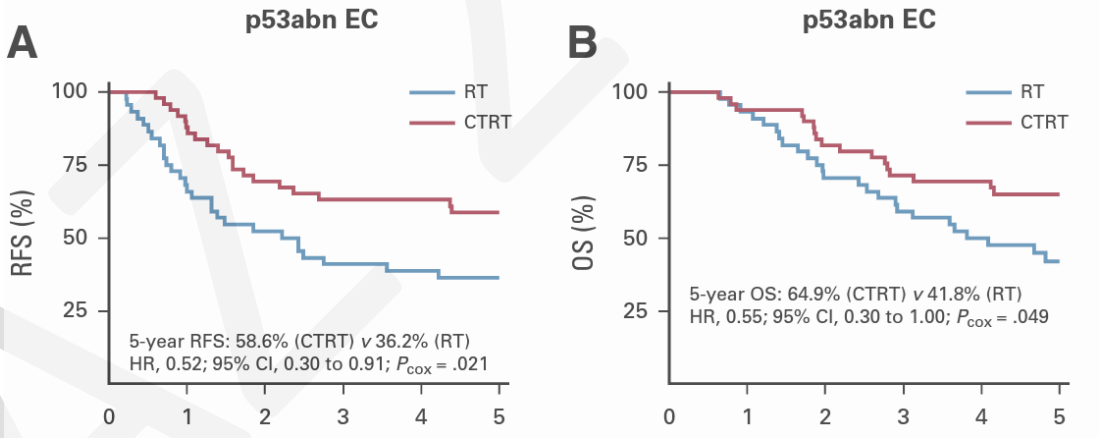
Sec. Analysis PROTEC 3
Classification: 97% of high-risk EC = 410 samples into the 4 subgroups
p53abn Δ (n = 93; 23%), POLEmut (n = 51; 12%), MMRd (n = 137; 33%), No Specific Molecular Profile (n = 129; 32%).

Leon-Castillo, JCO 2020

5-year RFS		48%, 98% 72%, 74% (P < .001).
5-year RFS with CTRT vs. RT	p53abn	59% vs. 36% (P = .019)
	POLEmut	100% vs. 97% (P = .637)
	MMRd	68% vs. 76% (P = .428)
	NSMP	80% vs. 68% (P = .243)

CONCLUSION Molecular classification has strong prognostic value in high-risk EC, with significantly improved RFS with adjuvant CTRT for p53abn tumors, regardless of histologic type. Patients with POLEmut EC had an excellent RFS in both trial arms. EC molecular classification should be incorporated in the risk stratification of these patients as well as in future trials to target specific subgroups of patients.

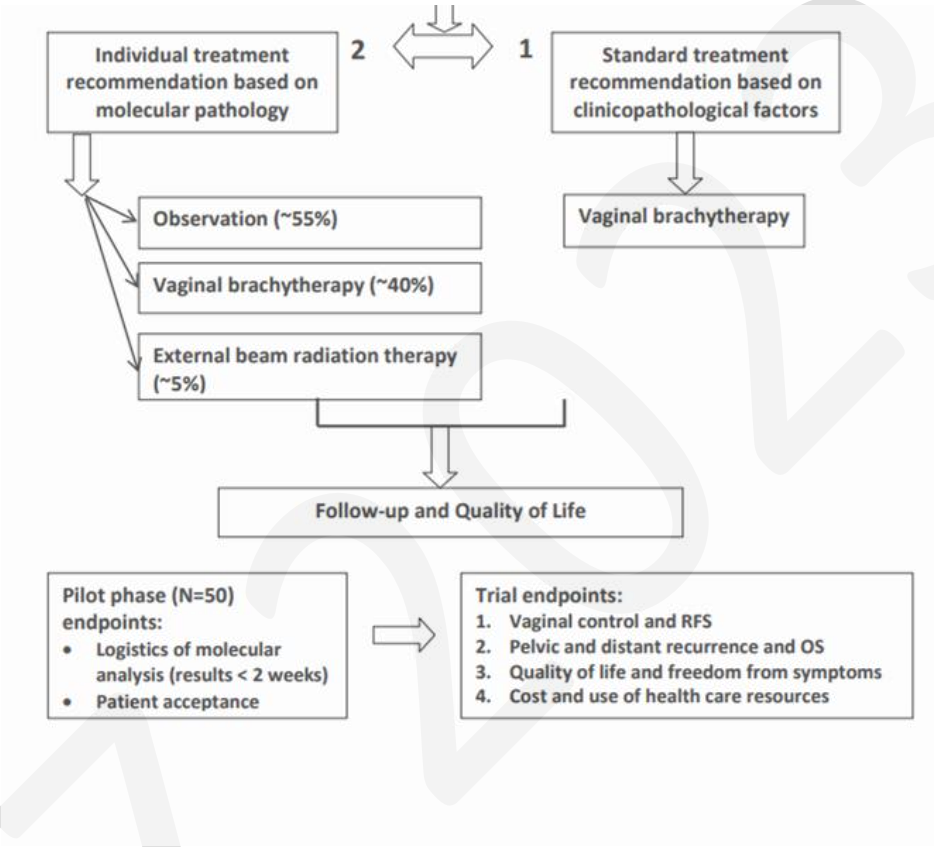




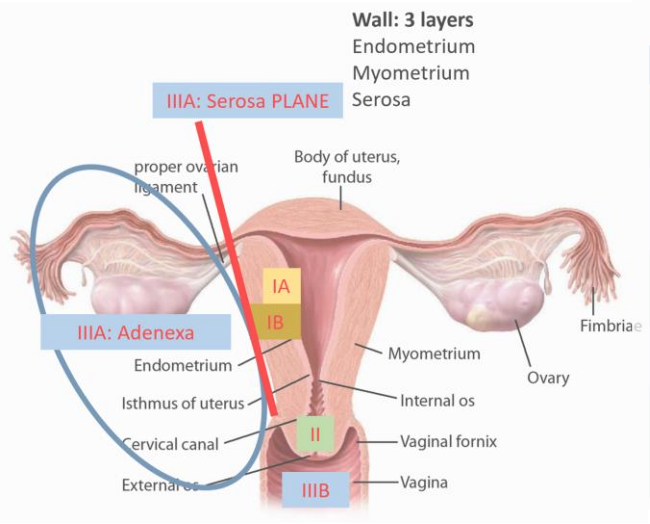
NOVEL TRIALS:

PORTEC-4a

- High-Intermediate risk Stage I EC
  - Stage IA (with +MMI), any age and grade 3 ± LVI
  - Stage IB (> 50%), Grade 1-2, age ≥ 60
  - Stage IB, Grade 1-2, +LVSI
  - Stage IB, grade 3, without LVI
  - Stage II (microscopic), Grade 1
- TH/BSO (LND not recommended, doesn't exclude pt)



Staging



FIGO	TNM	Endometrial Carcinoma
IA	T1a	< ½ myometrium
IB	T1b	≥ ½ myometrium
II	T2	cervical stroma (not beyond uterus)
IIIA	T3a	serosa, adnexal
IIIB	T3b	vaginal / parametria
IIIC1	N1	Pelvic nodes
IIIC2	N2	Para-aortic nodes
IVA	T4	bladder, bowel
IVB	M1	distant mets

OLD STAGING

- I – Uterus Confined
  - IA - Limited to endometrium
  - IB - < 1/2 of myometrium
  - IC - 1/2 or more of myometrium
- II - invades cervix
  - IIA - glandular epithelium of endocervix
  - IIB - stroma of cervix
- III - extra-uterine
  - IIIA - involves serosa and/or adnexa (direct extension or mets) and/or ascites or positive peritoneal washings
  - IIIB - vaginal involvement (direct extension or mets)
  - IIIC - LN+ (pelvic and/or paraaortic)
- IV - other organs
  - IVA - bladder or bowel
  - IVB - distant mets

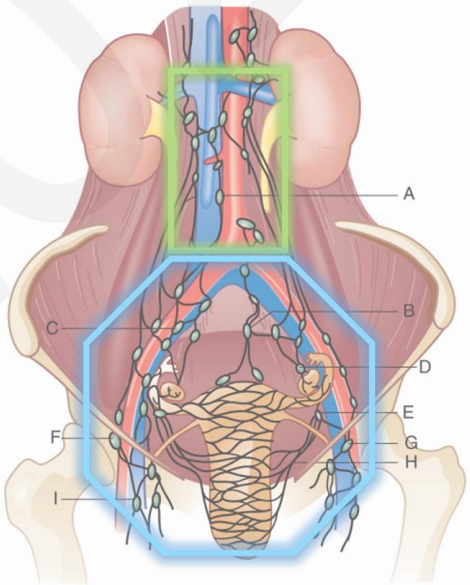
Regional Lymph Nodes:

N0 - none
N1 (IIIC1) - metastasis to pelvic lymph nodes
N2 (IIIC2) - metastasis to para-aortic lymph nodes

Note: Regional nodes include obturator, internal iliac, external iliac, common iliac, para-aortic, presacral, and parametrial
Note: For pathologic staging, FIGO classifies cases with < 6 resected LNs as pNX

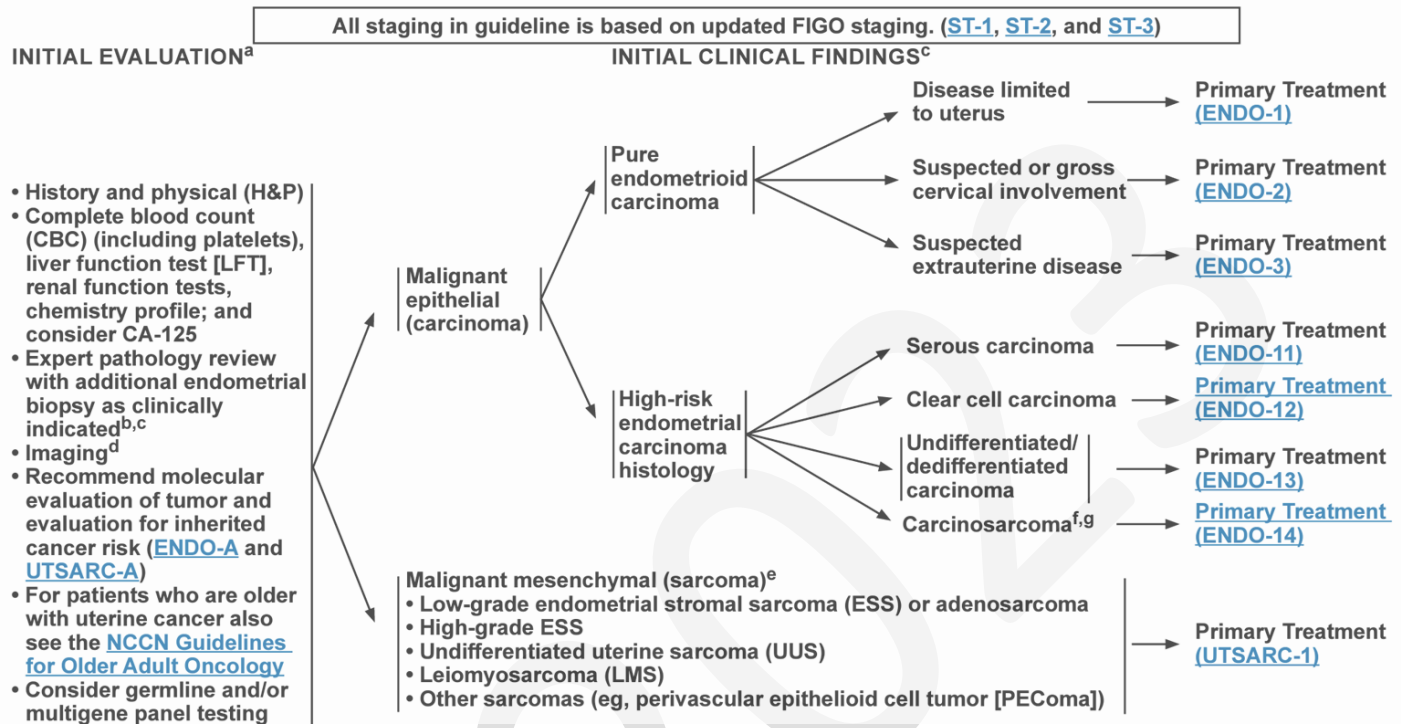
Distant Metastases:

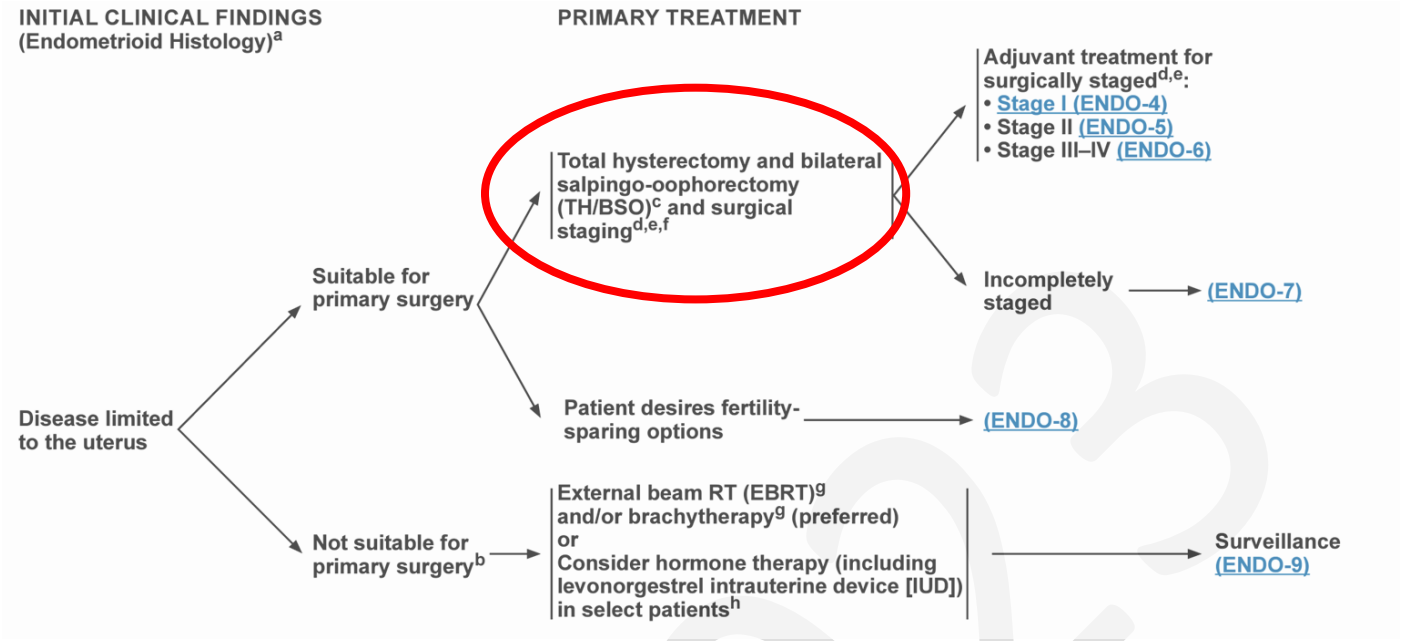
M0 - none
M1 (IVB) - distant metastasis - includes inguinal LN, intraperitoneal disease (including omentum), lung, liver, or bone.

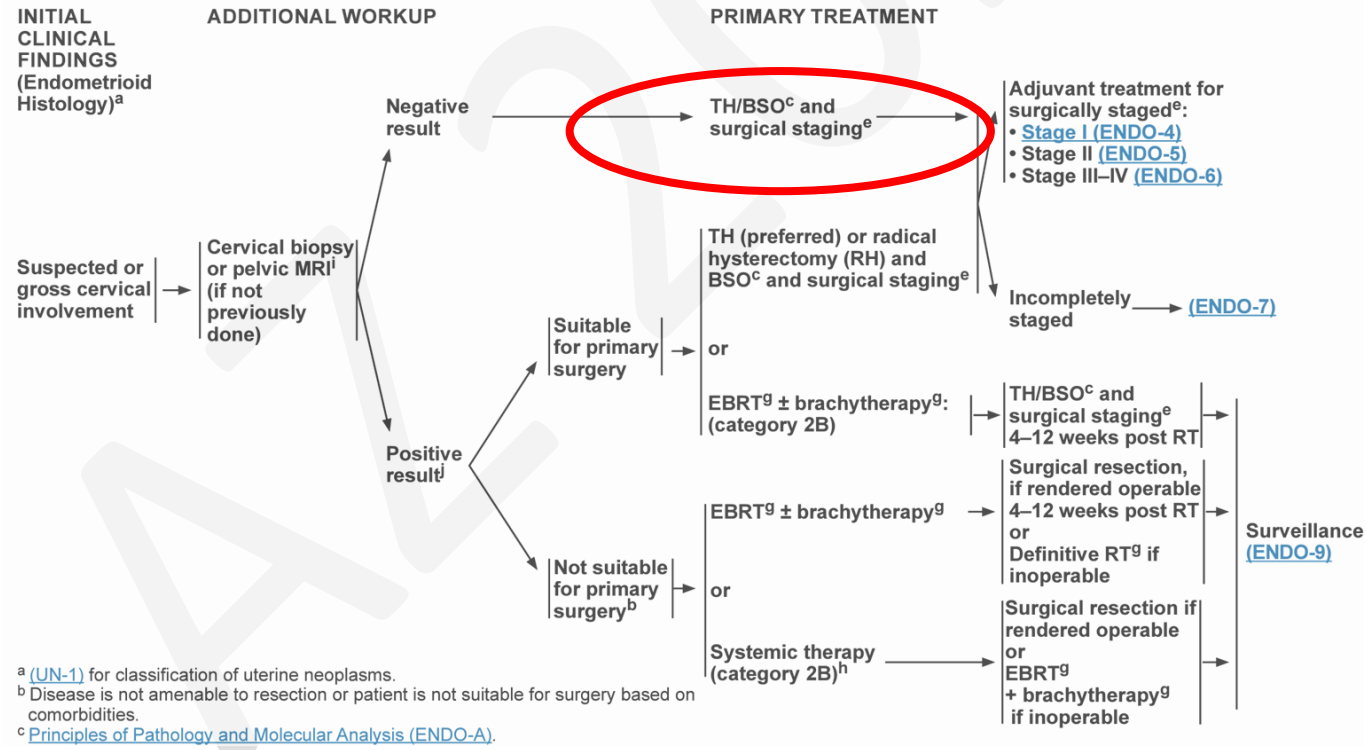


Treatment Paradigm

Primary Workup → Surgery







[a] (UN-1) for classification of uterine neoplasms.
[b] Disease is not amenable to resection or patient is not suitable for surgery based on comorbidities.
[c] Principles of Pathology and Molecular Analysis (ENDO-A).

Hysterectomy Types

Piver-Rutege-Smith	EORTC-GOG	Querteu and Morrow
Class I Extrafascial Hysterectomy	**Type I** Simple (Total) Hysterectomy	**Type A** Extrafascial Hysterectomy
Class II Modified Radical (Wertheim)	**Type II** **Modified Radical**	**Type B** Modified Radical (B1 = w/o lateral paracervical LN) (B2 = WITH lateral paracervical LN)
Class III Radical	**Type III** Radical	**Type C** Radical (C1 = preserve autonomic nerves) (C2 = sacrifice autonomic nerves)
Class IV Extended Radical	**Type IV** Extended Radical	**Type D** Extended Radical (D1 = preserve muscle + fascia) (D2 = sacrifice muscle + fascia)
Class V "More radical than IV"	**Type V** Partial pelvectomy	N/A

Comparison with Cervical Cancer Surgery:

PRINCIPLES OF EVALUATION AND SURGICAL STAGING

TABLE 1: Resection of Cervical Cancer as Primary Therapy[h]

	Comparison of Hysterectomy Types			Comparison of Fertility-Sparing Trachelectomy Types	
	Extrafascial Hysterectomy (Type A)[i]	Modified Radical Hysterectomy (Type B)[i]	Radical Hysterectomy (Type C1)[i]	Simple Trachelectomy	Radical Trachelectomy[j]
Indication	Stage IA1	Stage IA1 with LVSI and IA2	Local disease without obvious metastasis, including: Stage IB1-IB2 Selected stage IB3-IIA1	Carcinoma in situ and stage IA1	Stage IA2-IB1 Select IB2
Intent	Curative for microinvasion	Curative for small lesions	Curative for larger lesions	Curative for microinvasion Fertility preserved	Curative for select stage IA2-IB2 Fertility preserved
Uterus	Removed	Removed	Removed	Spared	Spared
Ovaries	Optional removal	Optional removal	Optional removal	Spared	Spared
Cervix	Completely removed	Completely removed	Completely removed	Majority removed (approximately 5mm of the cranial aspect of the cervix typically left for cerclage)	Majority removed (approximately 5mm of the cranial aspect of the cervix typically left for cerclage)
Vaginal margin	Minimal	1-2 cm margin	Upper 1/4 to 1/3 of vagina	Minimal	1-2 cm margin
Ureteral Disesection	Not mobilized	Ureters unroofed and dissected from cervix	Ureters unroofed and dissected from cervix and from lateral parametria	Not mobilized	Ureters unroofed and dissected from cervix
Paracervix/Parametrial Resection	None	Resection at the level of ureter bed (horizontal resection 1-2cm)	Divided at medial aspect of internal iliac vessels. The deep margin is the deep uterine vein	Resected at cervical border	Resection at the level of ureter bed (horizontal resection 1-2cm)
Recto-uterine (Uterosacral ligaments)	Divided at cervical border	1-2cm dorsal from cervix (preserves hypogastric nerve plexus)	Type C1 is nerve preserving, divided at least 2cm dorsal from cervix	Divided at cervical border	1-2cm dorsal from cervix (preserves hypogastric nerve plexus)
Bladder	Mobilized caudal to cervix	Mobilized to upper vagina	Mobilized to middle vagina	Mobilized to peritoneal reflection	Mobilized to upper vagina
Rectum	Not mobilized	Mobilized below cervix	Mobilized below middle vagina	Mobilized to peritoneal reflection	Mobilized below cervix
Surgical approach	Laparotomy or minimally invasive	Laparotomy or minimally invasive	Laparotomy or minimally invasive	Vaginal or laparotomy or minimally invasive	Vaginal or laparotomy or minimally invasive

- **IF PAP SEROUS Consider OMENTAL BIOPSY**

Surgical Staging

PRINCIPLES OF EVALUATION AND SURGICAL STAGING

Principles of Surgical Staging for Endometrial Cancer[1-15]

- TH/BSO and lymph node assessment is the primary treatment for apparent uterine-confined endometrial carcinoma, unless patients desire (and are candidates for) fertility-sparing options (ENDO-8).[1-3] Select patients with metastatic endometrial carcinoma are also candidates for hysterectomy (Principles of Pathology and Molecular Analysis [ENDO-A]).
- Endometrial carcinoma should be removed en bloc to optimize outcomes; intraperitoneal morcellation or tumor fragmentation should be avoided.
- TH/BSO and lymph node assessment may be performed by any surgical route (eg, laparoscopic, robotic, vaginal, abdominal), although the standard in those with apparent uterine-confined disease is to perform the procedure via a minimally invasive approach. Randomized trials, a Cochrane Database Systematic Review, and population-based surgical studies support that minimally invasive techniques are preferred in this setting due to a lower rate of surgical site infection, transfusion, venous thromboembolism, decreased hospital stay, and lower cost of care, without compromise in oncologic outcome.[4-9]
- The lymph node assessment includes evaluation of the nodal basins that drain the uterus, and often comprises a pelvic nodal dissection with or without para-aortic nodal dissection. This continues to be an important aspect of surgical staging in patients with uterine-confined endometrial carcinoma, as the procedure provides important prognostic information that may alter treatment decisions.
- Pelvic lymph nodes from the external iliac, internal iliac, obturator, and common iliac nodes are frequently removed for staging purposes.
- Para-aortic nodal evaluation from the inframesenteric and infrarenal regions may also be utilized for staging in patients with high-risk tumors such as deeply invasive lesions, high-grade histology, and tumors of serous carcinoma, clear cell carcinoma, or carcinosarcoma.
- SLN mapping is preferred (see pages 2–6 of ENDO-C)[15]
- Excision of suspicious or enlarged lymph nodes in the pelvic or aortic regions is important to exclude nodal metastasis.
- Some patients may not be candidates for lymph node dissection.
- Visual evaluation of the peritoneal, diaphragmatic, and serosal surfaces with biopsy of any suspicious lesions is important to exclude extrauterine disease.
- While peritoneal cytology does not impact staging, FIGO and AJCC nonetheless recommend that surgeons continue to obtain this during the TH/BSO.
- Cytology results should not be taken in isolation to guide adjuvant therapy.
- Omental biopsy is commonly performed in those with serous carcinoma, clear cell carcinoma, or carcinosarcoma histologies.
- For stage II disease, TH/BSO is the standard procedure. RH should only be performed if needed to obtain negative margins.

Principles of Sentinel Lymph Node(s) Mapping for Endometrial Cancer Staging[10-26]

- Prospective and retrospective studies demonstrate that compared to systemic lymphadenectomy, SLN mapping with ultrastaging may increase the detection of lymph node metastasis with low false-negative rates in patients with apparent uterine-confined disease.[10-23,26] If SLN mapping is considered, the expertise of the surgeon and attention to technical detail is critical. Recent evidence indicates that SLN mapping may also be used in high-risk histologies (ie, serous carcinoma, clear cell carcinoma, carcinosarcoma).[24,25]
- SLN mapping can be considered for the surgical staging of apparent uterine-confined malignancy when there is no metastasis demonstrated by imaging studies or no obvious extrauterine disease at exploration.
- A cervical injection with dye has emerged as a useful and validated technique for identification of lymph nodes that are at high risk for metastases (ie, SLN in patients with early-stage endometrial cancer[10-12]).
- Superficial (1–3 mm) and optional deep (1–2 cm) cervical injection leads to dye delivery to the main layers of lymphatic channel origins in the cervix and corpus, namely the superficial subserosal, intermediate stromal, and deep submucosal lymphatic sites of origin (see Figure 1 on ENDO-C 4 of 6).[26]
- Injection into the uterine cervix provides excellent dye penetration to the uterine vessels and main uterine lymphatic trunks that condense in the parametria and appear in the broad ligament leading to pelvic and occasionally paraaortic sentinel nodes.
- The uterine body lymphatic trunks commonly cross over the obliterated umbilical artery with the most common location of pelvic SLN being medial to the external iliac, ventral to the hypogastric, or in the superior part of the obturator region (see Figure 2 on ENDO-C 4 of 6).
- A less common location is usually seen when the lymphatic trunks do not cross over the obliterated umbilical and move cephalad following the mesoureter; in these cases, the SLN is usually seen in the common iliac presacral region (see Figure 3 on ENDO-C 4 of 6).
- The radiolabeled colloid most commonly injected into the cervix is technetium-99m (99mTC); colored dyes are available in a variety of forms (Isosulfan Blue 1%, Methylene Blue 1%, and Patent Blue 2.5% sodium).
- Indocyanine green (ICG) recently emerged as a useful imaging dye that requires a near-infrared camera for localization, provides a very high SLN detection rate, and is commonly used in many practices at the present time.[20,26,27]
- Low-volume nodal metastasis to SLN detected only by enhanced pathologic ultrastaging is another potential value to staging with SLN.[10,21-23]
- The key point to a successful SLN mapping is the adherence to the SLN algorithm, which requires the performance of a side-specific nodal dissection in cases of failed mapping and removal of any suspicious or grossly enlarged nodes regardless of mapping (see Figure 4 on ENDO-C 5 of 6).[10-12,23,25]
- For cases of failed SLN mapping, reinjection of the cervix may be considered.
- If there is no mapping on a hemi-pelvis, then a side-specific lymphadenectomy is recommended. However, if expert gynecologic pathology is available, a frozen section to assess myoinvasion can be obtained and lymphadenectomy can be avoided if no myoinvasion or cervical invasion is identified.
- SLN identification should always be done prior to hysterectomy, except in cases where a bulky uterus must be removed to allow access to iliac vessels and lymph nodes.

Principles of Sentinel Lymph Node(s) Mapping for Endometrial Cancer Staging (continued)[10-26]

- SLNs are processed using ultrastaging, which typically includes two components: serial sectioning with review of multiple hematoxylin and eosin (H&E)-stained slides with or without cytokeratin IHC staining.
  - Protocols of serial sectioning and ultrastaging vary among gynecologic pathologists.[28] Comparison of two different ultrastaging protocols in endometrial cancer SLN did not reveal significant advantages when serial H&E sectioning and IHC staining were used.[29]
- Recent data highlight the potential importance of ultrastaging for detection of low-volume metastasis. In general, SLN mapping allows for increased intraoperative surgical precision to identify nodes more likely to harbor metastasis combined with enhanced pathology protocols, which has been shown to increase the detection of nodal metastasis, which may alter stage and adjuvant therapy recommendations.
- Lymph nodes with isolated tumor cells should be clearly reported. In endometrial cancer, when isolated tumor cells are detected in the absence of macrometastasis and micrometastasis, the lymph node stage is designated pN0(i+).[30]

PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

Figure 1: Common cervical injection sites for mapping uterine cancer[a]

Figure 2: Most common location of SLNs (blue, arrow) following a cervical injection[a]

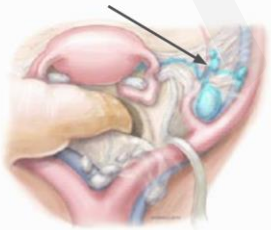


Figure 3: Less common location of SLNs (green, arrow) usually seen when lymphatic trunks are not crossing over the umbilical ligament but following the mesoureter cephalad to common iliac and presacral region[a]

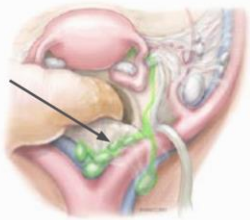
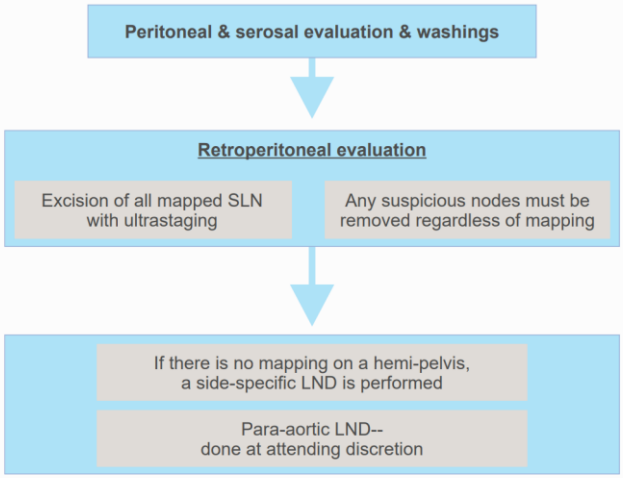


Figure 4: The SLN algorithm for surgical staging of endometrial cancer[b]



Adjuvant TX Overview

Stage	Endometroid	PS / CC	Carcinosarcoma
Stage IA, grade I-II	Obs or VB *	**Non-Invasive IA**: VB ± Chemo (if washings -) VB + Chemo (if washings +)	Chemo ± EBRT ± VB
	VB (obs if no risk factors)	**Invasive IA – Stg IV**: Chemo ± EBRT ± VB	Chemo ± EBRT ± VB
Stage IB, grade I-II	VB or EBRT *		
Stage IB, grade III	VB ± EBRT ± chemo **		
Stage II, grade I-II	EBRT ± VB **		
Stage II, grade III	EBRT ± VB (+ chemo cat. 2B)		
Stage IIIA -IVA	Chemo ± Immunotherapy ± EBRT ± VB		

* The more aggressive option reasonable especially if RF present age > 60, or LVSI.

Endometroid (STD Risk)

Surgically staged: Stage I[e]

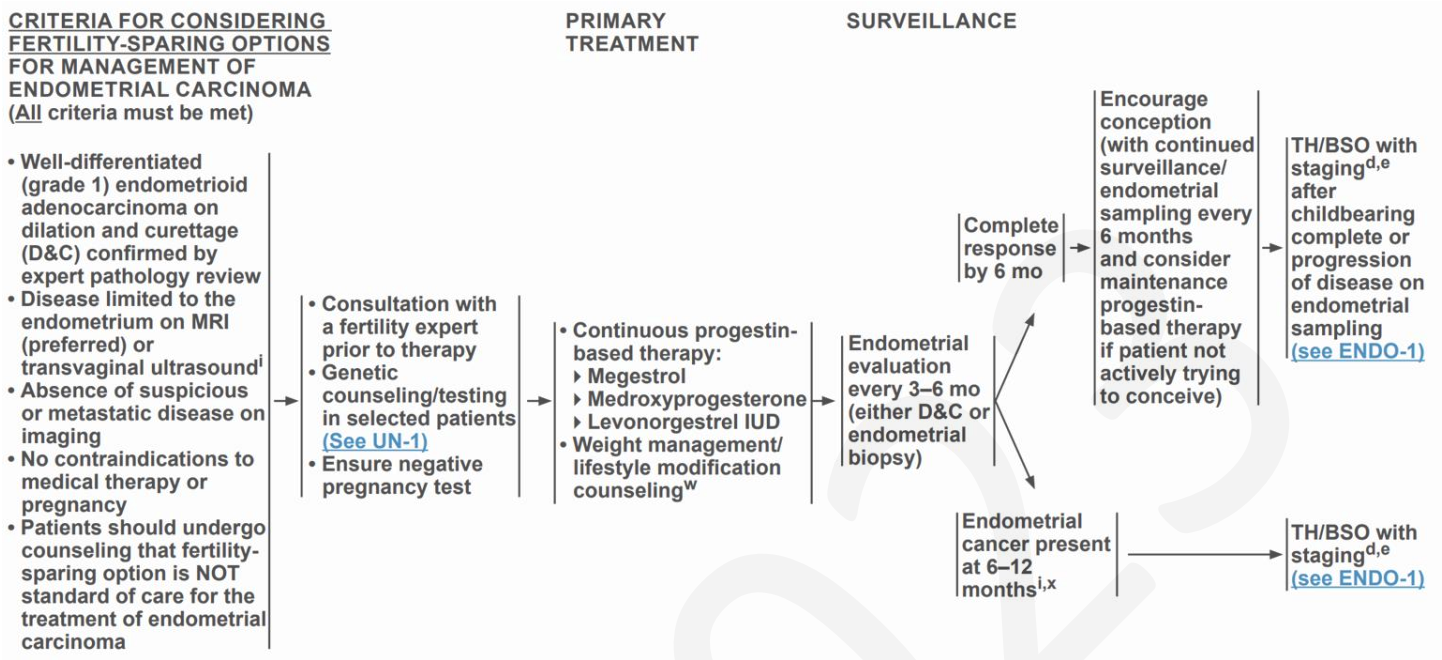
FIGO Stage	Histologic Grade	Adjuvant Treatment
IA	G1, G2	Observation preferred or Consider vaginal brachytherapy if lymphovascular space invasion (LVSI) and/or age ≥60 y[n]
	G3	Vaginal brachytherapy preferred or Consider observation if no myoinvasion or Consider EBRT if either age ≥70 y or LVSI (category 2B)
IB	G1	Vaginal brachytherapy preferred or Consider observation if age <60 y and no LVSI
	G2	Vaginal brachytherapy preferred or Consider EBRT if ≥60 y and/or LVSI or Consider observation if age <60 y and no LVSI
	G3	RT (EBRT and/or vaginal brachytherapy) ± systemic therapy (category 2B for systemic therapy)

Surgically staged[e]: Stage II[o,p]

FIGO Stage	Histologic Grade	Adjuvant Treatment
II	G1–G3	EBRT (preferred) and/or vaginal brachytherapy[q] ± systemic therapy (category 2B for systemic therapy)

Surgically staged[e]: Stage III, IV[r] → Systemic therapy ± EBRT[s] ± vaginal brachytherapy[s]

Fertility Sparing



General Principles–Uterine Neoplasms

- RT is directed at sites of known or suspected tumor involvement and may include EBRT and/or brachytherapy. Imaging is required to assess locoregional extent and to rule out distant metastases before administration of RT. In general, EBRT is directed to the pelvis with or without the para-aortic region. Brachytherapy can be delivered: 1) to an intact uterus, either preoperatively or definitively; or 2) more commonly, to the vagina after hysterectomy. For the purposes of these guidelines, whole abdominal radiotherapy is not considered to be tumor-directed RT.
- Chemoradiation can be given concurrently or sequentially.

General Treatment Information

- Target Volumes
  - Pelvic radiotherapy should target the gross disease (if present), the lower common iliacs, external iliacs, internal iliacs, obturators, parametria, upper vagina/para-vaginal tissue, and presacral lymph nodes (in patients with cervical involvement).
  - Extended-field radiotherapy should include the pelvic volume and also target the entire common iliac chain and para-aortic lymph node region. The upper border of the extended field depends on the clinical situation but should at least be 1–2 cm above the level of the renal vessels.
  - Pelvic tissues at risk, especially in the post-hysterectomy setting, can be highly variable depending on bowel and bladder filling. In this situation, the internal target volume (ITV), which encompasses the range of organ movement and deformation, is considered the clinical target volume (CTV), and should be fully covered in the treatment volume.

General Treatment Information (continued)

- Dosing Prescription Regimen – External Beam
  - External-beam doses for microscopic disease should be 45–50 Gy. CT treatment planning should be utilized, and intensity-modulated RT (IMRT) for normal tissue sparing should be considered, with appropriate attention to quality assurance (QA) and tissue interfraction mobility.
  - Treating with IMRT technique is preferred to minimize toxicities in definitive treatment of the pelvis with or without para-aortic treatment. Regular use of image-guided RT (IGRT) with orthogonal imaging and/or routine volumetric imaging (such as cone beam CT) at the time of treatment delivery is essential to ensure appropriate coverage of targets and sparing of normal tissues.
  - Postoperatively, if there is gross residual disease and the area(s) can be sufficiently localized, a boost can be added to a total dose of 60–70 Gy, respecting normal tissue sensitivity.
  - For gross nodal disease, consider boost to 60–65 Gy while respecting normal tissue constraints.
  - For neoadjuvant radiation, doses of 45–50 Gy are typically used. One could consider adding 1–2 high dose-rate (HDR) insertions to a total dose of 75–80 Gy low dose-rate (LDR) equivalent, to minimize risk of positive or close margins at hysterectomy.
  - For pelvic-confined recurrent endometrial cancer without a prior history of radiation, fields would mirror adjuvant radiation. For reirradiation, fields should be limited to gross disease and target dose prescribed to maximize control while minimizing risk to normal tissues.
- Dosing Prescription Regimen – Brachytherapy
  - Initiate brachytherapy as soon as the vaginal cuff is healed, preferably 6–8 weeks after surgery but in general initiation of brachytherapy should not exceed 12 weeks. For vaginal brachytherapy, the dose should be prescribed to the vaginal surface or at a depth of 0.5 cm from the vaginal surface; the dose depends on the use of EBRT. The target for vaginal brachytherapy after hysterectomy should be no more than the upper two-thirds of the vagina; in cases of extensive LVSI or positive margins, a longer segment of the vagina may be treated.
    - For postoperative HDR vaginal brachytherapy alone, regimens include 6 Gy x 5 fractions prescribed to the vaginal surface, or 7 Gy x 3 fractions or 5.5 Gy x 4 fractions prescribed to 5 mm below the vaginal surface. While 7 Gy x 3 fractions prescribed at a depth of 0.5 cm from the vaginal surface is a regimen used by many, the use of smaller fraction sizes may be considered to potentially further limit toxicity in selected patients.
    - When HDR brachytherapy is used as a boost to EBRT, doses of 4–6 Gy x 2 to 3 fractions prescribed to the vaginal mucosa are commonly used.
  - For medically inoperable uterine cancer, risk of extrauterine spread determines the combination of EBRT plus brachytherapy or brachytherapy alone. Brachytherapy doses for definitive therapy are individualized based on the clinical situation. When available, image-guided therapy should be used. Based on the best available evidence, an Equivalent Dose in 2 Gy fractions (EQD2) D90 of at least 48 Gy should be delivered to the uterus, cervix, and upper 1–2 cm of vagina if brachytherapy alone is used, and should be increased to 65 Gy for the combination of EBRT and brachytherapy. If an MRI is used as part of planning, the target dose for the gross tumor volume (GTV) would be an EQD2 of ≥80 Gy.

General Treatment Information (continued)

- Interstitial Brachytherapy
  - Interstitial brachytherapy is an advanced technique where multiple needles/catheters are inserted in the gross disease/target. Interstitial brachytherapy may be preferred to maximize dose to the target and minimize dose to the organs at risk (OARs) for cases where intracavitary brachytherapy is not possible, or anatomy favors interstitial brachytherapy. Three-dimensional treatment planning allows volumetric delineation of targets and OARs on CT and/or MRI with dose-volume histograms. Dose and fractionation depend on prior RT dose, target volume, and OAR doses.

Stereotactic Radiosurgery (SRS) and Stereotactic Body RT (SBRT) for Metastatic Disease

- SRS and SBRT are radiation treatment modalities that utilize advanced three-dimensional anatomic targeting accuracy to deliver precise, ablative, high-dose ionizing radiation. The therapy maximizes the cell-killing effect of ionizing radiation while minimizing radiation-induced injury in adjacent sensitive normal tissues. SRS and SBRT demand precise target localization, reproducibility of patient setup, and a sharp radiation dose gradient. SRS is delivered exclusively to intracranial targets while SBRT describes stereotactic therapy to extracranial targets. SRS and SBRT are delivered in 1 to 5 fractions of therapy with the expectation of durable control at the radiated site.

HDR Dosing

Vaginal Brachytherapy Dose Comparison

Cervix

- 2 insertions 2 weeks M-Tu discharge, M-Tu discharge.
- 45 Gy + 7 Gy x 4 (UCSF) OR 5 Gy x 6 6 Gy x 5 (> 4 cm) 5.5 Gy x 5 (≤ 4 cm)

- With Gross disease, Max EQD2 87 Gy to cervix.

Endometrial

- HDR alone 10.5 Gy x 3 to surface **7 Gy x 3 to 0.5 cm (PORTEC 2)** → **6 Gy x 3 to 0.5 cm (Yale), unless large cylinder then 7 Gy x 3**
  5.5 Gy x 4 to 0.5 cm
  3-4 cm, but no more than treat upper 2/3s vagina.
  BUT with PS/CC extend to 5 cm.
- EBRT 45 Gy + HDR 6 Gy x 3 to surface **4 Gy x 3 to 0.5 cm** → **5 Gy x 2 to 0.5 cm (PORTEC 3)**
  8 Gy x 2 to surface 5.5 Gy x 2 to 0.5 cm

- With Gross disease, Max EQD2 GTV ≥ 80 Gy.

Vaginal Length HDR Study

Background: Full-length vaginal (FLV) brachytherapy for patients with endometrial cancer and high-risk features should be considered as per the American Brachytherapy Society to reduce distal vaginal recurrence in patients with endometrial cancers with papillary serous/clear cell histologies, grade 3 status, or extensive lymphovascular invasion. We sought to investigate this patient population and report outcomes of treatment with high-dose-rate (HDR) brachytherapy in women treated with FLV brachytherapy versus partial-length vaginal (PLV) brachytherapy.

RR 240 patients endometrial cancer + **high-risk features** → adjuvant HDR between 2004 and 2010.
1. FLV (21 Gy in 3) or 2. PLV (18 Gy in 3). ABS Guideline to 0.5 cm depth.
PLV = ↑ 1/3 vagina = median length of 4.0 cm (range, 3.5-5.5 cm) (Fig. 1).
VBT was administered via a single-channel vaginal cylinder using radioactive source iridium 192.

Table 2 Summary of acute toxicities

Toxicity	FLV No. (%)	PLV No. (%)	*P* value
Vaginal mucositis grade 3	121 (100)	0 (0)	<.0001
GI toxicity grade 3	0 (0)	0 (0)	
GU toxicity grade 3	0 (0)	0 (0)	
UTI	10 (8)	4 (2)	<.001
Analgesic use	121 (100)	0 (0)	<.0001

Table 3 Summary of late toxicities

Toxicity	FLV No. (%)	PLV No. (%)	*P* value
Grades 1-2	61 (51)	28 (23)	<.001
Grades 3-4	60 (49)	0 (0)	<.0001
Vaginal stenosis grade 3	28 (23)	0 (0)	<.0001

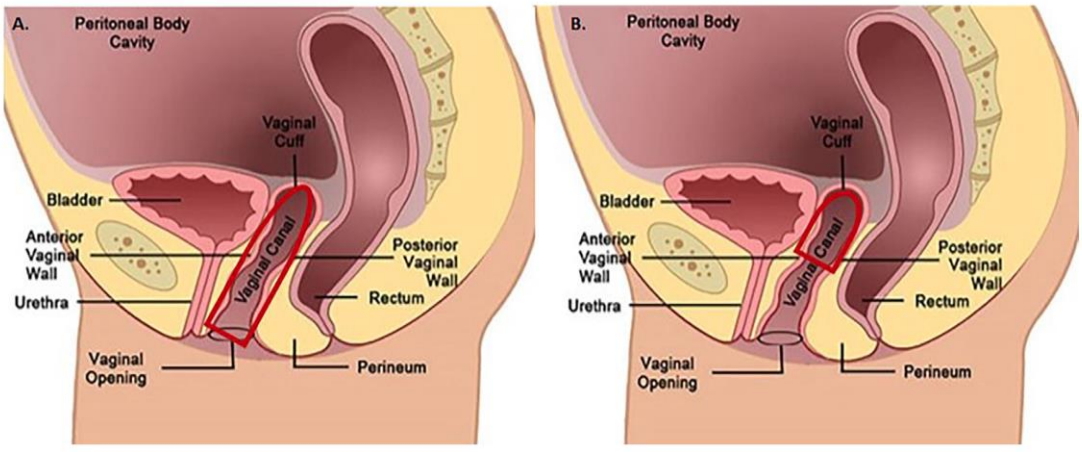
Abbreviations: FLV = full-length vaginal brachytherapy; No. = number of patients; PLV = partial-length vaginal brachytherapy.

Wernicke, PRO 2023 8.5-9.5 years

Proximal Vaginal Recurrences FLV 1.4% vs. PLV 0.9% (P = .54).
All patients treated with FLV brachytherapy developed grade 3 mucositis of the lower vagina/introitus (P < .0001) and had increased analgesics use compared with those treated with PLV brachytherapy (P < .0001). In total, 23% of patients treated with FLV brachytherapy developed grade 3 stenosis of the lower vagina/introitus, in contrast to 0% of patients treated with PLV brachytherapy (P < .0001).

Conclusions

PLV brachytherapy is as effective as FLV brachytherapy in reducing local recurrence and causes a significantly lower incidence of acute and late toxicities. The results of this study caution radiation oncologists regarding the careful use of FLV brachytherapy in patients with endometrial cancer and high-risk features.



TIME-C RTOG 12-03
300 patients uterine cancer eligible PORT alone (2 of 3: tumor size ≥ 4 cm, deep stromal invasion, and LVI) | 1. IG-IMRT | 2. 3D-CRT |.
If 3Ps (Parametrial, LN+, SM+) → concurrent chemotherapy was recommended.
Ineligible: Patients with multiple previous abdominopelvic surgeries, residual pelvic or para-aortic nodal disease, previous pelvic radiotherapy, or HIV.
1^{O} 3-year grade ≥ 2 late GI toxicity.
Arm 1: Image Guided IMRT → Small Bowel V15 Gy < 190 cc , V40 Gy < 100 cc.
Arm 2: 4-field 3D conformal with weekly portal imaging.
RT = pelvic radiation therapy (RT; 50 Gy in 25 fractions over 5 weeks) + HDR VBT (12 Gy in two fractions over 1 week) 5 mm depth.
Chemo = Eligible patients received weekly cisplatin at a dose of 40 mg/m2 once weekly for up to 5 weeks.

Chopra, JCO 2021 46 months
3-year CI grade ≥ 2 late GI toxicity 21.1% vs. 42.4% (HR 0.46; P < .001).
3-year CI grade ≥ 2 any late toxicity 28.1% vs. 48.9% (HR 0.50; P < .001).
Patients reported reduced diarrhea (P = .04), improved appetite (P = .008), and lesser bowel symptoms (P = .002) with IG-IMRT.
However, no difference was observed in the time by treatment interaction.
3-year pelvic RFS 81.8% vs. 84% (NS)
3-year DFS 76.9% vs. 81.2% (NS).
CONCLUSION
IG-IMRT results in reduced toxicity with no difference in disease outcomes.

Note: Yeung, JCO 2020 shows that patient reported outcomes are also better with IMRT: https://ascopubs.org/doi/10.1200/JCO.19.02381

	Grade ≥ 2 Toxicity			Grade ≥ 3 Toxicity		
Adverse Event	IG-IMRT (n = 151), No. (%)	3D-CRT (n = 149), No. (%)	*P*	IG-IMRT (n = 151), No. (%)	3D-CRT (n = 149), No. (%)	*P*
Diarrhea	6 (3.9)	11 (7.4)	.20	2 (1.3)	4 (2.6)	.44
Anorexia	1 (0.6)	10 (6.7)	.005	0 (0)	1 (0.6)	.50
Nausea	1 (0.6)	3 (2.0)	.37	0 (0)	0 (0)	NA
Vomiting	2 (1.3)	7 (4.7)	.10	0 (0)	0 (0)	NA
Abdominal bloating	20 (13.2)	39 (26.2)	.006	2 (1.3)	1 (0.6)	1.0
Abdominal pain	16 (10.5)	22 (14.8)	.27	0 (0)	4 (2.6)	.06
Malabsorption	2 (1.3)	2 (1.3)	1.0	0 (0)	0 (0)	NA
Bowel perforation	1 (0.6)	2 (1.3)	.62	1 (0.6)	2 (1.3)	.62
Bowel obstruction	1 (0.6)	8 (5.3)	.01	1 (0.6)	8 (5.3)	.02
GI stricture	0 (0)	0 (0)	.49	0 (0.0)	1 (0.6)	.50
Rectal bleeding	2 (1.3)	5 (3.4)	.28	1 (0.6)	2 (1.3)	.62
Cystitis	8 (5.3)	9 (6)	.78	2 (1.3)	2 (1.3)	1.0
Urinary frequency	3 (1.9)	6 (4.0)	.33	1 (0.6)	0 (0)	1.0
Urinary incontinence	1 (0.6)	3 (2.0)	.37	0 (0)	1 (0.6)	.50
Bladder spasms	0 (0.0)	2 (1.3)	.25	0 (0)	0 (0)	NA
Urinary fistula	0 (0.0)	0 (0.0)	NA	0 (0)	0 (0)	NA
Induration or fibrosis	0 (0.0)	5 (3.4)	.03	0 (0)	1 (0.6)	.50
Lymphedema	2 (1.3)	2 (1.3)	1.0	0 (0)	0 (0)	NA
Vaginal stenosis	2 (1.3)	8 (5.3)	.06	0 (0)	0 (0)	NA
Fatigue	7 (4.6)	20 (13.4)	.008	0 (0)	1 (0.6)	.50
Constitutional symptoms	3 (1.9)	11 (7.4)	.03	0 (0)	2 (1.3)	.24
Any GI toxicity	29 (19.2)	54 (36.2)	.004	5 (3.3)	20 (13.4)	.002
Any GU toxicity	9 (6)	15 (10.1)	.42	2 (1.3)	3 (2)	.68
Any GI toxicity or GU toxicity	34 (22.5)	59 (39.6)	.001	7 (4.6)	22 (14.7)	.003
Any late toxicity	37 (24.5)	61 (40.9)	.002	7 (4.6)	22 (14.7)	.003

Contour

- Contour on full bladder.
- IV contrast, full bladder and empty bladder.
- Supine. Hand on chest.

- MUST ALWAYS CONTOUR L5 "presacral"
- But, there is no need to contour S1-2 if no stromal invasion.

TABLE 1

Consensus Clinical Target Volume (CTV) for Adjuvant (Post-operative) Radiotherapy for Cervical and Endometrial Cancer

Target Site	
Common iliac lymph nodes	From 7mm below the L4/L5 interspace to the level of the bifurcation of the common iliac arteries into the external and internal iliac arteries.
External iliac lymph nodes	From the level of the bifurcation of the common iliac artery into the external artery to the level of the superior aspect of the femoral head where it becomes the femoral artery.
Internal iliac lymph nodes	From the level of the bifurcation of the common iliac artery into the internal artery, along its branches (obturator, hypogastric) terminating in the paravaginal tissues at the level of the vaginal cuff.
Upper vagina	Vaginal cuff and 3 cm of vagina inferior to the cuff.
Parametrial/Paravaginal tissue	From the vaginal cuff to the medial edge of the internal obturator muscle/ischial ramus on each side.
Presacral lymph nodes*	Lymph node region anterior to S1and S2 region.

*If patient has cervical cancer or endometrial cancer with cervical stromal invasion

	CTV1	CTV2	CTV3
Post-op	Vaginal Cuff All tissue between bladder and rectum	Paravaginal/parametrial Proximal Vagina (0-3 cm length) --- up to 4-5 cm if PS/CC.	LN (common, int, ext, ± presacral) + 0.7 cm expansion Sup Border: 7mm ↓ L4/L5 Inf Border: femoral heads
Intact	Entire uterus as well	Same	Same

- CTV 1+2 FULL BLADDER + CTV 1+2 EMPTY BLADDER → **ITV** + **expansion** → PTV 1+2 PELVIS
  - **Expansion** = Consider 1 cm radially, but 1-2 cm anterior and post via clinical judgement.

- CTV 3 "LN" → PTV 3 "LN"
  - **Expansion** = 0.7 cm all around.
  - **Of note…**Remember, cover sacrals ONLY if PS/CC or cervical stroma involvement (not gland).
  - CTV LN is 0.7 cm around all LN. You need to fuse prior imaging if there are LNs that are bulkly.
  - So let's say like a January CT shows bulky LN+ endometrial Ca. You do surg → chemo March. And you plan to RT April. Then you need to fuse your Jan CT and contour where the LNs are so that you can cover all that area in your CTV LN.

- CTV PA (if PA field) → PTV PA =
  - 0.5-0.7 cm all around.
  - PA field starts from **T12/L1** and ends at the top of the LN field (below bifurcation of aorta) at L4/L5. No exact levels.

- Also your CTV nodes should be 7 mm around vessels **not cropping for bowel or bladder** which move everyday
- Also, you can't do an ITV if both scans are the same!
- The CTV of the vagina s/p TAHBSO starts **AT** the vaginal cuff **OR post-surgical tissue above the vaginal cuff** (which is really directly below the bowel) and you contour laterally to the pelvic side walls, and anterior the posterior border of bladder. The posterior border is just the posterior of vaginal. No need to contour all the way to the anterior border of rectum.
- When you get lower, the lateral borders are constrained by muscle…and DO NOT contour to pelvic side wall.

a) The presacral nodal CTV (magenta) sits anterior to S1/S2 vertebral bodies and should be 1-1.5cm wide and may encompass adjacent bowel if present, to account for motion of the bowel.

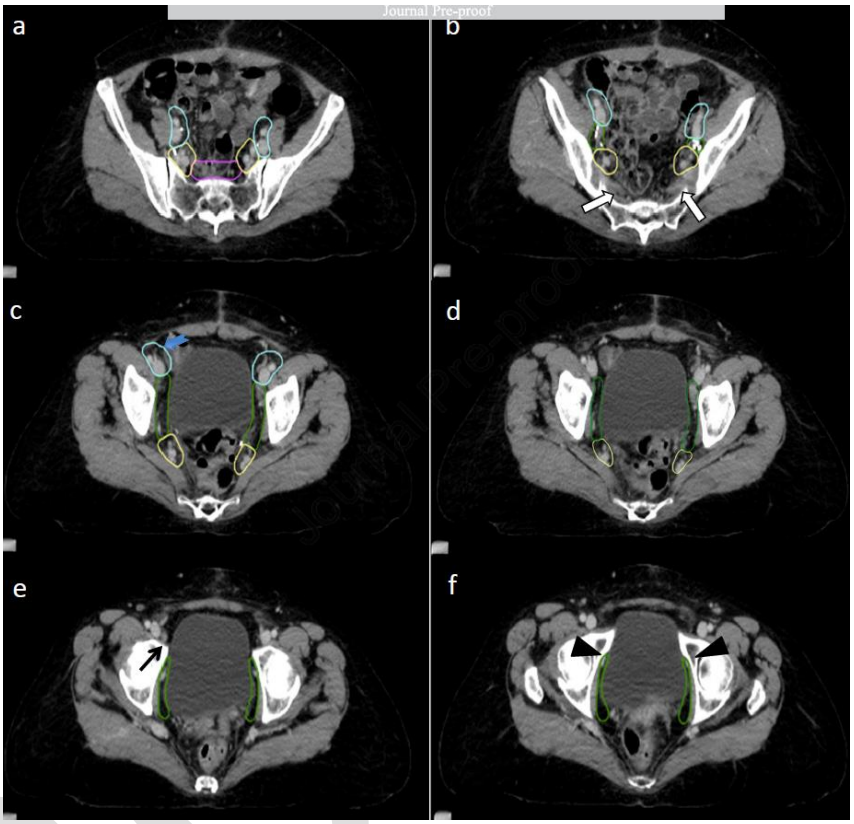
b) The insertion of the piriformis muscle (white arrows) on the sacrum marks the inferior extent of the presacral nodes.

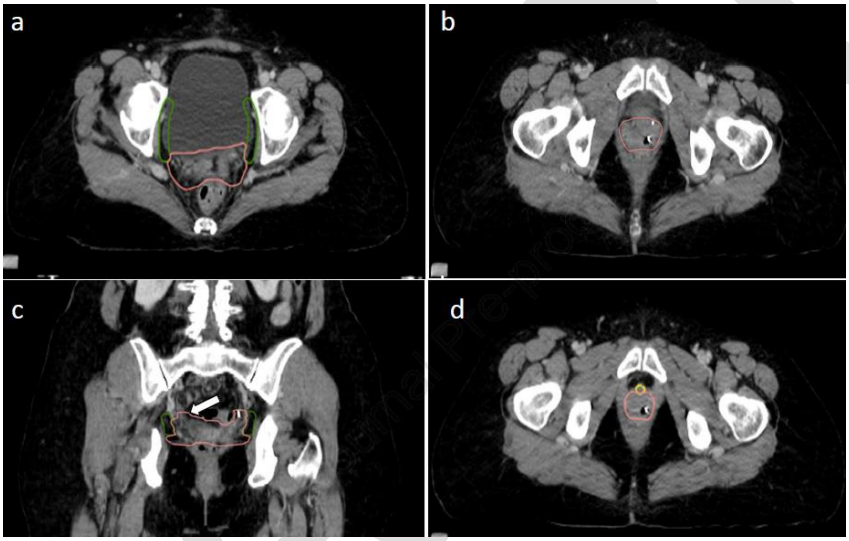
c) The inferior extent of the external iliac nodal CTV (cyan) is seen either where the circumflex vessels originate from the external iliac vessels (blue arrow) or where external iliac vessels turn laterally to become the inguinofemoral vessels.

d) Similarly, the inferior extent of the internal iliac nodal CTV (yellow) should stop as the internal iliac vessels turn laterally to leave the pelvis.

e) Inferior to the external iliac CTV lays the **circumflex node** (black arrow), which is often enlarged, but it is rarely malignant, thus is not typically included.

f) The obturator vessels leave the pelvis through the obturator notch (black arrowheads) which marks the inferior extent of the obturator nodal CTV (green).

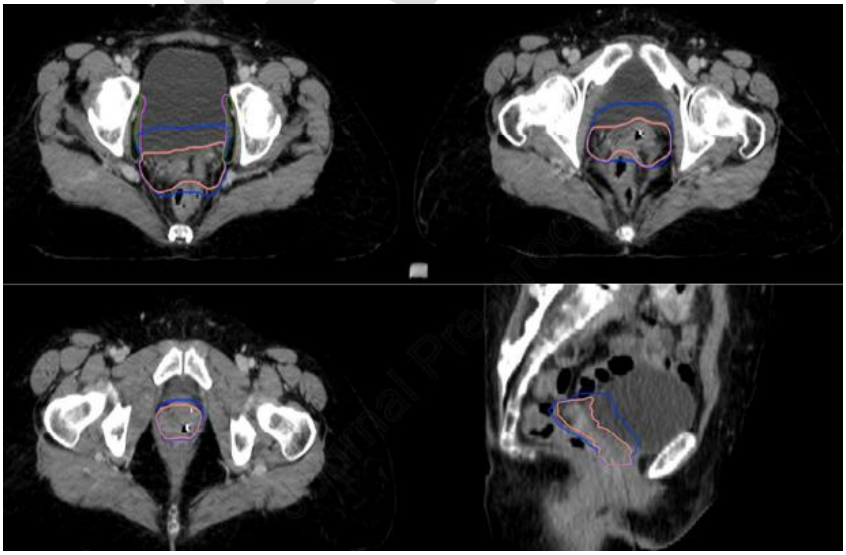




a-d) The vaginal CTV (pink) includes the proximal vagina and any remaining parametrial tissue and should extend laterally to the obturator CTV (green) or b) to the medial aspect of the obturator internus muscle.

c) On coronal view, one can appreciate the lateral “ears” of the vaginal cuff that should be included and can extend superior to the vaginal apex (white arrow)

d) For routine cases, the urethra (yellow) is not at risk and can be carved out of the inferior, anterior extent of the vaginal CTV.



The vaginal ITV (blue) accounts for motion of the vaginal CTV (pink) in various states of bladder and rectal filling as show in in the upper, mid, and lower vagina (4a-c) and on sagittal CT (4d). a)

The obturator nodal CTV (green) is carved out of bladder, however an obturator nodal ITV (magenta) should also be considered, accounting for changes in bladder filling.

d) A sagittal view showing vaginal CTV and ITV**.**

If ITVs are not used, then one should use a larger PTV to account for bladder and rectal filling.

Primary or Adjuvant Therapy (Stage I–IV)	
Chemoradiation Therapy	**Systemic Therapy**
Preferred Regimens • Cisplatin plus RT followed by carboplatin/paclitaxel[1,2] **Other Recommended Regimens[a]** **(if cisplatin and carboplatin are unavailable)** • Capecitabine/mitomycin[3] • Gemcitabine[4] • Paclitaxel[5,6]	**Preferred Regimens** • Carboplatin/paclitaxel[7] • Carboplatin/paclitaxel/pembrolizumab (for stage III–IV tumors, except for carcinosarcoma) (category 1)[b,c,d,8] • Carboplatin/paclitaxel/dostarlimab-gxly (for stage III–IV tumors) (category 1)[c,d,e,9] • Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive uterine serous carcinoma)[d,f,g,10] • Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive carcinosarcoma)[d,f,g,10]

REGIMEN	DOSING
Adjuvant Therapy When Used for Uterine-Confined Disease	
Chemotherapy[a]	
Preferred Regimens	
Carboplatin + Paclitaxel[2-4,b]	**Day 1:** Paclitaxel 175mg/m^2 IV over 3 hours, **followed by:** **Day 1:** Carboplatin AUC 6-7.5 IV over 30 minutes. Repeat cycle every 3 weeks for 6 cycles.

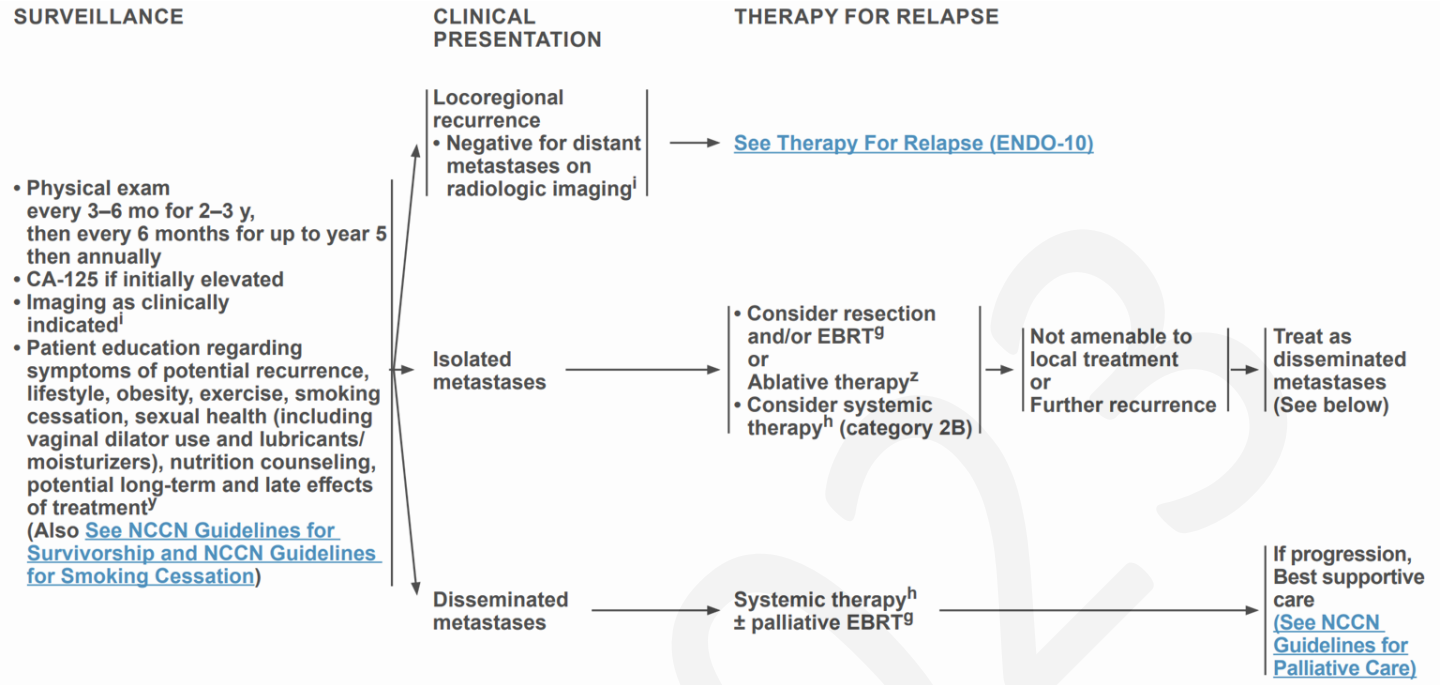
SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Hormonal Therapy for Recurrent or Metastatic Endometrial Carcinoma[s]		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Megestrol acetate/tamoxifen (alternating) • Everolimus/letrozole	• Medroxyprogesterone acetate/tamoxifen (alternating) • Progestational agents ▸ Medroxyprogesterone acetate ▸ Megestrol acetate • Aromatase inhibitors • Tamoxifen • Fulvestrant	• ER-positive tumors ▸ Letrozole/ribociclib ▸ Letrozole/abemaciclib

Hormonal Therapy for Uterine-Limited Disease Not Suitable for Primary Surgery or for Those Desiring Uterine Preservation for Fertility (ENDO-1)[s]	
Preferred Regimens	**Other Recommended Regimens**
• Levonorgestrel IUD	• Progestational agents ▸ Megestrol acetate ▸ Medroxyprogesterone acetate

NOTE: PD-1 Inhibitor dostarlimab can target dMMR tumors (https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2811234)

Surveillance / FU



Early Stage Endometrial (Stage IA/IB – Uterine Confined)

LN Risk

GOG 33

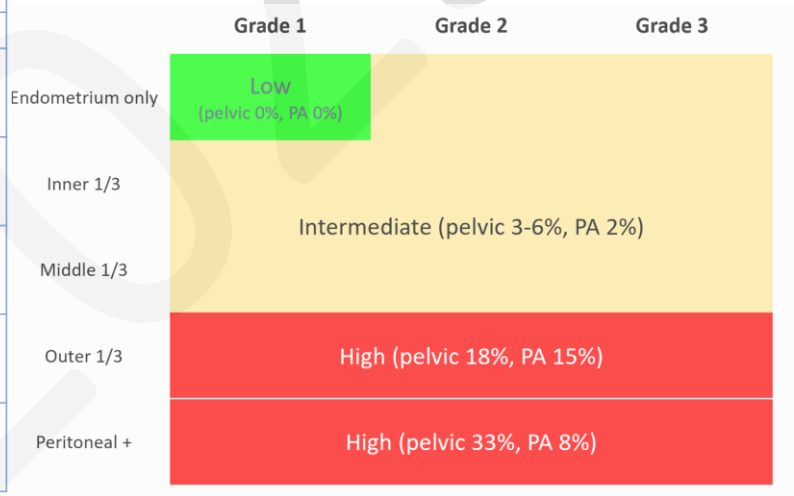
Prospective. 621 Endometrial carcinoma. Stage I, Grade 1. TAHBSO. Selective pelvic and PA lymphadenectomy (any #). Peritoneal Washing (cytology). Ineligible: Stage II +, Grade 2 +. Cervix involve. Less extensive surgery. Pre-operative RT.

Grade + Depth of Invasion | LN involvement						
	Pelvic			Paraaortic		
	G1	G2	G3	G1	G2	G3
Endometrium only	0	3	0	0	3	0
Inner 1/3	3	5	9	1	4	4
Middle 1/3	0	9	4	5	0	0
Outer 1/3	11	19	**34%**	6	14	**23%**

Creasman, Cancer 1987

- Risk factors: **Age, Depth of invasion, Grade, LVSI.**
  - Depth of invasion identified as the most important risk factors for LN risk.
  - Grade is positively associated with depth of invasion.
- High risk patients may benefit from lymphadectomy.
  - Must have enough LNs.
  - < 10% of pathologically LN +, were clinically + at time of surgery.
- Criticisms
  - Observational study.
  - No data on if lymphadectomy actually improves outcomes.

Other Factors Associated with Lymph Node Involvement			
	n	Pelvic	Aortic
Peritoneal Cytology			
negative	537	**7**	**4**
positive	75	**25**	**19**
Tumor location			
Fundus	524	**8**	**4**
Lower segment	97	**16**	**14**
Adnexal involvement			
negative	587	**8**	**5**
positive	34	**32**	**20**
Extrauterine spread			
negative	586	**7**	**4**
positive	35	**51**	**23**
LVSI			
negative	528	**7**	**9**
positive	93	**27**	**19**

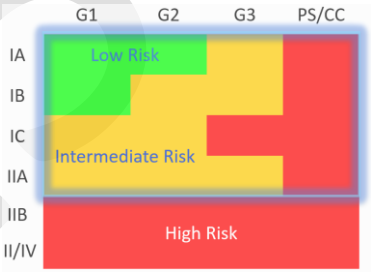


Lymphadenectomy

- Controversy over whether it is better to do **extensive nodal staging or limited / no nodal staging** and frequent adjuvant therapy
- Some surgeons believe that visual inspection/palpation is sufficient for Stage IA-B Grade 1-2, since survival 94-97% regardless.
- **NEW NCCN**: Recommended to do SLN algorithm.
  - Society of Gynecological Oncology is now on board (whereas they previously recommended PLND)
  - SLNB algorithm has a < 5% false negative rate!!!

FIRES TRIAL, Ross Lancet 2017.

SLNB vs. PLND in Stg 1. 12% pLN+. 293 (86%) patients had successful mapping of at least one sentinel lymph node.
SLNB = 97% sens = safely replace PLND.
Indocyanine green (ICG) 3^{O} and 9^{O} inject.



ASTEC Lymphadenectomy

←R→ 1408 Endometrial carcinoma. **Clinically contained within Uterus Included high risk features (G3, PS/CC, IIA)**
| 1. Standard Surgery (TAHBSO / peritoneal washings / PA LN palpation) 5% sampled. **|**
| 2. Standard Surgery + Lymphadenectomy (iliac and obturator LNs, PA LN sampling at discretion of surgeon) **|**
Excluded: Stage IIB (Cervix) or greater.

NOTE: Patients at intermediate/high risk (high grade, IC, or IIA) further randomized to the ASTEC adjuvant RT trial. 33% randomized.
Median LN removed with LND: 12. In PLND arm, 9% had involved nodes

Kitchener, Lancet 2009
Conclusion: No benefit of pelvic LND in early endometrial CA.

		5Y Relapse Rates			5Y Outcomes	
	n	Vag (%)	Pelvic (%)	DM (%)	RFS (%)	OS (%)
Standard	704	2.5	1.5	5.4	79	81
Lymphadenectomy	704	3.4	1.5	7	73	80

Italian Trial

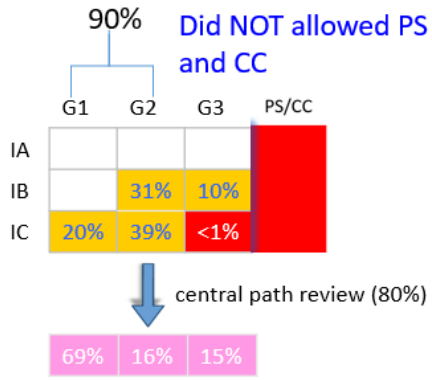
←R→ 514 clinical stage I (80% Stage I/IIA) randomized to | 1. TAH/BSO | 2. TAH/BSO + lymphadenectomy |.
Excluded if Grade 1 < 50% invasion.

Bendetti, JNCI 2008.
50 month follow-up. pN+ was 3% vs 13% (SS).
This did NOT translate to 5-year DFS 82% or 5-year OS 86-90%.

Cochrane Meta-analysis

2 RCT, 1851 women with presumed Stage I
Outcome: No difference in OS (HR 1.07, NS) and RFS (HR 1.23, NS)
Toxicity: Lymphadenectomy higher risk of surgically-related morbidity (surgically related systemic morbidity or lymphedema/lymphocyst formation)
Conclusion: No evidence that lymphadenectomy decreases risk of death or disease recurrence, but more surgically-related morbidity

Adjuvant EBRT



PORTEC-1
←R→ 715 patients with Stage IB (G2-3) or IC (G1-2), specifically no IC G3.
All had TAH/BSO with washings ± LN sampling, (BUT NOT lymphadenectomy).
|1. Pelvic RT: 46 Gy/2 Gy; Sup border: L5/S1 | 2. Obs |.

Scholten, IJROBP 2005.
Central pathology review for 569 patients (80%). Poor reproducibility for G1 vs. G2
10-year outcome: LR: 5% vs. 14% (SS); OS 66% vs. 73% (p=0.09), cancer-related deaths 11% vs. 9% (NS)
Poor prognosis for LR: age >60, Stage IC, Grade 3.
LVI poor prognosis for DM
Conclusion: LRC benefit, RT indicated if high-risk features (2 of 3: age >60, G3, IC)

Note: 75% failure are in vaginal vault
* P < 0.0001.

	N = 715	10Y Relapse		10Y Outcomes		Toxicity	
		LRR (%)	DM (%)	CSS (%)	OS (%)	Any (%)	G3-4 (%)
Obs	361	14*	7	91	73	6	0
RT	354	5*	7.9	89	66	25	2

Prognostic Factors on MVA	LRF		Cancer Death	
	HR	P	HR	p
Age ≥ 60	3.4	0.0005	2.6	0.003
MMI > ½ (Stage IC)	1.9	0.03	1.7	0.048
Grade 3	3.5	0.0003	9.3	<0.0001

This 25% vs 5% or 15% vs 5% are pretty much EVERY MAJOR RESULT OF PORTEC-1.
SIDE EFFECTS, LRF etc.

Comment: Since ~50% deaths due to competing causes, overall survival not a good metric. Number of events even less than GOG-99, since high risk IC G3 disallowed. Trial not really powered to show survival difference.

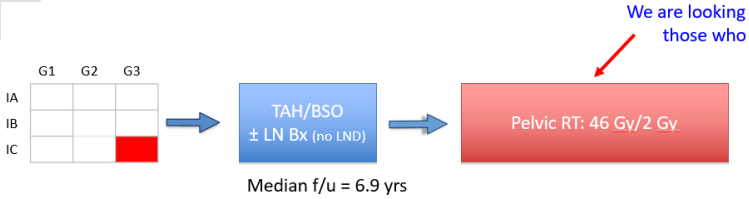
LRF in "High" Risk (≥ 2/3 RF) Patients	10Y LRF
Obs	23%
RT	5%

Nout, JCO 2011. 15 years
15 yr LRR 5.8% (RT) vs 15.5% (no RT); OS 52% vs 60%, NS.
Pts treated with RT had significant increases in urinary incontinence, diarrhea, fecal leakage, and more limitations in daily activities.
Conclusion: EBRT for endometrial cancer is associated with **long-term urinary and bowel symptoms and lower functioning**. "Despite its efficacy in reducing locoregional recurrence, EBRT should be avoided in patients with low- and intermediate-risk EC."

QUESTION: Are we not afraid of vaginal recurrences in these patients not treated with RT? **SEE BELOW!**

Vaginal Reoccurrences + Salvage, Creutzberg Gynecol Oncol 2003.
8-year outcome: LRF: RT 4% vs. control 15% (SS), **majority failures after surgery only in vagina**.
Of the 39 pts with isolated vaginal relapse; 31 of these treated with curative intent (usually RT+brachy).
CR obtained in 31 of 35 (89%), with long term control in 24 of 31 (77%).
Total long-term control rate is thus 24/35 (68%).

Subset IC G3, Creutzberg, JCO 2004.
Analysis of 99 IC G3 registered but ineligible patients.
Treated per same protocol. Median F/U 6.9 years

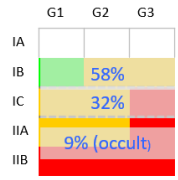


	n	5Y Relapse Rates		5Y Outcomes	
		LR (%)	DM (%)	CSS (%)	OS (%)
IC, G3	99	**14**	**31**	**70**	**58**
PORTEC (RT)	354	1-3	3-8 20 (IB, G3)	91	83-85 74 (IB, G3)

GOG-99

←R→ 392 patients, treated with TAH/BSO, selective PLN and PALND.

1. Removal all suspicious nodes.
2. If none seen, remove nodal tissue from:
   a. Distal half of each common iliac artery,
   b. Anterior + medial of proximal half of ex. iliac a + v.
   c. Distal half of obturator fat pad
   d. Inferior mesenteric artery to the mid com iliac a.



Exclusion: Stage IA, LN+, PS / CC, Stage III or greater
Inclusion: Only "high intermediate risk" 70 yo + 1 risk factor. 50 yo + 2 risk factors. Any age + 3 risk factors.
Risk factors (Based on GOG 33) G 2-3, LVI, outer 1/3 MMI
| 1. Obs | 2. postoperative pelvic EBRT | . Fields: superior border at L4/L5, lateral borders 1cm beyond pelvis, posterior border at posterior border of S3, ant border at symphysis pubis. Dose: 50.4 Gy. No brachytherapy.

Keys, Gynecol Oncol 2004.

Outcome: 2-year recurrence rate: 3% vs 12% (SS). 2-year isolated LR 2% vs 7%. 4-year OS 92% vs 86% (NS). In HIR subgroup (34%): 2-yr recurrence, 6% vs 26%.
Conclusion: Strong benefit for adjuvant EBRT in high intermediate risk group
Comment: OS not primary survival, not powered for it. Primary end-point DFS, which was significantly better with RT

	N = 392	2Y Relapse Rates		4Y Outcomes		GI Toxicity
		LR (%)	DM (%)	CSS (%)	OS (%)	G3-4 (%)
Obs	202	12	6.4	83	86	1
RT	190	3	5.3	95	92	8

But 55% Grade 2 Tox!!!

Risk Factors:
G 2-3, LVI, outer 1/3 MMI

		n	All Recurrence		LRR		OS	
			Obs (%)	RT (%)	Obs (%)	RT (%)	Obs (%)	RT (%)
High	• ≥ 70 + 1 RF • ≥ 50 + 2 RF • any age + 3 RF	132	28	13	13%	5%	74	88
Low	All Others	260	8.3	4	-	-	92	94

"Consistent reduction in proportional risk but dramatic difference in absolute reductions"

Risk Factors	Risk Groups and Relapse Rates	
	PORTEC 1	GOG 99
Age	≤ 60 | > 60	≤ 50 | 51-70 | > 70
Grade	1-2 | 3	1 | 2-3
MMI	≤ 50% | > 50%	Inner 2/3 | Outer 1/3
LVSI	n/a	Absent | Present
High-Int Group	2 of 3 factors	≥ 70 + 1 RF ≥ 50 + 2 RF any age + 3 RF
Results for High-Int Group	10-year LRR: RT: 5% Obs: 23% RR: 0.22 **With GOG criteria:** RT: 8% Obs: 22% RR: 0.36	4-year LRR: RT: 5% Obs: 13% RR: 0.38 4-year relapse (any): RT: 13% Obs: 28% RR: 0.48

Adjuvant Brachy

Norwegian Trial
←R→ 540 patients. Endometrial carcinoma. **Clinically contained within Uterus.**
Exclusion: Stage II (Cervix) or greater.
All patients had TAH/BSO (no lymphadenectomy) + postoperative brachytherapy 60 Gy to the surface of the vagina (~40 Gy LDR / ~ 24 Gy HDR @ 0.5 cm).
| 1. no further treatment | 2. pelvic RT 40 Gy (central shielding after 20 Gy) |.

Aalders, Obstet Gynecol 1980.
9-year outcome: OS BT alone 90% vs BT+EBRT 87% (NS). EBRT decreased LR (7% vs 2%) but there were more distant mets (5% vs 10%, borderline SS). Similar recurrence rate in both groups, but more deaths in XRT group.
Subset analysis: Improved OS for BT+EBRT in IC Grade 3 (82% vs. 72%); probably due to improved local control (LR 5% vs. 20%) with comparable DM (14% vs. 15%). IC G1-2 had no difference in OS, LR, and DM.
Poor prognosis: Age >60, Stage IC, Grade 3, LVI+
Conclusion: No benefit for EBRT after vaginal BT, except for Stage IC G3 patients

	N = 540	Relapse Rates*		9Y Outcomes	
		LRR (%)	Dist Met (%)	DRR (%)	OS (%)
Obs	277	7	5	12.3	90
EBRT	263	2	10	11.8	87

Subset Analysis of High Grade (G3) Tumors By Depth of Invasion (IC)

	MMI ≤ 0.5					MMI > 0.5				
	n	DRR (%)	CSS (%)	LRR (%)	DM (%)	n	DRR (%)	CSS (%)	LRR (%)	DM (%)
Obs	36	8.3	92	6	6	51	31	72	20	15
EBRT	47	17	83	2	17	44	18	82	5	14

MRC ASTEC and NCIC CTG EN.5 (1996-2005) -- EBRT vs Observation.
Two randomized trials merged in 1998 to pool results and facilitate data monitoring. 906 Stage I-IIA endometrial CA patients, with intermediate or high risk features (one or more of the following: IA-IB Grade 3, IC Grade 1-3, serous papillary or clear cell type, FIGO stage IIa). PLND not required; women with positive pelvic LN eligible for ASTEC but not EN.5.
Patient characteristics: 30% PLND; 84% endometrioid; IA 3%, IB 20%, IC 77%; Grade 1 26%, Grade 2 42%, Grade 3 31%.
Exclusion: - PA LN+ excluded, - PLN + allowed in ASTEC, not allowed in EN.5),
- Peritoneal cytology + allowed +/- Stage IIB or greater

All patients had TAH/BSO ± LND (not required) **BT given in ~52% both arms.**

	G1	G2	G3	PS/CC
IA	<1%	<1%	1%	2%
IB	<1%	1%	11%	5%
IC	24%	37%	11%	3%
IIA	1%	2%	1%	<1%
IIB	<1%	0	0	<1%

| 1. EBRT 40-46 Gy daily | 2. Observation |.
Vaginal brachy allowed by institutional preference (ASTEC HDR 8/2 or LDR 15/1, EN.5 per institution).

Median f/u=4.8 yrs

	N = 905	Relapse Rates (%)		5Y Outcomes (%)		Acute Toxicity (%)		Late Toxicity (%)	
		LR	DM	DSS	OS	Any	Mod-Sev	Any	Sev
Obs	453	6	8	90	84	27	8	45	3
EBRT	452	3	9	89	84	57	25	61	7

Lancet, 2009
Outcome: 5-year OS OBS 84% vs EBRT 84% (NS), DSS 90% vs 89% (NS).
Recurrence 15% vs. 15%, Isolated vaginal or pelvic recurrence OBS 6% vs. EBRT 3% (SS)
Subset analysis: No difference in intermediate risk, high risk, no PLND, and PLND for both OS and DSS
Toxicity: Any acute toxicity OBS 27% vs. EBRT 57%, Grade 3 <1% vs. 3%; Any late toxicity 45% vs. 61%, any Grade 3-4 3% vs. 8%
Updated Meta-analysis (GOG99, PORTEC1, ASTEC/EN.5): HR 1.04 for benefit of RT (0.84-1.29, NS)
Conclusion: Adjuvant EBRT cannot be recommended as part of routine treatment for women with intermediate/high risk early stage endometrial CA. There is no benefit on OS or DFSS, and absolute benefit for isolated local recurrence is small and not without toxicity

Swedish Low Risk
←R→ 645 patients with MI 0-50%, grades 1 and 2 endometrioid adenocarcinoma
All had TAHBSO Randomized after surgery to | 1. Obs | 2. VBT (3-8 Gy in 3-6 fx to 5mm depth) |

Sorbe, Int J Gyn Cancer 2009.
No diff in vag rec rates: **3.1%** in obs vs **1.2%** in IVRT arm (p=0.11)
No diff in pelvic rec rates: 0.9% in obs vs 0.3% in IVRT arm (p = .326)
No OS difference
Thus, VB likely no benefit for these low-risk pts

Swedish Intermediate Risk
←R→ 527 patients with Stage I endometroid with ONE RF (G3, MMI > 50%, or DNA aneuploidy)
TAHBSO + VBT then | 1. WPRT | 2. Obs | VB is either 4 Gy x 6, 5.9 Gy x 3, or 20 Gy x 1 to 0.5 cm. EBRT 46 Gy

Sorbe, IJROBP 2012.
5-year LRR 1.5% vs. 5% (*p* = 0.013) 5-year OS 90%. CSM 3.8% vs. 6.8% (NS).
Pelvic recurrences (exclusively vaginal recurrence) were reduced by 93% by the addition of EBRT to VBT.
MMI significant prognostic factor in this medium-risk group of endometrioid carcinomas BUT NOT DNA or Grade.
Conclusions: Despite a significant locoregional control benefit with combined radiotherapy, no survival improvement was recorded, but increased late toxicity was noted in the intestine, bladder, and vagina. Combined RT should probably be reserved for high-risk cases with two or more high-risk factors. VBT alone should be the adjuvant treatment option for purely medium-risk cases.

	G1	G2	G3
IA			
IB			> 60y
IC	>60y	>60y	
IIA	any	any	<1/2 MMI

PORTEC-2
←R→ 427 patients, intermediate-high risk endometrial CA.
Eligible if: (1) age greater than 60 years and stage 1C grade 1 or 2 disease, or stage 1B grade 3 disease (2) stage 2A disease, any age (apart from grade 3 with greater than 50% myometrial invasion).
All received TAH/BSO but PLND not allowed.
Exclusion: papillary serous and clear cell and the IC G3 and IIA G3.
| 1. EBRT 46/23 | 2. HDR 21/3 or LDR 30/1 to 0.5 cm| . Primary endpoint vaginal relapse.

Nout, Lancet 2010.
Outcome: 5-year vaginal recurrence VBT 1.8% vs EBRT 1.6% (NS); 5-year loco-regional relapse 5.1% vs 2.1% (NS); isolated pelvic recurrence 1.5% vs 0.5% (NS); DM 8.3% vs 5.7% (NS). 5-year OS 85% vs 80% (NS).
Toxicity: Acute G1-2 at completion of RT VBT 13% vs EBRT 54%
Conclusion: VBT is effective, with fewer toxic effects
Editorial (PMID 20206759): Agree that VBT should be the standard of care for these patients

	N = 427	5Y Relapse Rates				5Y Outcomes		Acute Toxicity
		Vag (%)	Pelvic (%)	LRR (%)	DM (%)	DFS (%)	OS (%)	Gr 1-2 GI
EBRT	214	1.6	0.5	2.1	5.7	78.1	79.6	53.8
VBT	213	1.8	3.8	5.1	8.3	82.7	84.8	12.6

Although SS, this may not be clinically significant: "Almost all pelvic recurrences were due to widespread disease recurrence."

Stage II Cervical Involvement

Chemotherapy

GOG 99 HR: G 2-3, LVSI, MMI > 66%
Age ≥ 70 years with 1 risk factor
Age ≥ 50 years with 2 risk factors
Age ≥ 18 years with 3 risk factors

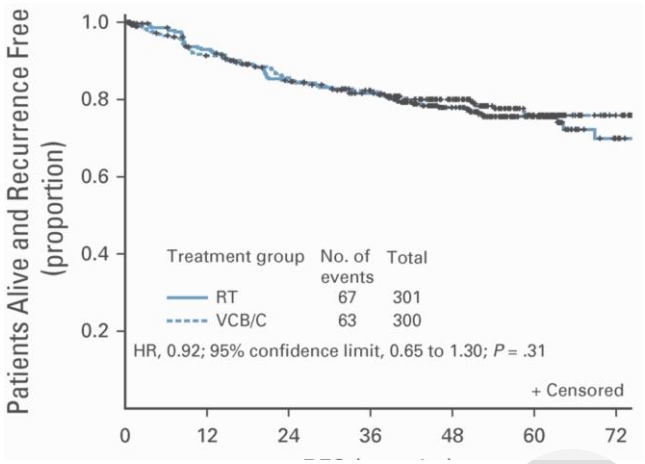
GOG 249

←R→ 601 patients meeting 1 of the following criteria:

- Stage I with high-intermediate risk factors (per GOG 99), +/- cytology
- Stage II with or without risk factors
- Stage I-II serous (15%) or clear cell (5%)

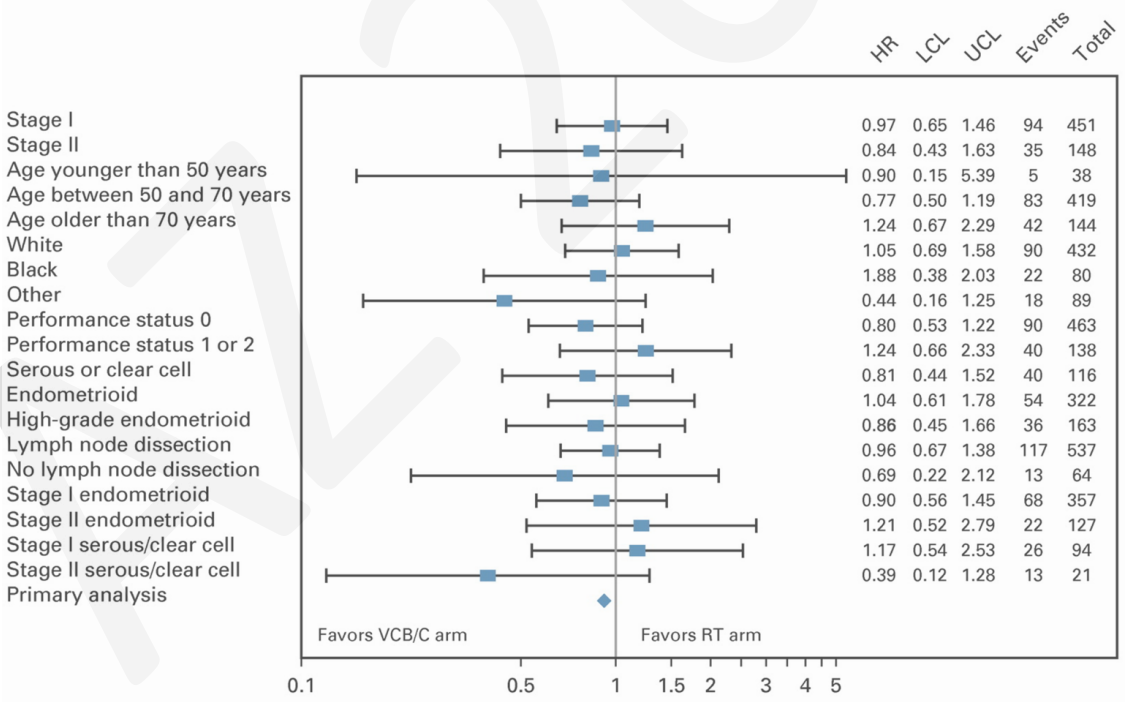
1. Pelvic RT: 45-50.4 Gy (can use IMRT) + If stage II or stage I clear cell or pap serous, optional VBT boost x1-2
2. VBT (HDR x3-5 treatments, or LDR x1-2) + paclitaxel 175 mg/m^2 (3 hours) plus carboplatin (AUC 6) q21 days x 3c

1 ^{O} RFS.



Randall, JCO 2019.

5-year RFS was HR 0.75 both arms (NS). 5-year OS was ~0.85 (NS). Vaginal and distant recurrence rates were similar between arms. Pelvic or para-aortic nodal recurrences were more common with VB+C (9% *v* 4%). There was no heterogeneity of treatment effect with respect to RFS or overall survival among clinical or pathologic variables evaluated. **CONCLUSION** Superiority of VCB/C compared with pelvic RT was not demonstrated. Acute toxicity was greater with VCB/C; late toxicity was similar. Pelvic RT alone remains an effective, well-tolerated, and appropriate adjuvant treatment in high-risk early-stage endometrial carcinomas of all histologies.



Stage III/IV Locally Advanced Disease

- Heterogeneous group by stage, risk and histologic type
- High risk of abdominal recurrence
- Management is controversial
- Main ADJUVANT options **after surgery**:
    - chemo alone
    - sequential chemo and RT
    - concurrent chemoRT
    - chemo-RT-chemo ("sandwich" regimen)

Adj C vs. Adj RT

GOG 122
←R→ 388 patients, Stage III-IV with any histology **(20% pap serous)**
Required TAH/BSO, surgical staging, debulking to ≤ 2 cm residual tumor deposits
| 1. Whole-abdominal irradiation (WAI) alone | 2. Chemo alone | .
RT = 30 Gy in 20 fx AP/PA → boost to pelvis to 45 Gy (4 field) +/- PALNs
Chemo = doxorubicin and cisplatin q3 wks x 7 cycles → cisplatin x1x
Note: ***Adjusted outcome data for stage b/c more stage IIIC and IV pts in chemo arm (but LN+ not prognostic in study)

Randall, JCO 2006
5-year stage-adjusted **PFS** was **38%** for WAI versus **50%** for chemo (P<0.01) ***w/o adjustment PFS was 38% vs 42%
5-year stage-adjusted **OS** was **42%** for WAI versus **55%** for chemo (p<0.01) ***w/o adjustment, OS was 42% vs 53%

Recurrences (LEFT GRAPH) Chemo had more acute grade 3-4 heme and GI toxicity (RIGHT GRAPH)

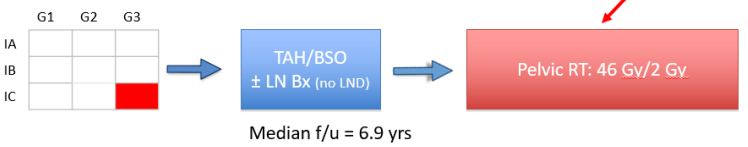
	WAI (%)	AP Chemo (%)
Pelvis	13%	18%
Peritoneal Cavity	16%	14%
Distant	22%	18%
None	46%	50%

	chemo	WART
Stopped/toxicity	17%	3%
Completed tx	63%	84%
Max heme tox	88%	14%
GI toxicity	20%	13%
cardiac	15%	0%

Conclusions: chemotherapy ↑ PFS and OS as compared to WAI for stage III/IV pts after surgery, though many argue statistical rationale not justified. Chemo has some effect on distant recurrence rates but toxicity and pelvic recurrence rates higher
After this study, interest in chemo alone increased
Comments:
Statistical rationale of this study is questioned as all statistically significant data is given for post-hoc stage-adjusted patients
Uses old RT and low doses, given that residual macroscopic dz in abdomen was allowed

Italian Trial **(AKA RECALL OF PORTEC 1 SUBSET of IC G3…)**
←R→ 345 high risk pts (mix) s/p TAH/BSO with nodal sampling. **Eligibility**: IC G3 MMI > 50%, II G3 MMI > 50% III (64%)
| 1. Pelvic RT 45-50 Gy | 2. Chemo (Cyclophos, Dox, cisplatin) x 5 cycles |.

Maggi, Br J Ca 2006
No difference in
7-year OS: 62% **7-year PFS: 56–60%**
EBRT reduced Local recurrence (vaginal, pelvic) (11 -> 7%)
Chemo reduced DM (21→16%)
Chemo G3 heme toxicity 35%



Median f/u = 6.9 yrs

	n	5Y Relapse Rates		5Y Outcomes	
		LR (%)	DM (%)	CSS (%)	OS (%)
IC, G3	99	**14**	**31**	**70**	**58**
PORTEC (RT)	354	1-3	3-8 20 (IB, G3)	91	83-85 74 (IB, G3)

Japanese Trial, JGOG 2033
←R→ 385 pts with >50% MMI stages IC or II (75%) – III A (13%), IIIC (15%) All got **TAH/BSO+ pelvic +/-PA LN dissection**
| 1. Pelvic RT (45–50 Gy) | 2. Chemo (cis/adria/cytoxan q4 weeks ≥ 3 cycles)

Susumu, Gynecol Oncol 2008
No Difference In:
- Pelvic recurrences (6-7%) – although fewer VC failures with RT
- Extrapelvic recurrences (~14-16%)
- PFS (82–84%)
- OS (85–87%)

No significant difference in toxicity (more bowel with RT, more heme with chemo)
Benefit seen with chemo for **unplanned high-risk** subgroup (stage IC > 70 year, IC grade 3, stage II or stage IIIA [cytology], *n* = 120)
- PFS 66% vs. 84% (p=.024) OS 74% vs. 90% (p=.006)

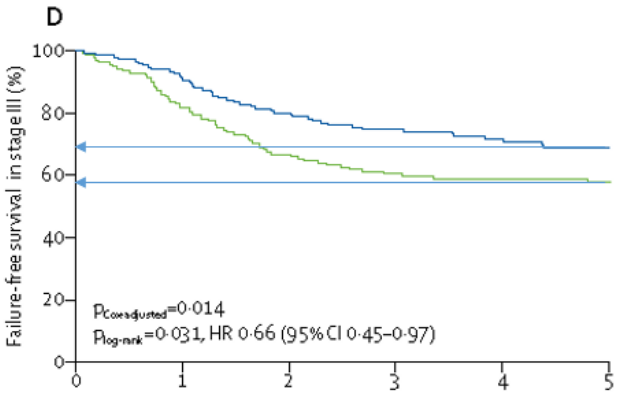
Pelvic recurrence found in 30-50% with node+ disease and chemo only
Conclusion: Adjuvant chemo *may* be beneficial in their high-risk endometrial cancer subgroup

META ANALYSIS, Galaal Cochrane Database
4 RCTS of nearly 1300 FIGO III-IV pts, 620 of whom were evaluable
CHT improved:
- OS: HR 0.75 (CI .57-.99)
- PFS: HR 0.74 (CI .59-.92)

Survival time increased ~25% with adjuvant chemo vs adjuvant RT
Conclusion: Chemo vs CRT should be explored

If chemo reduces DM, and pelvic RT reduces locoregional failures, what if we combine them?

Adj CRT vs. Either alone



PORTEC 3 **(HYSTERECTOMY Study vs. GOG 258)** **± C**
←R→ 686 women with high-risk endometrial cancer.
Inclusion Criteria:
FIGO 2009 stage I, endometrioid-type grade 3 with >50% MMI or LVI (or both)
Endometrioid-type stage II or III
Stage I to III with serous or clear cell histology (~25%)
ALL HAD HYSTERECTOMY → NO residual macroscopic tumor allowed
| 1. WPRT (48.6 Gy in 1.8s) |
| 2. WPRT + 2 cycles of cisplatin 50 mg/m2 → adj 4 cycles carbo/taxol |
Both arms ~48% got VBT boost Carbo AUC 5, taxol 175 mg/m^2
VBT = (EQD2 = 14 Gy) → recommended 10 Gy high-dose rate in fractions of 5 Gy.
Treatment was recommended to start within 4–6 weeks of surgery, but no later than 8 weeks.
Overall radiotherapy treatment time was not to exceed 50 days.

De Boer, Lancet 2018.
5-year OS was 76.7% vs. 81.8% with CRT (trend, p = 0.11)
5-year FFS was 68.6 vs. 75.5% (p=0.02)
Subset: For Stage I-II patients, NO benefit: 5-year FFS 75-80% (NS)
For Stage III patients YES benefit: 5-year FFS 58% vs. 69% (SS)
5-year OS 70% vs. 80% (TREND, p=0.074)
AGE > 70 has OS and FFS BENEFIT with CRT **5-year OS 58% vs. 76% (SS)**
5-year FFS 53% vs. 75% (SS).

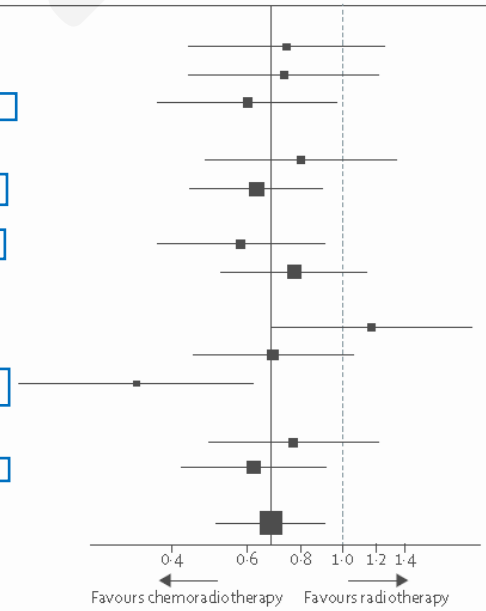
"Because pelvic control was high with radiotherapy alone, this chemoradiotherapy schedule cannot be recommended as a new standard for patients with stage I–II endometrial cancer. However**, in view of the higher risk of recurrence among women with stage III disease, this chemoradiotherapy schedule should be considered to maximise failure-free survival, and benefits and risks should be individually discussed**."

Grade 3+ adverse events during treatment occurred in 60% of CRT v 12% RT pts (p<0·0001)
Late neuropathy worse in CRT (8%) than RT (1%), (p<0·0001) - duh!
Most deaths were due to endometrial cancer
Conclusion: Adding adjuvant chemo doesn't improve 5-yr OS, but does improve FFS, in high risk (FIGO III) patient population **(and AGE > 70)**.

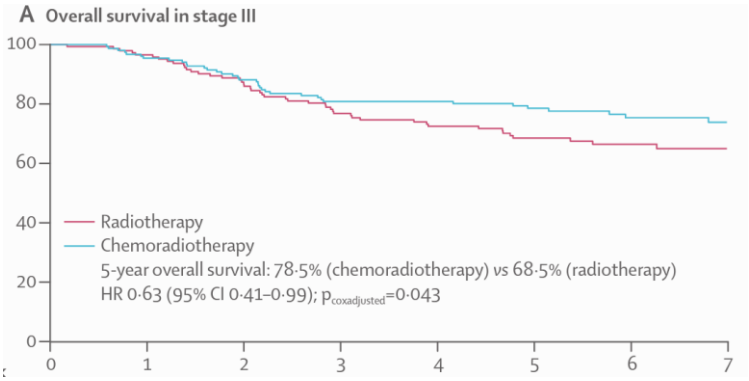
Takeaway: Consider chemo if > age 70, LVSI +, PS/CC, Stage III. AND p53abn patients (see Mol. Markers) NOT G3…!!!

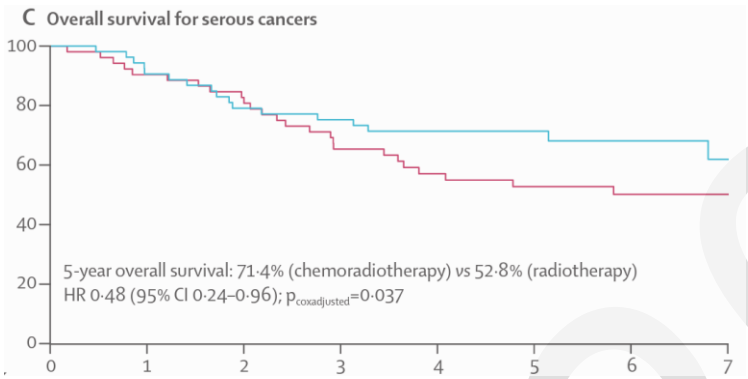
B

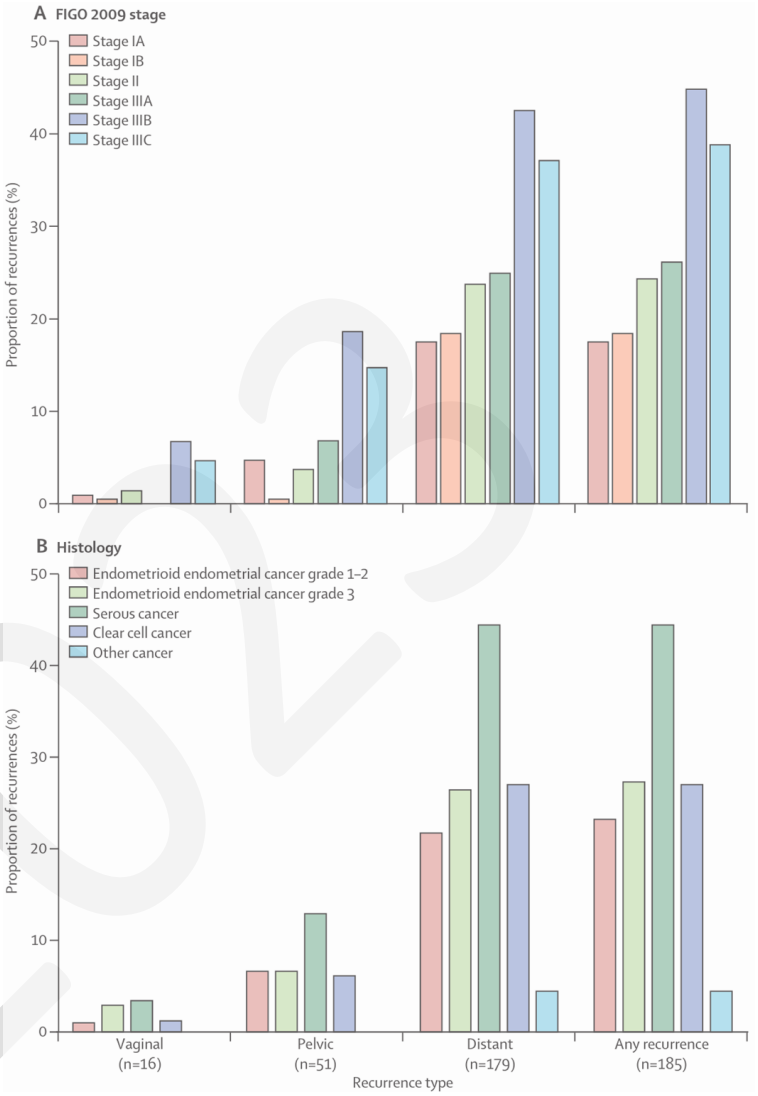
	Radiotherapy		Chemoradiotherapy		Chemoradiotherapy vs radiotherapy		
	Events/ patients	5-year failure-free survival (95% CI)	Events/ patients	5-year failure-free survival (95% CI)	HR (95% CI)	p value	$P_{interaction}$
Histology and grade							
Endometrioid grade 1–2	32/131	75% (66–82)	26/127	82% (74–88)	0·74 (0·44–1·26)	0·27	0·79
Endometrioid grade 3	32/106	69% (59–77)	28/106	74% (64–81)	0·73 (0·44–1·22)	0·23	
Serous, clear cell, other	39/93	59% (48–68)	29/93	69% (58–77)	0·60 (0·37–0·97)	0·036	
LVSI							
No	32/138	77% (68–83)	30/133	78% (69–84)	0·80 (0·48–1·33)	0·39	0·45
Yes	71/192	63% (55–69)	53/197	74% (67–80)	0·63 (0·44–0·90)	0·012	
Lymphadenectomy							
No	46/138	67% (58–74)	35/140	76% (68–83)	0·58 (0·37–0·91)	0·016	0·34
Yes	57/192	70% (63–76)	48/190	75% (68–81)	0·77 (0·52–1·14)	0·19	
Age (years)							
<60	26/140	81% (73–87)	28/128	81% (72–87)	1·17 (0·68–2·00)	0·57	0·012
60–69	47/128	62% (53–71)	40/144	71% (62–79)	0·69 (0·45–1·06)	0·094	
≥70	30/62	53% (40–65)	15/58	75% (61–85)	0·33 (0·18–0·63)	<0·001	
FIGO stage							
Stage I and II	43/187	77% (70–82)	35/178	81% (74–86)	0·77 (0·49–1·21)	0·26	0·47
Stage III	60/143	58% (49–66)	48/152	69% (61–76)	0·62 (0·42–0·91)	0·014	
Total	**103/330**	**69% (63–73)**	**83/330**	**76% (70–80)**	**0·68 (0·51–0·91)**	**0·010**	



De Boer, Lancet 2019. **Updated OS**
5-year ABS **OS ↑ Δ** 5% (HR 0·70; 95% CI 0·51–0·97)
DFS ↑ Δ 7% (0·70; 95% CI 0·52–0·94)







	Number of events	5-year probability (95% CI)	Hazard ratio (95% CI)	Log-rank p value*
Vaginal recurrence (first recurrence)				
Chemoradiotherapy	1	0·3% (0·0–2·1)	0·99 (0·06–15·90)	0·99
Radiotherapy alone	1	0·3% (0·0–2·1)	..	..
Pelvic recurrence (first recurrence)				
Chemoradiotherapy	3	0·9% (0·3–2·8)	0·75 (0·17–3·33)	0·71
Radiotherapy alone	4	0·9% (0·3–2·8)	..	..
Distant metastases (first recurrence)				
Chemoradiotherapy	78	21·4% (17·3–26·3)	0·74 (0·55–0·99)	0·047
Radiotherapy alone	98	29·1% (24·4–34·3)	..	..
Vaginal recurrence (total)				
Chemoradiotherapy	8	2·1% (1·0–4·4)	0·99 (0·37–2·65)	0·99
Radiotherapy alone	8	2·1% (1·0–4·4)	..	..
Pelvic recurrence (total)				
Chemoradiotherapy	20	5·5% (3·5–8·6)	0·63 (0·36–1·11)	0·11
Radiotherapy alone	31	8·5% (5·9–12·1)	..	..
Distant metastases (total)				
Chemoradiotherapy	80	22·1% (17·9–27·0)	0·75 (0·56–1·01)	0·057
Radiotherapy alone	99	29·4% (24·7–34·6)	..	..

*Unadjusted for stratification factors.

Table 2: **Recurrence outcomes by treatment group**

GOG-258 (DEBULKING STUDY – ↑ Risk vs. PORTEC-3) ± RT
←R→ 813 Stage III-IVA (< 2 cm residual disease) or Stage I/II serous/clear cell and positive cytology
All patients underwent "OPTIMAL DEBULKING" to less than < 2cm residual)
| 1. CRT | 2. C alone | CRT = 45 pelvis +/- VB +/- boost + concurrent Cisplatin → consolidation carbo/taxol x4
Chemotherapy = Carbo/taxol x 6

Matei, ASCO 2017 Abstract
RFS HR was 0.9 (NS)
Recurrence Vaginal 3% vs. 7%, HR = 0.36 (SS). Pelvic and PA 10% vs. 21%, HR=0.43 (SS)
Distant 28% vs. 21%, HR 1.36, (Trend, CI 1 to 1.86).
Similar G3 toxicity: 58% vs. 63% NS
Conclusion: Although CRT reduced the rate of local recurrence compared to CT; the combined modality regimen did not increase RFS in optimally debulked, stage III/IVA UC.

Matei, NEJM 2019
5-year RFS 59%-58% (NS)
5-year vaginal recurrence 2% vs. 7% (SS) 5-year pelvic and paraaortic LN recurrence 11% vs. 20% (SS)
5-year distant recurrence 27% vs. 21% (CI, 1.00 to 1.86).
Grade 3, 4, or 5 adverse events were reported in 202 patients (58%) vs. 227 patients (63%).
CONCLUSIONS: Chemotherapy plus radiation was not associated with longer relapse-free survival than chemotherapy alone in patients with stage III or IVA endometrial carcinoma. .

Italian Retrospective PA-LN Study (IIIC2)
RR 105 endometrial cancer → primary surgery 1984 2014 (all hysterectomy ± salpingo-oophorectomy + lymphadenectomy PA ± pelvic nodes).
Included all patients with stage III endometrial cancer and documented para-aortic lymph node metastases.
EBRT (24%), chemotherapy (23%), CRT (53%).
Most patients receiving chemotherapy and external beam radiotherapy (80%) had chemotherapy first.

Bogani, Int J Gynecol Cancer 2020
Total Recurrences 44% → The majority of relapses had a distant component (31/46, 67%) → only one patient isolated para-aortic recurrence.
Non-endometrioid (vs. endometroid) subtypes ↓ DFS (HR 2.57; 95% CI 1.38 to 4.78) and ↓ OS (HR 2.00; 95% CI 1.09 to 3.65).
If Endometrioid histology (n=60), CRT (vs. either one) ↑ DFS (HR 0.22; 95% CI 0.07 to 0.71) and ↑ OS (HR 0.28; 95% CI 0.09 to 0.89).
Combination therapy did not improve prognosis for patients with non-endometrioid histology (n=45).
Conclusions In our cohort of patients with stage IIIC2 endometrioid endometrial cancer, those receiving chemotherapy and external beam radiotherapy had improved survival compared with patients receiving chemotherapy or external beam radiotherapy alone. However, the prognosis of patients with non-endometrioid endometrial cancer remained poor, regardless of the adjuvant therapy administered. Distant recurrences were the most common sites of failure.

Safety Trial RTOG 97-08: Concurrent Chemo-RT
Phase II trial. N = 46 pts + **grade 2–3** + **1.** >50% MMI (23% Stage I), **2.** cervical stromal (Stage II) or **3.** pelvic-confined extrauterine disease (62% Stage III)
Exclusion: Omitted pts with abd involvement or PA node involvement (pelvic RT alone not adequate)
Pelvic RT (45 Gy) and cisplatin d1 and d28 -> VC brachy -> maintenance cisplatin/paclitaxel x4

Greven, IJROBP 2004
4 yr pelvic and regional recurrence rates, both 2%
4-yr distance recurrence rate was 19%
4 yr OS and DFS: 85% and 81% - quite good
Acute toxicity was significant (mostly heme)
Chronic toxicity was high –
- 41% grade 2, 16% grade 3, 5% grade 4

Conclusion: LRC is excellent with CMT, and CMT appears to be tolerable

POOLED results NSGO-EC-9501/EORTC-55991 and **MaNGO** ILIADE-III **RT alone vs. C→RT (EORTC) or RT→C (Mango)**
←R→ 540 patients s/p TAH-BSO pooled from 2 randomized trials – differences in eligibility and chemo.
ILIADE-III included stage IIB, IIIA-C (not +cytology alone). Excluded CC and serous
NSGO/EORTC included I-III with ALL high risk factors including serous, clear cell, or anaplastic histology. Included very few Stage II & III patients
| 1. Pelvic RT (≥44 Gy) ± VC brachy (40%) | 2. Sequential chemo before (NSGO) or after RT (ManGO) |
Chemo was (all over the place):
- doxorubicin/epirubicin/cisplatin
- epirubicin/paclitaxel
- doxorubicin/carboplatin
- carboplatin/paclitaxel
- doxorubicin/cisplat on MaNGO

Hogberg, Eur J Cancer, 2010
Outcomes: CRT is better → PFS HR 0.63 (P=0.009) CSS HR 0.55 (P = 0.01).
NS → OS (P = 0.07)
5-year PFS 69% vs. 78% (p=0·01)
5-year OS 75% vs. 82%; p=0·07.
SUBSET: NO benefit to C for Serous/CC vs. Endometroid (but it was not planned and not powered for this)
Conclusion: Sequential chemo and RT improves PFS and CSS for high risk tumors, trend for improves OS

Sequencing Adjuvant Modality

2015 Review: Sandwich Approach https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4479067/

Phase II Sandwich
Prospective 33 patients stage III/IV endometrial cancer.
| Carboplatin/paclitaxel q3 weeks × 4 cycles → pelvic RT (45 Gy) (PA RT and VC brachy optional) → 2 more cycles chemo |
Para-aortic RT and/or HDR vault brachytherapy (BT) were added at the discretion of the treating physician.
Stage distribution was as follows: IIIA (21%), IIIC (70%), IVB (9%).
Combination chemotherapy was successfully administered to 30 patients (91%) and 25 patients (76%), before and after RT respectively.

Lupe, IJROBP 2007 21 months
Initial chemo completed in 91% of pts
Nine patients (27%) experienced acute Grade 3 or 4 chemotherapy toxicities.
All pts completed RT (60% 4-field, 40% IMRT); 12% had acute gr 3-4 toxicities, 18% had chronic toxicities.
2-year DFS and OS both 55%
3% pelvic relapse (1 patients)
Conclusions: Adjuvant treatment with combination chemotherapy interposed with involved field radiation in advanced endometrial cancer was well tolerated. This protocol may be suitable for further evaluation in a clinical trial.

Duke RR Sandwich Approach
RR 356 patients DUKE, UNC surgical stage III/IV TAHBSO ± pelvic/PA LND → C ± RT
48% RT alone, 29% C alone, 23% (n=83) CRT.
The median age was 66 years; 38% had endometrioid tumors; and 83% were optimally debulked.

Secord, Gynecol Oncol 2007

HIGHEST 3-year	C→RT→C	OS 91%	PFS 69%
…compared to	C→RT	OS 47%	PFS 19%
	RT→C	OS 65%	PFS 60%.

Conclusion: Combined adjuvant chemotherapy and radiation was associated with improved survival in patients with advanced stage disease compared to either modality alone. Future clinical trials are needed to prospectively evaluate multi-modality adjuvant therapy in women with advanced staged endometrial cancer to determine the appropriate sequencing and types of chemotherapy and radiation.

Multicenter RR Sandwich Approach
RR 109 patients Stage III / IV advanced endometrial cancer Multicenter.
All patients: comprehensive staging procedure (TAH BSO +/- selective pelvic/aortic lymphadenectomy) → adjuvant chemotherapy and radiation.
Looked at outcomes of C→RT→C (41%), RT→C (17%), and C→RT (42%).
The median age was 62 years (range: 35-83); 48% had endometrioid tumors; and 90% underwent optimal cytoreduction.
RT included whole pelvic RT, pelvic +/- extended field and VBT, VBT
No difference in frequency of adverse effects between groups

Secord, Gyn Oncol 2009
Significant improvements for C-RT-C vs. C-RT vs. RT-C

HIGHEST 3-year	C→RT→C	OS 88%	PFS 69%	(SS)
…compared to	C→RT	OS 57%	PFS 52%	
	RT→C	OS 54%	PFS 47%.	

After adjusting for stage, age, grade, race, histology and cytoreduction status the **OS HR for therapy**:

Compared to C→R→C…		
R→C	5.74 (95% CI, 1.96 to 16.77)	
C→ R	2.60 (95% CI, 1.01 to 6.71)	p=0.003.

When the analysis was restricted to optimally cytoreduced patients, those who were treated with RC were at higher risk for disease progression [HR=3.53 (95% CI, 1.29 to 9.71)], p=0.024, and death [HR=7.24 (95% CI, 2.25 to 23.37)], p=0.001, than patients who received sequential CRC.
Conclusion: Sequential CRC associated with improved survival in women with advanced stage disease compared to other sequencing modalities with a similar adverse effect profile

Node Positive

CURRENTLY UPDATING

MDACC Retrospective
RR 71 patients stage IIIC (LN+) TAHBSO → Lymphadenectomy w/o high-risk histology (no serous or CC)
18 pts had platinum based chemo or hormone therapy without RT.
50 had regional RT +/- chemo (regional RT group)
Thirty-nine percent (28/71) of patients had involved paraaortic lymph nodes while 61% (43/71) had only pelvic lymph nodes.

Klopp, Gyn Onc 2009
Pelvic RFS ↑ with regional RT – 98% vs 61% P=0.001
DSS ↑ with regional RT – 78% vs 40% P=0.01
OS ↑ with regional RT – 73% vs 40% P=0.03
Patterns of relapse
w/o RT -> primary site of failure was pelvis
w/ RT -> primary site of failure was distant
Conclusions: Patients treated without regional RT had a high rate of locoregional recurrence. Patients with stage IIIC endometrial adenocarcinoma who underwent surgical staging followed by external beam irradiation had a high rate of cure. Relapses in patients treated with EBRT primarily occurred in patients with grade 3 cancer who may be most likely to benefit from combined-chemoradiation treatment.

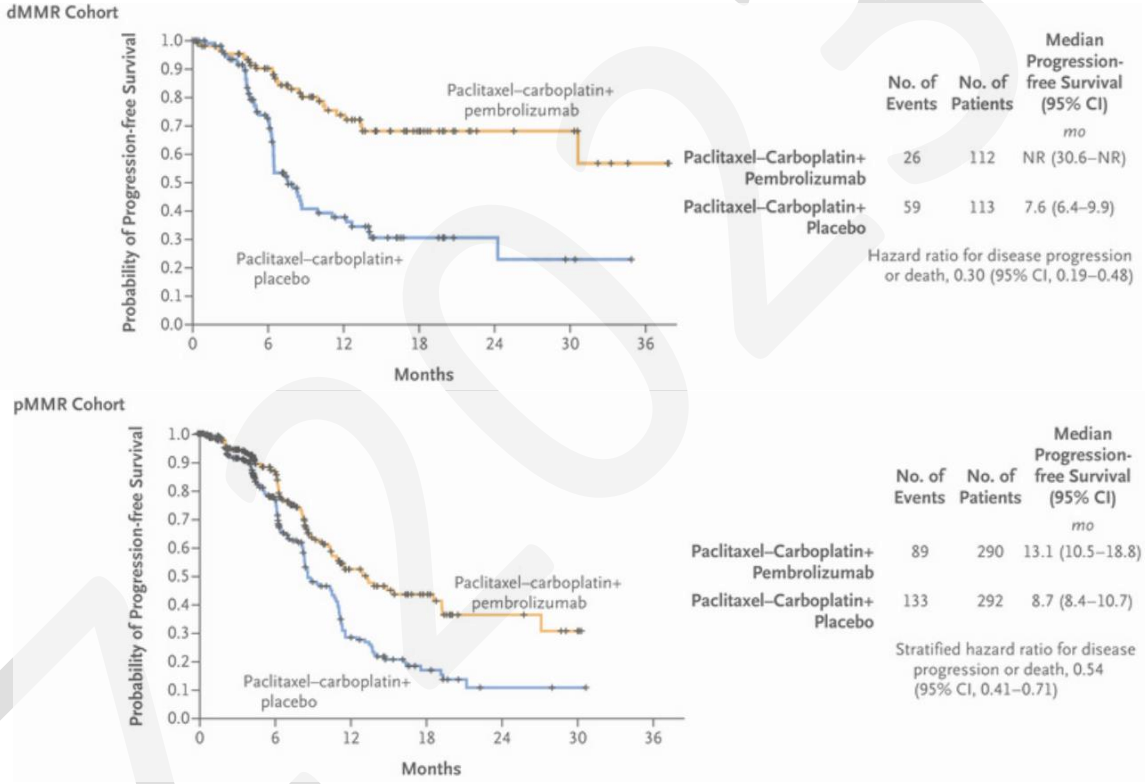
Immunotherapy

Pembrolizumab Trial
←R→ 816 measurable disease (stage III or IVA) or stage IVB or recurrent endometrial cancer | 1. Chemo + pembrolizumab | 2. Chemo + placebo |.
Chemo = paclitaxel plus carboplatin.
Pembrolizumab or placebo was planned in 6 cycles every 3 weeks, followed by up to 14 maintenance cycles every 6 weeks.
1^{O} PFS in dMMR cohort or pMMR cohort.

Eskander, NEJM 2023

12-month PFS	dMMR	74% vs. 38% (HR 0.30; P<0.001).
Median PFS	pMMR	13.1 months vs. 8.7 months (HR 0.54; P<0.001).

Adverse events were as expected for pembrolizumab and combination chemotherapy.
CONCLUSIONS In patients with advanced or recurrent endometrial cancer, the addition of pembrolizumab to standard chemotherapy resulted in significantly longer progression-free survival than with chemotherapy alone.



RUBY Dostarlimab "Jemperli" (immune-checkpoint inhibitor)

←R→ 494 primary advanced stage III or IV or first recurrent endometrial cancer | 1. Chemo + dostarlimab (500 mg) | 2. Chemo + placebo |
Chemo = carboplatin (AUC–time curve, 5 mg / mm / min) and paclitaxel (175 mg / m^2 BSA), every 3 weeks (six cycles).
→ dostarlimab (1000 mg) or placebo every 6 weeks for up to 3 years.
1^O PFS and OS
118 (23.9%) had mismatch repair–deficient (dMMR), microsatellite instability–high (MSI-H) tumors.

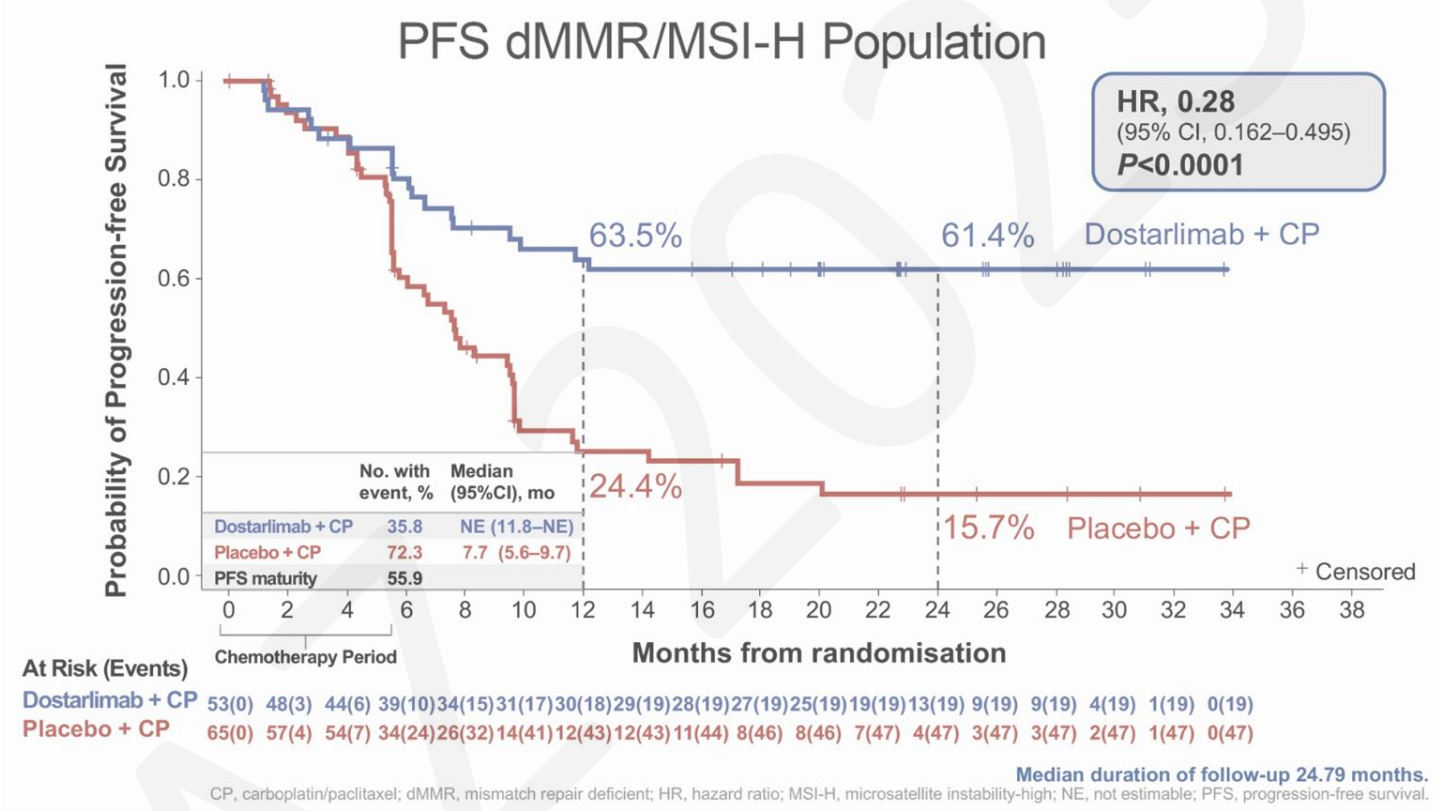
Mirza, NEJM 2023

24- month PFS	dMMR–MSI-H	61.4% vs. 15.7% (HR 0.28; P<0.001).
	Overall	36.1% vs. 18.1% (HR 0.64; P<0.001).
24- month OS		71.3% vs. 56.0% (HR 0.64; SS).
Nausea		53.9% vs. 45.9%
Alopecia		53.5% vs. 50.0%
Fatigue		51.9% vs. 54.5%.

Severe and serious adverse events were more frequent in the dostarlimab group than in the placebo group.

CONCLUSIONS

Dostarlimab plus carboplatin–paclitaxel significantly increased progression-free survival among patients with primary advanced or recurrent endometrial cancer, with a substantial benefit in the dMMR–MSI-H population.



KEYNOTE 775

←R→ 827 advanced endometrial cancer w/ previously ≥ 1 platinum-based chemotherapy regimen.

697 with pMMR disease and 130 with mismatch repair–deficient disease

| 1. lenvatinib (20 mg PO qday) + Pembro (200 mg, IV q 3 weeks) | 2. chemotherapy of the treating physician's choice |

Chemo = (doxorubicin at 60 mg / m^2 body-surface area, IV q3 weeks, or paclitaxel 80 mg / m^2, IV weekly [with a cycle of 3 weeks on and 1 week off]).

1^{O} PFS and OS. The end points were evaluated in patients with mismatch repair–proficient (pMMR) disease and in all patients. Safety was also assessed.

Makker, NEJM 2022

Median PFS	pMMR	6.6 months vs. 3.8 months (HR 0.60; P<0.001)
	Overall	7.2 months vs. 3.8 months (HR 0.56; P<0.001).
Median OS	pMMR	17.4 month vs. 12.0 month (HR 0.68; P<0.001)
	Overall	18.3 month vs. 11.4 month (HR 0.62; P<0.001).

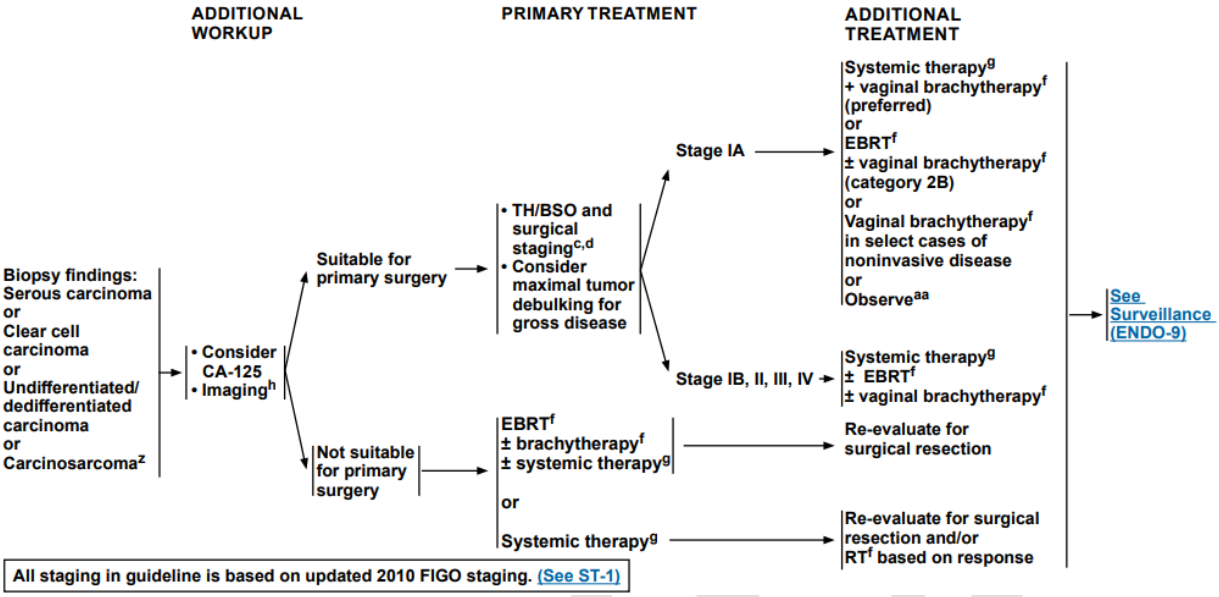
Adverse events of grade 3 or higher occurred in 88.9% of the patients who received lenvatinib plus pembrolizumab and in 72.7% of those who received chemotherapy.

CONCLUSIONS Lenvatinib plus pembrolizumab led to significantly longer progression-free survival and overall survival than chemotherapy among patients with advanced endometrial cancer.

Table 2. Confirmed Tumor Responses.*

End Point	pMMR Population		All Patients		dMMR Population	
	Lenvatinib plus Pembrolizumab (N=346)	Chemotherapy (N=351)	Lenvatinib plus Pembrolizumab (N=411)	Chemotherapy (N=416)	Lenvatinib plus Pembrolizumab (N=65)	Chemotherapy (N=65)
Objective response						
No. of patients	105	53	131	61	26	8
Percent (95% CI)	30.3 (25.5 to 35.5)	15.1 (11.5 to 19.3)	31.9 (27.4 to 36.6)	14.7 (11.4 to 18.4)	40 (28 to 53)	12 (5 to 23)
Best overall response						
Complete response						
No. of patients	18	9	27	11	9	2
Percent (95% CI)	5.2 (3.1 to 8.1)	2.6 (1.2 to 4.8)	6.6 (4.4 to 9.4)	2.6 (1.3 to 4.7)	14 (7 to 25)	3 (<1 to 11)
Partial response						
No. of patients	87	44	104	50	17	6
Percent (95% CI)	25.1 (20.7 to 30.1)	12.5 (9.3 to 16.5)	25.3 (21.2 to 29.8)	12.0 (9.1 to 15.5)	26 (16 to 39)	9 (3 to 19)
Stable disease						
No. of patients	168	139	193	167	25	28
Percent (95% CI)	48.6 (43.2 to 54.0)	39.6 (34.4 to 44.9)	47.0 (42.0 to 51.9)	40.1 (35.4 to 45.0)	38 (27 to 51)	43 (31 to 56)
Progressive disease						
No. of patients	54	108	61	123	7	15
Percent (95% CI)	15.6 (11.9 to 19.9)	30.8 (26.0 to 35.9)	14.8 (11.5 to 18.7)	29.6 (25.2 to 34.2)	11 (4 to 21)	23 (14 to 35)
Could not be evaluated†						
No. of patients	2	7	5	8	3	1
Percent (95% CI)	0.6 (0.1 to 2.1)	2.0 (0.8 to 4.1)	1.2 (0.4 to 2.8)	1.9 (0.8 to 3.8)	5 (1 to 13)	2 (0 to 8)
Not assessed‡						
No. of patients	17	44	21	57	4	13
Percent (95% CI)	4.9 (2.9 to 7.8)	12.5 (9.3 to 16.5)	5.1 (3.2 to 7.7)	13.7 (10.5 to 17.4)	6 (2 to 15)	20 (11 to 32)
Median duration of response (range) — mo§	9.2 (1.6 to 23.7)	5.7 (0.0 to 24.2)	14.4 (1.6 to 23.7)	5.7 (0.0 to 24.2)	NR (2.1 to 20.4)	4.1 (1.9 to 15.6)
Median time to response (range) — mo	2.1 (1.5 to 9.4)	3.5 (1.0 to 7.4)	2.1 (1.5 to 16.3)	2.1 (1.0 to 7.4)	2.9 (1.7 to 16.3)	1.9 (1.8 to 3.7)
Disease control¶						
No. of patients	248	163	296	194	48	31
Percent (95% CI)	71.7 (66.6 to 76.4)	46.4 (41.1 to 51.8)	72 (67.4 to 76.3)	46.6 (41.8 to 51.6)	74 (61 to 84)	48 (35 to 60)

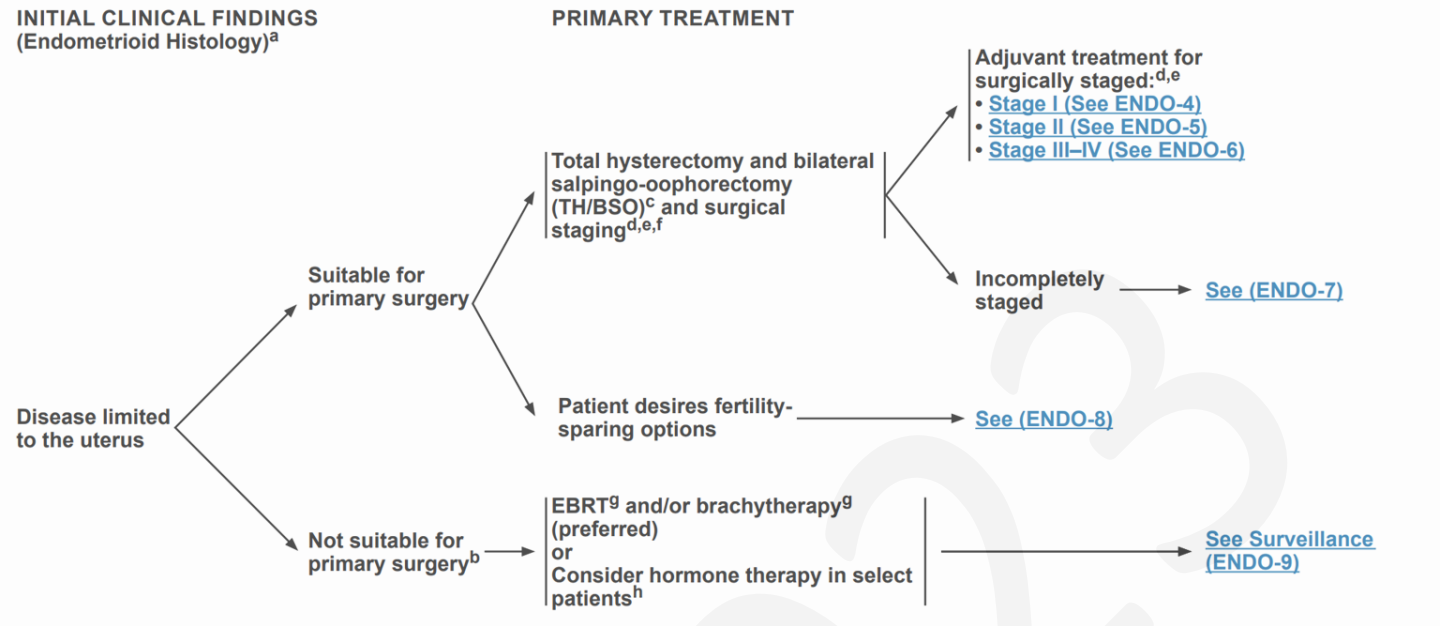
Serous/CC/Carcinosarcoma HR Histology



- Serous, clear cell, carcinosarcoma/MMMT
  - Workup: NCCN and SGO recommend **CA-125 and MRI** or CT C/A/P prior to surgery to look for extrauterine disease
- Higher risk for upper abdominal relapse (like ovarian cancer)
- Account for 50% of endometrial cancer deaths
- Comprehensive surgical staging is important
- NCCN recommends:
  - Stage IA - Chemo +/- VBT preferred, also observation or EBRT +/- VBT allowed
  - Stage IB+: Chemo +/- VBT +/- EBRT

- **Yale Recommendations:**
  - Early Stage: Chemo and **VB** only (we use 7 Gy x 2)
  - Advanced Stage: 3 cycles of Carbo/Taxol -> IMRT to 45 Gy + **VB** -> 3 Cycles of Carbo/Taxol

Medially Inoperable



CONSENSUS GUIDELINES

Although specific contouring guidelines do not exist, the panel recommends contouring a CTV, which includes the entire uterus, cervix, and upper 1-2 cm of the vagina (Fig. 1). If MR is available, the tumor itself should be contoured as a gross tumor volume (GTV). GTV is defined as visible abnormality on T2-weighted MRI. It is recommended that the bladder, rectum, sigmoid, vagina (not included in the CTV), and bowel be contoured for OAR dose calculations.

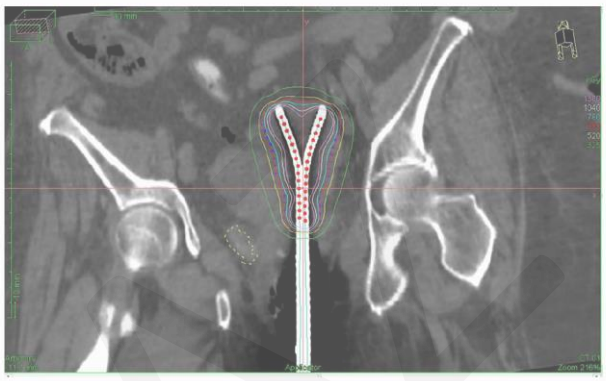


Fig. 2. Optimization of a magnetic resonance (MR)–based treatment plan using points. Coronal MR with dual tandem and superimposed dose distribution. The optimization points (blue + symbols) were placed in accordance with the computer tomography–defined uterine wall thickness along the course of the tandems and the location of the adjacent recto sigmoid and bladder. In this example, optimization points were placed laterally from each tandem in the following manner: for dwells 1 to 9, at a distance of 15 mm, and for dwells 12 to 15, at a distance of 10 mm. Optimization and prescription were performed by the planning software to make the average of the optimization points equal to the prescription and to minimize the standard deviation of the points compared with the average.

Based on the best available evidence, this panel recommends that patients with Stage I endometrial cancer should receive an EQD_2 of at least 48 Gy for brachytherapy alone and at least 65 Gy for the combination of external beam plus brachytherapy to 90% of the (D_{90}) CTV volume encompassing the whole uterus, depending on tumor-specific (i.e., presence or absence of deep invasion on pretreatment MRI) and patient-specific (inability of the patient to undergo pretreatment MRI) factors (see "Clinical Scenarios"). A GTV may also be defined using T2-weighted MRI and may be prescribed a dose of ≥80 Gy (Fig. 1).

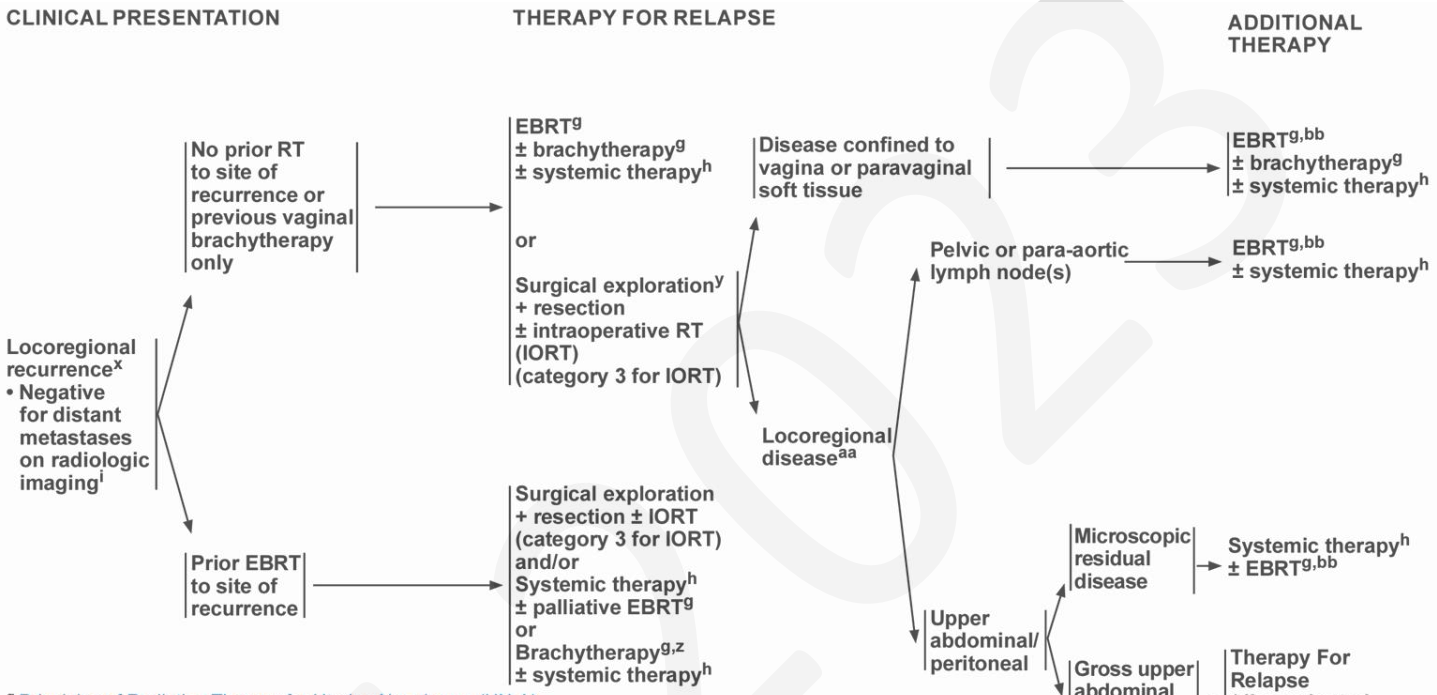
Table 4
Recommended structures for volume-based planning in medically inoperable endometrial cancer

Structure	Image data set	Definition
Gross tumor volume	T2-weighted MRI	Visible abnormality if present
Clinical target volume	MRI or CT	Entire uterus, cervix, and upper 1–2 cm of the vagina
Organs at risk	MRI or CT	Sigmoid, rectum, bladder, bowel, and uninvolved lower third of the vagina

CT = computed tomography; MRI = magnetic resonance imaging.
Note. MRI is required if a gross tumor volume is to be contoured. The clinical target volume includes the entire uterus, cervix, and upper vagina. Organs at risk include bladder, rectum, and sigmoid.

Recurrence

- Local recurrences in endometrial cancer are usually treated with EBRT (45 Gy) and brachytherapy (SELECTION BELOW).
    - Brachytherapy technique (intracavitary vs. interstitial) is based on the depth of vaginal wall invasion and the distribution of the disease.
        - If more superficial (<5 mm) recurrences, intracavitary vaginal brachytherapy may be selected
            - Something like 6 Gy x 5 fx to surface.
        - If depth ≥ 5 mm, cannot do intracavitary vaginal brachytherapy → must transition to interstitial technique.
            - Something like interstitial 5.5 Gy x 5 BID (Goal EQD2 = 75 - 85 Gy)
- Combination therapy with EBRT and vaginal brachytherapy is generally preferred because, according to some reports, it is associated with better control and studies have shown that more than 50% of a selected group of patients are curable.

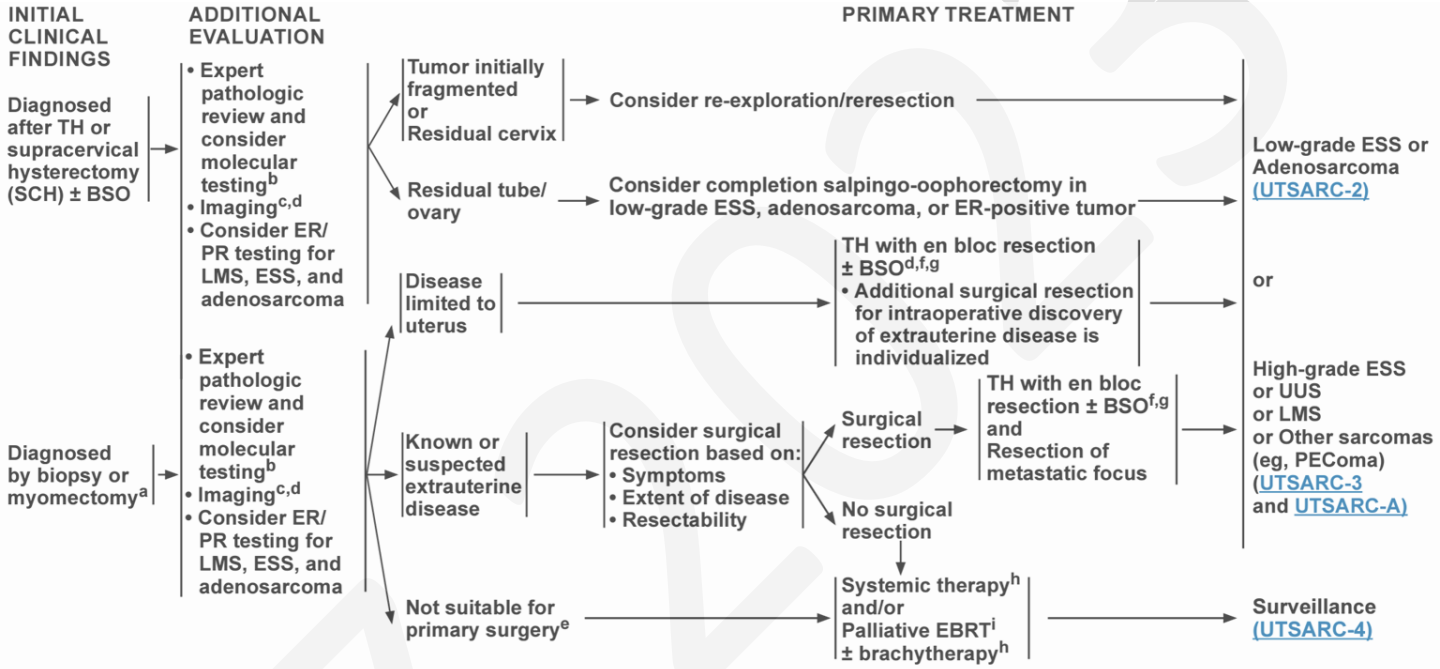


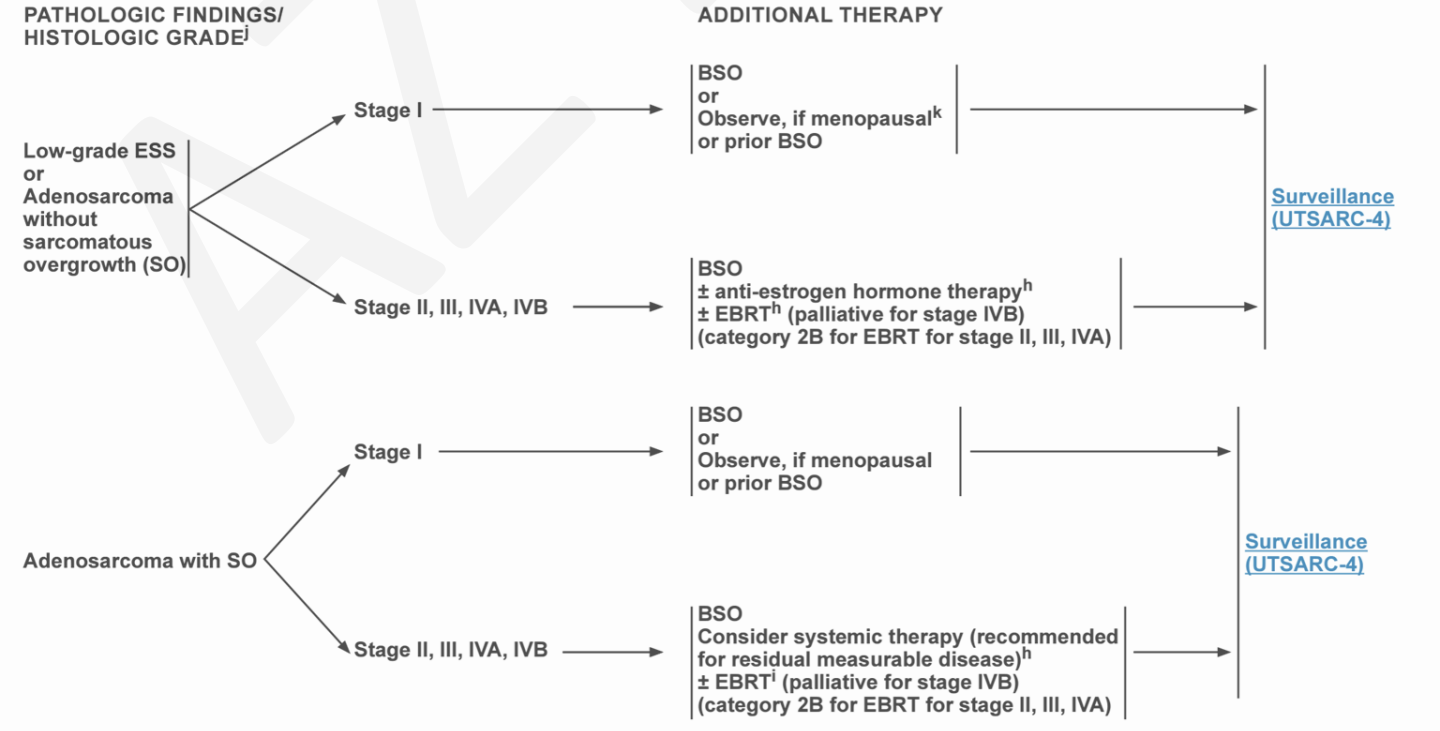
[g] Principles of Radiation Therapy for Uterine Neoplasms (UN-A).
[h] Systemic Therapy for Endometrial Carcinoma (ENDO-D).
[i] Principles of Imaging (ENDO-B).
[x] May include patients with isolated common iliac or para-aortic lymph node recurrence.
[y] Consider preoperative EBRT in select patients.
[z] Recommended for small-volume vaginal and/or paravaginal disease.
[aa] Consider brachytherapy for locoregional disease with a vaginal component.
[bb] Post-resection consolidation EBRT can be considered in patients who were not previously irradiated or who are deemed to have additional tolerance for radiation.

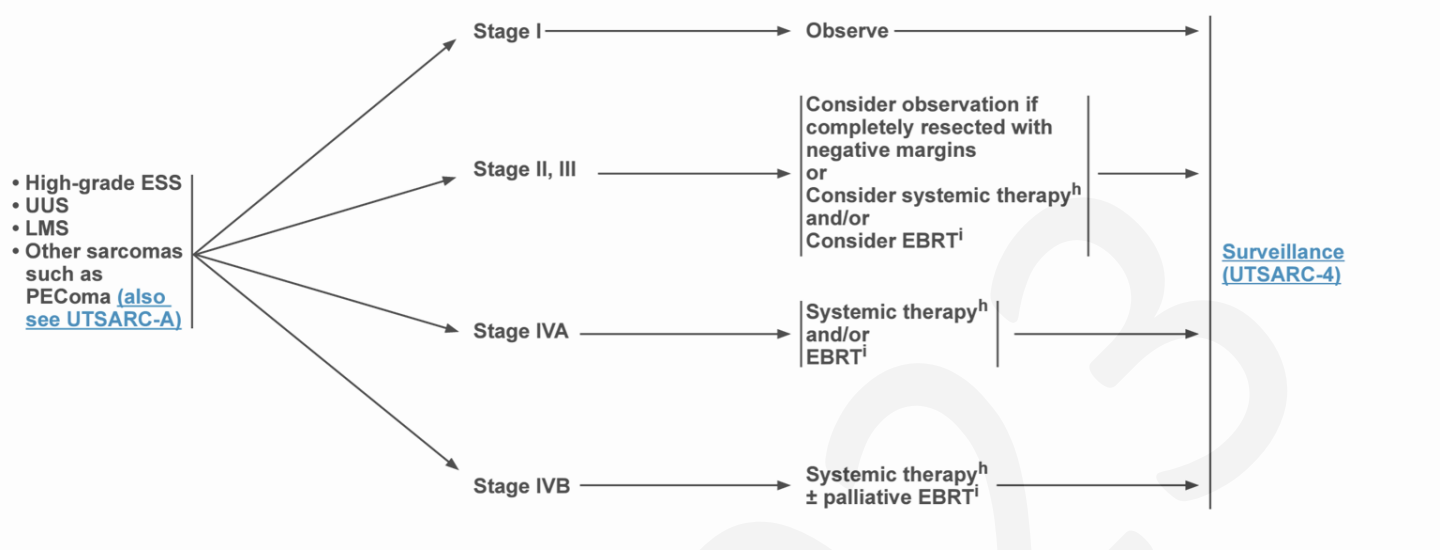
Uterine Sarcoma

T2 = beyond uterus (WITHIN pelvic)
T3 = abdominal tissue

FIGO	TNM	Endometrial Stromal Sarcoma & Leiomyosarcoma
IA	T1a	≤5 cm in size
IB	T1b	> 5 cm in size
IIA	T2a	Adnexal Involvement
IIB	T2b	Other pelvic tissues
IIIA	T3a	One site
IIIB	T3b	Multiple sites
IIIC	N1	Regional Nodes
IVA	T4	bladder, rectum
IVB	M1	distant mets






• High-grade ESS
• UUS
• LMS
• Other sarcomas such as PEComa (also see UTSARC-A)
Stage I
Observe
Stage II, III
Consider observation if completely resected with negative margins
or
Consider systemic therapy[h]
and/or
Consider EBRT[i]
Stage IVA
Systemic therapy[h]
and/or
EBRT[i]
Stage IVB
Systemic therapy[h]
± palliative EBRT[i]
Surveillance (UTSARC-4)

Advanced, Recurrent/Metastatic or Inoperable Disease	
First-Line Therapy[b]	**Second-Line or Subsequent Therapy**
Preferred Regimens • Doxorubicin • Docetaxel/gemcitabine • Doxorubicin/trabectedin (for LMS)[1] • Doxorubicin/ifosfamide • Doxorubicin/dacarbazine **Useful in Certain Circumstances** • Biomarker-directed therapy ‣ *NTRK* gene fusion-positive tumors ◊ Larotrectinib ◊ Entrectinib ‣ IMT with ALK translocation ◊ Crizotinib[2] ◊ Ceritinib[3] ◊ Brigatinib[4,5] ◊ Lorlatinib ◊ Alectinib • PEComa ‣ Albumin-bound sirolimus	**Preferred Regimens** • Trabectedin[c] **Other Recommended Regimens** • Gemcitabine/dacarbazine • Gemcitabine/vinorelbine • Dacarbazine • Gemcitabine • Epirubicin • Ifosfamide • Liposomal doxorubicin • Pazopanib • Temozolomide • Eribulin (category 2B) **Useful in Certain Circumstances** • Biomarker-directed therapy ‣ TMB-H tumors[d] ◊ Pembrolizumab ‣ Consider PARP inhibitors for *BRCA*-altered LMS[e,6,7-9] ◊ Olaparib[10] ◊ Rucaparib ◊ Niraparib • PEComa ◊ Sirolimus ◊ Everolimus ◊ Temsirolimus

Anti-Estrogen Hormone Therapy for Low-Grade ESS or Adenosarcoma Without SO or Hormone Receptor-Positive (ER/PR) Uterine Sarcomas[f]	
Preferred Regimens	**Other Recommended Regimens**
• Aromatase inhibitors for low-grade ESS or adenosarcoma without SO[g]	• Aromatase inhibitors[g] (for ER/PR-positive uterine sarcomas) • Fulvestrant[g] • Megestrol acetate (category 2B for ER/PR-positive uterine sarcomas) • Medroxyprogesterone acetate (category 2B for ER/PR-positive uterine sarcomas) • GnRH analogs (category 2B for low-grade ESS, adenosarcoma without SO, and ER/PR-positive uterine sarcomas)