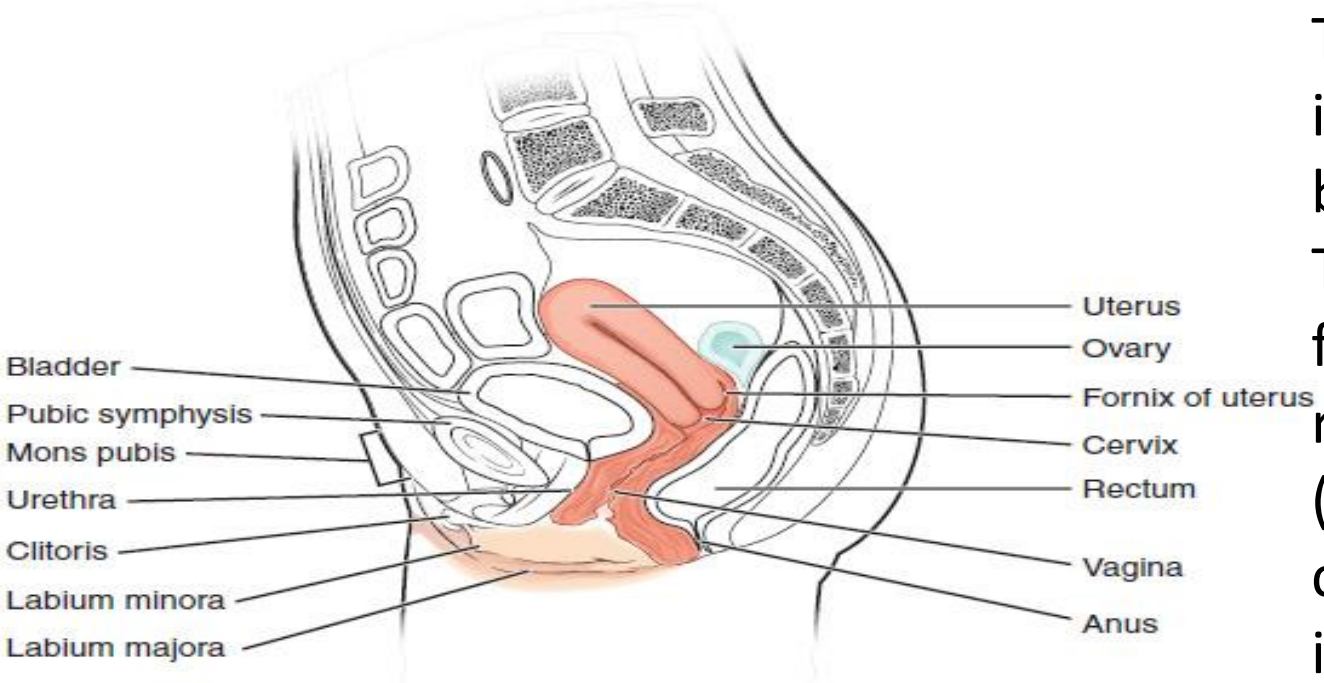
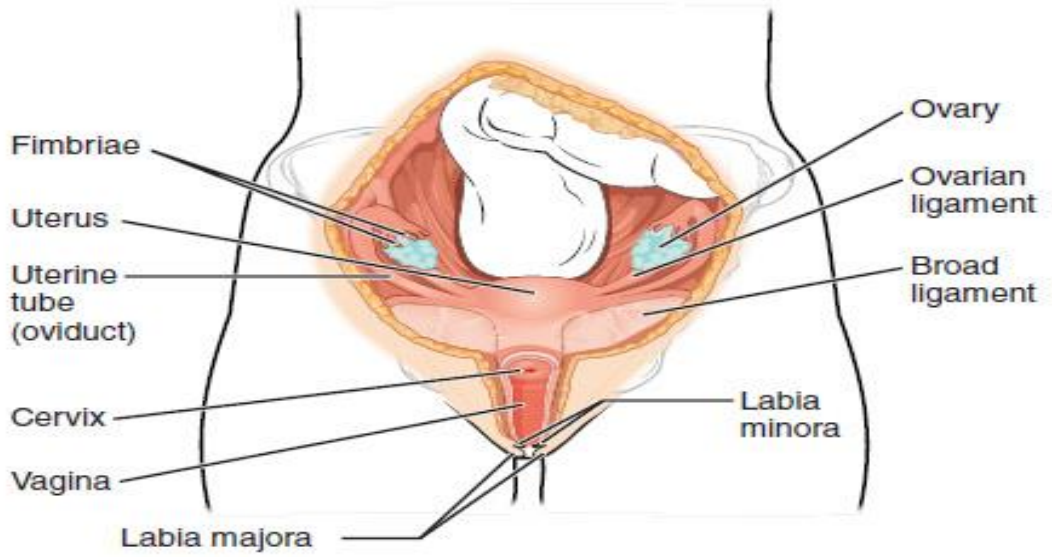
ENDOMETRIAL CARCINOMA



(a) Human female reproductive system: lateral view



(b) Human female reproductive system: anterior view

The uterus is located within the pelvic region immediately behind and almost overlying the bladder, and in front of the sigmoid colon. The uterus can be divided anatomically into four regions: the fundus – the uppermost rounded portion of the uterus, the corpus (body), the cervix, and the cervical canal. The cervix protrudes into the vagina. The uterus is held in position within the pelvis by ligaments, which are part of the endopelvic fascia. These ligaments include the pubocervical ligaments, the cardinal ligaments, and the uterosacral ligaments. It is covered by a sheet-like fold of peritoneum, the broad ligament

Endometrioid adenocarcinoma is the most common endometrial carcinoma, constituting 75% to 80% of all cases

Risk factors for endometrial cancer:

1. Exogenous unopposed estrogen
2. Endogenous estrogen (obesity, functional ovarian tumors, late menopause, nulliparity, chronic anovulation/polycystic ovarian syndrome)
3. The use of tamoxifen in patients with breast cancer has been associated with increased risk of endometrial cancer
4. Advancing age (75% postmenopausal)
5. Hereditary (HNPCC); 27%–71% lifetime risk of endometrial cancer
6. Family Hx
7. Non–insulin-dependent diabetes mellitus and hypertension (RR, 1 to 3) also increases the risk of endometrial cancer

What are protective factors for endometrial cancer?

Protective factors for endometrial cancer include combination oral contraceptives and physical activity.

it is well established that the use of estrogen-only hormone replacement therapy and sequential oral contraceptives greatly increases endometrial cancer risk, whereas combined preparations, that is, those that contain a progestogen as well as estrogen throughout the treatment period, have a protective effect (RR, 0.3 to 0.5)

Mutations in one of the four mismatch repair (MMR) genes hMLH1, hMSH2, hMSH6, or hPMS2 have been identified in patients with Lynch syndrome. Although HNPCC is thought of primarily in terms of risk of developing colorectal cancer, it is important to note that lifetime cumulative risk of endometrial cancer for women with HNPCC is 40% to 60%

Forms of endometrial cancer:

1. Type I: endometrioid, 70%–80% of cases, estrogen related, 75–80% of tumors arise from endometrial hyperplasia.
2. Type II: nonendometrioid, typically papillary serous or clear cell, high grade, aggressive clinical course, not stimulated by estrogen, arise from atrophic endometrium or from an endometrial polyp in older pts., not associated with obesity

Up to 5% of uterine cancers are sarcomas, including carcinosarcoma (most common), leiomyosarcoma, and endometrial stromal sarcomas.

74. Which of the following molecular abnormalities is MOST consistent with a sporadic endometrial cancer?

A. MLH1 promoter methylation
B. MSH2 loss of expression
C. PMS2 loss of expression
D. EPCAM deletion

Key: A

Rationale:
Lynch syndrome-related cancers commonly do not demonstrate hypermethylation of the MLH1 promoter https://www.ncbi.nlm.nih.gov/books/NBK1211/.

Reference:
Kohlmann, W. (2018). Lynch Syndrome Synonyms: HNPCC, Hereditary Non-Polyposis Colon Cancer. *Gene Reviews*, 1993-2019.

What is the most common clinical presentation of endometrial cancer?

Endometrial cancer presents with abnormal vaginal bleeding in 90% cases. Only 5%–20% of postmenopausal women with abnormal vaginal bleeding have endometrial cancer

What are the most aggressive histologies of epithelial endometrial cancer?

serous, clear cell, and squamous cell variants (i.e., Adenosquamous)

lymphatic drainage of the uterus

The primary lymphatic drainage of the cervix and lower uterine segment is to the pelvic LNs (parametrial, internal and external iliacs, obturator, common iliac, presacral).

The fundus has direct drainage to the para-aortic nodes.

The round ligament can drain directly to the inguinal nodes.

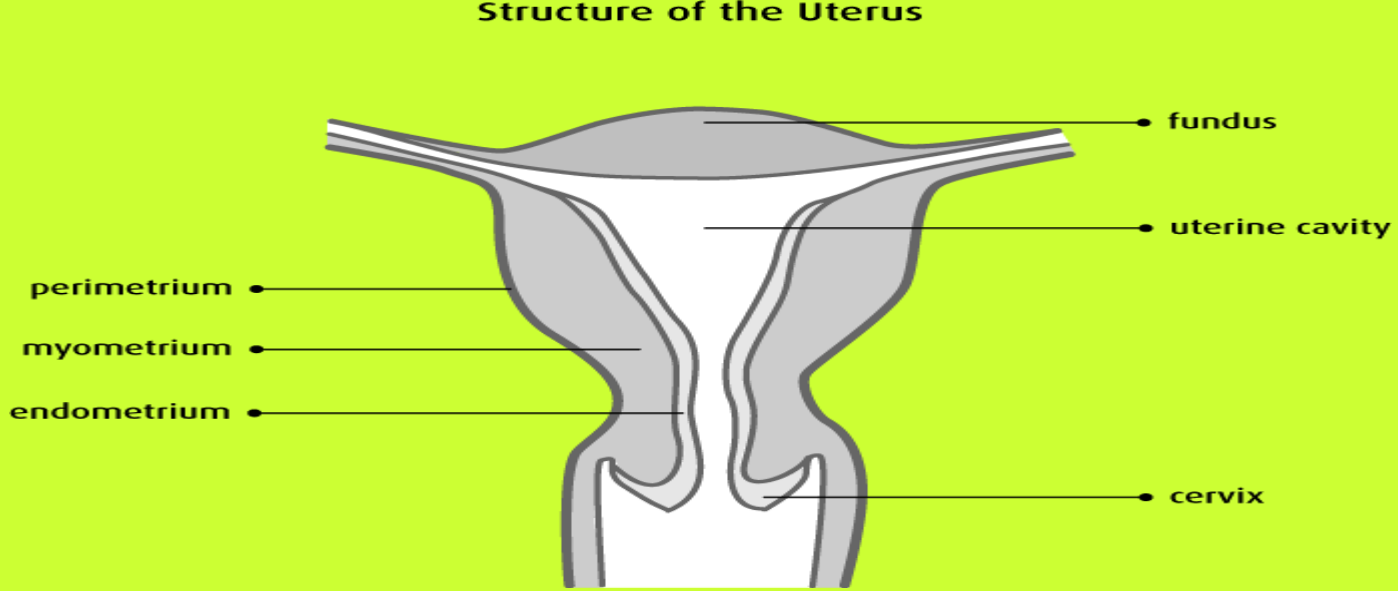
Work up :

H&P, CBC, PAP smear has limited sensitivity (as low as 40%) , endometrial Bx, and CXR. If extrauterine Dz is suspected, consider CA125, MRI/CT/PET, cystoscopy, and sigmoidoscopy.

Transvaginal ultrasonography (TVU) may be considered as a useful tool to assess patient's vaginal bleeding. Normal endometrium looks thin and homogeneously hyperechoic, but it is thickened and heterogeneous, with hyperplasia, polyps, and cancer, The consensus statement from the Society of Radiologists in Ultrasound defines an endometrial thickness of 5 mm or greater as being abnormal. If the thickness less than 5 mm the risk of endometrial cancer is minimal; the false negative rate is about 4%

Endometrial biopsy is diagnostic gold standard with >90% sensitivity and 85% specificity, thereby largely obviating need for D&C (D&C if endometrial biopsy is nondiagnostic)

MRI



diffusion-weighted (DW) MRI are equivalent in detecting deep myometrial invasion.

A clear junctional zone or preservation of a sharp delineation between the tumor and the myometrium implies disease limited to the endometrium.

Disease characterized by disruption of the junctional zone, increased–signal-intensity tumor in the inner half of the myometrium with preservation of the outer myometrium, or both correlates with superficial myometrial invasion.

If there is extension of the high–signal-intensity tumor into the outer myometrium with preservation of a peripheral rim of normal, intact myometrium, then that is considered deep myometrial invasion

96. What does the term "uterine junctional zone" refer to in MRI imaging?

a. Contrast enhancement of the serosal lining
b. High T2 signal corresponding to the endometrium
c. Intermediate T2 signal of the outer myometrium
d. Low T2 signal of the innermost myometrium

Key: D

Rationale: Junctional zone is a distinct area of low (bright) T2 signal in the uterus on pelvic MRI. It has been histologically correlated to the inner myometrium (i.e. situated just deep to the endometrium). Careful examination of the junctional zone appearance is helpful in the evaluation of the inoperable endometrial cancer. Breach or interruption of the junctional zone differentiates between tumors confined to the endometrium and those invading the myometrium.

References: Frei KA, J Magn Reson Imaging. 2001 Jun, 13(6):850-5.

PET SCAN

Positron emission tomography (PET)/CT is also being used in endometrial cancer. There seems to be little benefit in assessing the primary tumor extension. With regard to regional lymph node metastasis, the reported sensitivity is 72% and the specificity is 94%. The main advantage of PET-CT over other imaging modalities is its accuracy in detecting distant metastasis.

Primary tumor (T) (surgical–pathologic findings)

TNM categories	*FIGO stages*	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis*		Carcinoma in situ (preinvasive carcinoma)
T1	I	Tumor confined to corpus uteri
T1a	IA	Tumor limited to endometrium or invades less than one-half of the myometrium
T1b	IB	Tumor invades one-half or more of the myometrium
T2	II	Tumor invades stromal connective tissue of the cervix, but does not extend beyond uterus**
T3a	IIIA	Tumor involves serosa and/or adnexa (direct extension or metastasis)
T3b	IIIB	Vaginal involvement (direct extension or metastasis) or parametrial involvement
T4	IVA	Tumor invades bladder mucosa and/or bowel mucosa (bullous edema is not sufficient to classify a tumor as T4)

Regional lymph nodes (N)

TNM categories	*FIGO stages*	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC1	Regional lymph node metastasis to pelvic lymph nodes
N2	IIIC2	Regional lymph node metastasis to paraaortic lymph nodes, with or without positive pelvic lymph nodes

Anatomic stage/prognostic groups

Carcinomas[*]

0[**]	Tis N0 M0
I:	T1 N0 M0
IA:	T1a N0 M0
IB:	T1b N0 M0
II:	T2 N0 M0
III:	T3 N0 M0
IIIA:	T3a N0 M0
IIIB:	T3b N0 M0
IIIC1:	T1-T3 N1 M0
IIIC2:	T1-T3 N2 M0
IVA:	T4 any N M0
IVB:	any T any N M1

109. Following lymphadenectomy for endometrial cancer, a focus of tumor cells measuring 0.3 mm is detected by immunohistochemistry in a paraaortic node. What is the AJCC stage?

A. N0(i+)
B. N1mi
C. N1a
D. N2mi

Key: D
Domain: 7.1

Citations: National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology, Uterine Neoplasms version 2.2020 – July 24, 2020.

Rationale: N2mi - Regional lymph node metastasis (greater than 0.2 mm but not greater than 2.0 mm in diameter) to para-aortic lymph nodes, with or without positive pelvic lymph nodes. This was updated in the latest, 8th edition of AJCC staging manual. FIGO staging rules for endometrial cancer have not yet been revised to match AJCC.

Surgical subtypes

TAH removes the uterus and a small rim of vaginal cuff

Modified radical hysterectomy:

1. Removal of uterus and 1–2 cm of vaginal cuff
2. Wide excision of parametrial and paravaginal tissues (including median one-half of cardinal and uterosacral ligaments)
3. Ligation of uterine artery at ureter

Radical hysterectomy:

1. Resection of uterus and upper vagina
2. Dissection of paravaginal and parametrial tissues to pelvic sidewalls
3. Ligation of uterine artery at its origin at internal iliac artery

149. Which form of hysterectomy is preferred for low grade endometrial carcinoma, clinically confined to the uterus?

A. Laparoscopic total hysterectomy
B. Radical hysterectomy
C. Vaginal hysterectomy
D. Supracervical hysterectomy

Key: A

Rationale:
Surgery is the recommended initial intervention for endometrial cancer. Open and laparoscopic (including the robotic-assisted method) approaches are safe and effective. The role of vaginal hysterectomy is much less clear in neoplastic disease. Various forms of radical hysterectomy are used for cervical cancer.

Reference:
Colombo N, et al. ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up. Radiother Oncol. 2015 Dec; 117(3):559-81. doi: 10.1016/j.radonc.2015.11.013

Pelvic and P-A lymphadenectomy is recommended in which pts with endometrial cancer?

Although controversial, LNs are commonly assessed at the time of initial Sg for endometrial cancer. Pelvic lymphadenectomy may not be indicated in women with Dz clinically confined to the uterus. The ASTEC (A Study in the Treatment of Endometrial Carcinoma) trial randomized 1,408 pts with endometrial cancer that was clinically confined to the uterus to standard Sg (TAH + BSO, peritoneal washing, palpation of P-A nodes) vs. standard Sg + pelvic lymphadenectomy. Those at intermediate or high risk for recurrence (independent of nodal status) were further randomized to rcv pelvic RT or not. There was no benefit to pelvic lymphadenectomy in terms of OS or RFS; however pts had increased morbidity. (ASTEC Study Group et al., Lancet 2009)

Is pelvic nodal dissection necessary in early-stage disease?

Without suspicious intraoperative lymph nodes, elective pelvic and para-aortic nodal dissection likely does not change oncologic outcomes but may help to guide treatment in few who are upgraded pathologically. Two trials did not show difference in DFS or OS.

Simple Light Purple Journal

patients with grade 3 disease or serous or clear cell histology and those with deep myometrial invasion on frozen section will undergo lymphadenectomy

SLN mapping is gaining more acceptance in the staging of endometrioid adenocarcinoma for sure. This approach is gaining acceptance not only in the gynecologic oncology community but also in other histologies.
In a prospective study of 123 patients with grade 3 endometrioid histology, serous, clear cell, and carcinosarcoma, all underwent sentinel node mapping followed by lymphadenectomy. Overall, sentinel node detection rate was 89%, with an overall sensitivity of 95% and false-negative rate of 5% (1/20). The rate of positive node was 23% with only 1 patient having negative sentinel nodes but positive nonsentinel node

What is the risk of lymphedema following Sg for uterine malignancies?

According to an MSKCC retrospective review of 1,289 pts, the rate of lymphedema at a median f/u of 3 yrs was 1.2%. When ≥10 LNs were removed, the rate of symptomatic lymphedema was 3.4%. (Abu-Rustum NR et al., Gyn Oncol 2006)

Negative prognostic indicators for endometrial cancer:

1. LVSI
2. Age >60 yrs
3. Grade 3/nonendometrioid histology(serous and clear histology), Grade directly affects the depth of myometrial penetration and the frequency of lymph node involvement
4. Deep myometrial invasion (>50% based on GOG 249)
5. Cervical Involvement in which only **cervical stromal invasion** is considered stage II, Gross cervical involvement increases the risk of parametrial extension as well as spread to pelvic lymph nodes in a fashion similar to primary cervical cancer.
6. Lower uterine segment involvement, There seems to be a high rate of LUSI in patients with HNPCC associated endometrial ca
7. Peritoneal Cytology, In the 2009 FIGO staging, having positive peritoneal cytology is no longer considered stage IIIA
8. Adnexal/Serosal Involvement
9. Pelvic and Para-aortic Lymph Node Involvement
10. Molecular Prognostic Factors Patients with CTNNB1 (β catenin) mutations do significantly worse even in patients with early-stage endometrioid histology

Principles of surgical staging for endometrial cancer

TAH and BSO and lymph node assessment is the primary treatment for uterine confined endometrial ca

Fertility sparing options (ALL criteria must be met):

1-grade (1) endometriod adenoca on d&c confirmed by expert pathologist

2- DZ limited to endometrium on MRI (preferred) or transvaginal us

3- absence of suspicious met DZ on imaging

4- no contraindication to medical therapy or pregnancy

5- patients should undergo counseling that fertility sparing is not the standard care for the treatment of endometrial ca

TAH /BSO and LN assessment may be performed by any surgical route (laparoscopic –robotic –vaginal –abdominal)

The lymph nodes assessment includes evaluation of the nodal basin that drains the uterus and often a pelvic nodal dissection with or without para aortic LNs nodal dissection is done

Pelvic lns include (common iliac –external and internal iliac –obturator LNS)are frequently removed for staging purposes

Paraaortic lns evaluation is utilized for staging in women with high risk tumors (deeply invasive lesions –high grade-and tumors of serous ca ,clear cell ca or carcinosarcoma)

While peritoneal cytology does not affect staging (FIGO AND AJCC) recommends that surgeons continue to obtain during surgery

Omental biopsy should be done in (clear cell ,serous ,carcinosarcoma)

NCCN Guidelines Version 2.2021
Endometrial Carcinoma

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Discussion

All staging in guideline is based on updated FIGO staging. (See ST-1)

CLINICAL FINDINGS (Endometrioid Histology)[a]

HISTOLOGIC GRADE/ADJUVANT TREATMENT[g,h,m]

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 high-intermediate risk (HIR)[o] (category 2B)
IB	G1	Vaginal brachytherapy preferred[o] or Consider observation if no other adverse risk factors[o,p]
	G2	Vaginal brachytherapy preferred or Consider EBRT if HIR[o] or Consider observation if no other adverse risk factors[o,p]
	G3	RT (EBRT and/or vaginal brachytherapy) ± systemic therapy[q] (category 2B for systemic therapy)

Surgically staged:[e]
Stage II[r,s] →

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

[t]Vaginal brachytherapy is also an option for grade 1 or 2, ≤50% myometrial invasion, no LVSI, and microscopic cervical invasion.

Surgically staged:[e]
Stage III, IV[u] →

Systemic therapy
± EBRT
± vaginal brachytherapy[v]

[v]Combination therapy depends on assessment of both locoregional and distant metastatic risk. Combination therapy is preferred for stage III disease

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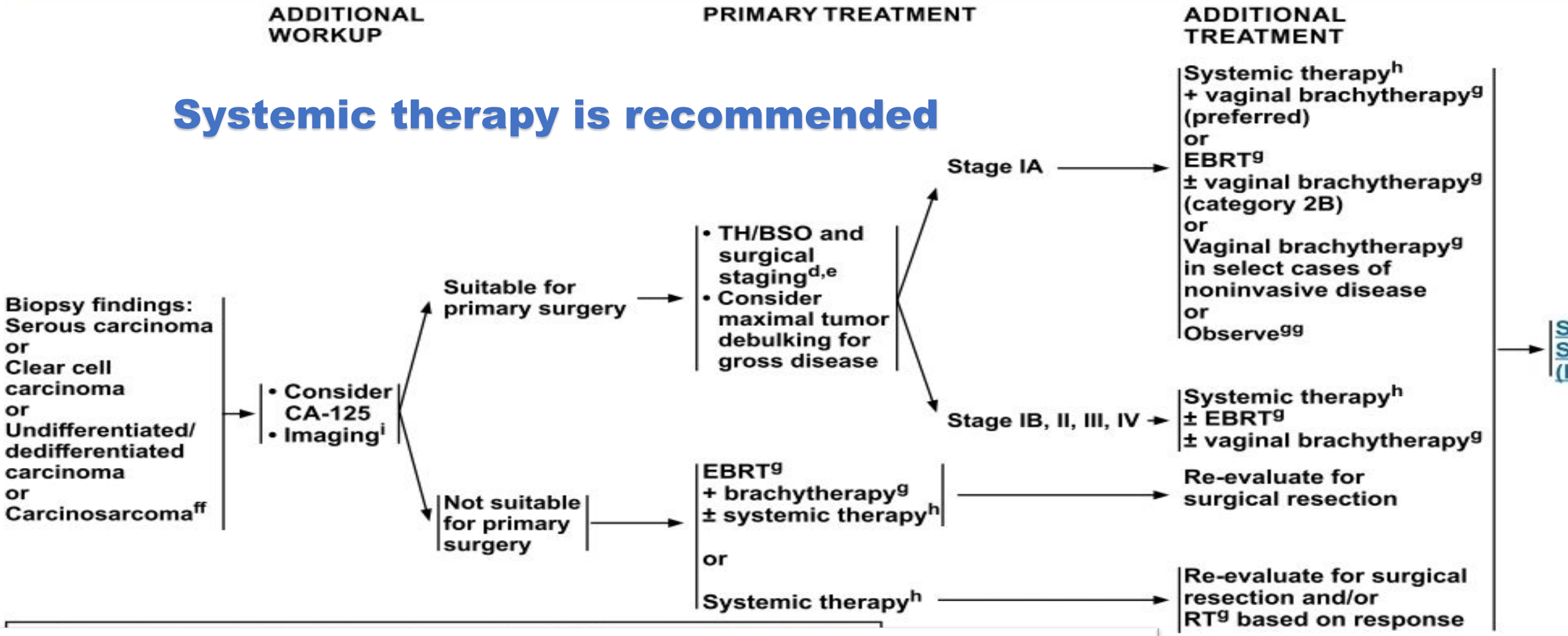
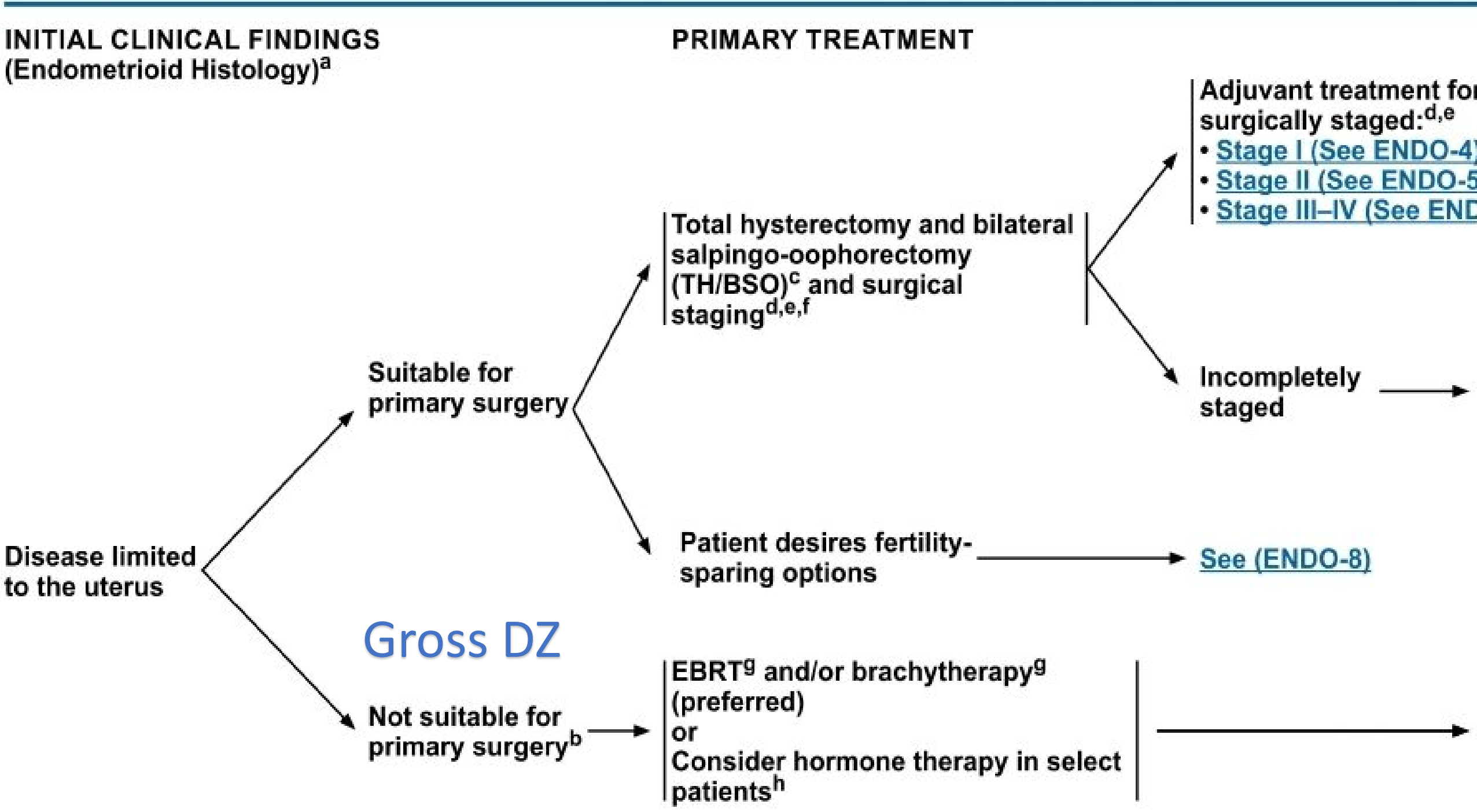
Endometrial Carcinoma

NCCN Guid
Table

Systemic therapy is recommended



[ff]Also known as malignant mixed mesodermal tumor or malignant mixed Müllerian tumor.
[gg]Observation only for select patients with no residual serous or clear cell carcinoma in the hysterectomy specimen.


INITIAL CLINICAL FINDINGS
(Endometrioid Histology)[a]
PRIMARY TREATMENT
Disease limited to the uterus
Suitable for primary surgery
Not suitable for primary surgery[b]
Total hysterectomy and bilateral salpingo-oophorectomy (TH/BSO)[c] and surgical staging[d,e,f]
Patient desires fertility-sparing options
See (ENDO-8)
EBRT[g] and/or brachytherapy[g] (preferred)
or
Consider hormone therapy in select patients[h]
Adjuvant treatment for surgically staged:[d,e]
• Stage I (See ENDO-4)
• Stage II (See ENDO-5
• Stage III–IV (See END
Incompletely staged
Gross DZ

216. What would be recommend for a 62 year old with FIGO IAG1 endometrioid adenocarcinoma of the endometrium after total hysterectomy without adverse risk factors?

a. EBRT
b. Observation
c. Concurrent chemoRT
d. Vaginal brachytherapy

Key: B

Rationale: Observation is preferred for low risk stage I endometrial cancer. In a randomized study by Sorbe et al, vaginal brachytherapy was compared to observation for women with IAG1 or IAG2 endometrioid adenocarcinoma. Fewer than 4% patients in the observation arm had vaginal or pelvic recurrence. The median age in the study was 62.7 years.

References: Sorbe B, Int J Gynecol Cancer, 2009 Jul, 19(5):873-8

175. A medically inoperable patient with endometrial cancer has disease confined to the uterus by MRI. When is treatment using only brachytherapy MOST appropriate?

a. Uterine serous carcinoma with >50% of myometrial invasion
b. FIGO grade 1 adenocarcinoma with <50% myometrial invasion
c. Uterine serous carcinoma with < 50% myometrial invasion
d. FIGO grade 3 endometrioid adenocarcinoma with > 50% myometrial invasion

Key: B

Rationale: Intracavitary brachytherapy, with implants placed into the uterine cavity, is an effective definitive treatment for endometrial cancer. Brachytherapy alone does not adequately treat adnexa or pelvic lymph nodes. Therefore, addition of EBRT is advised when tumor characteristics suggest elevated risk of subclinical cancer spread beyond corpus uteri, as in other scenarios listed here.

References: Schwarz JK, Brachytherapy, 2015 Sep-Oct, 14(5):587-99.

222. What is the approximate rate of distant metastases for FIGO stage IBG3 endometrioid adenocarcinoma treated with total hysterectomy and EBRT?

a. 3%
b. 10%
c. 20%
d. 30%

Key: D

Rationale: Patients with deeply invasive, high grade endometrioid adenocarcinoma of the endometrium (2009 FIGO stage IBG3) are at high risk of distant relapse and carcinoma-related death. Several phase III studies evaluating the role of adjuvant chemotherapy for similar patients have recently completed accrual.

References: Creutzberg CL, J Clin Oncol. 2004 Apr 1, 22(7): 1234-41.

TABLE 44.1: General Treatment Paradigm for Endometrial Cancer (see ASCO/ASTRO guidelines for details)[1,2]	
Stage	**Adjuvant Treatment Options (After TAH/BSO)**
Stage IA, grade I–II	Observation*
Stage IA, grade III or stage IB, grade I–II	Favor vaginal cuff brachytherapy**
Stage IB, grade III	Favor pelvic RT
Stage II	Pelvic RT + VBT boost ± CHT
Stage III–IV	ChemoRT vs. CHT +/− tumor-directed RT
Medically inoperable	Tumor-directed EBRT to uterus, cervix, upper vagina, pelvic LN, other involved areas (45–50.4 Gy) + intracavitary boost ± CHT

*Can consider vaginal cuff brachytherapy if higher risk features (age >60, LVSI).
**Can consider pelvic RT if other high-risk factors are present (age >60, LVSI) and surgical staging was inadequate.

241. Per ASTRO guidelines, which pathologic features in a patient with Stage I endometrioid endometrial cancer warrant postoperative vaginal cuff radiation alone?

A. Grade 1 and <50% invasion

B. Grade 2 and ≥ 50% invasion

C. Grade 3 and ≥ 50% invasion

D. Grade 3 and invasion involving serosa

Key: B

Citations: The Role of Postoperative Radiation Therapy for Endometrial Cancer: An ASTRO Evidence-Based Guideline, Klopp, 2014, 1-20, Practical Radiation Oncology.

Rationale: Vaginal cuff brachytherapy is as effective as pelvic RT in preventing vaginal recurrence for patients with grade 1 or 2 cancers with ≥ 50% myometrial invasion or grade 3 with < 50% myometrial invasion. In general grade 1 cancers with <50% do not require adjuvant radiation.

TABLE 44.3: Results of GOG 33 for Endometrial Cancer						
Depth of Invasion	% Para-Aortic and Pelvic LN Involvement					
	Grade 1		Grade 2		Grade 3	
	PA	Pelvic	PA	Pelvic	PA	Pelvic
Endometrium Only	0%	0%	3%	3%	0%	0%
Superficial Myometrial Invasion	1%	3%	4%	5%	4%	9%
Middle Myometrial Invasion	5%	0%	0%	9%	0%	4%
Deep Myometrial Invasion	6%	11%	14%	19%	23%	34%
Note: Risk of PA LN involvement is ⅔ risk of pelvic LN involvement, 30%–55% of +pelvic LNs have +PA LNs.						

No adj therapy is indicated for endometrial cancers limited to the endometrium (stage 1A), except for grade 3, where vaginal cuff brachytherapy is considered.

Which endometrioid endometrial cancers can be treated with vaginal brachytherapy (VBT) alone?

Surgically staged pts with true high-intermediate–risk Dz
stage IA tumors, grades 2–3
Stage IB tumors, grade 1–2
Stage 1B grade 3 tumors are controversial as they were not included in the PORTEC randomization, however, in well-staged pts, this may be an acceptable Tx option.
Stage 2 (grade 1 or 2),less than half myometrial invasion ,no LVSI ,and microscopic cervical invasion

When is chemo indicated for endometrial cancer?

Adj chemo should be considered for grade 3, nonendometrioid histology (serous and clear cell), and in pts with stage III–IV Dz

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Adjuvant Treatment When Used for Uterine-Confined Disease
Preferred Regimens • Carboplatin/paclitaxel

Recurrent, Metastatic, Or High-Risk Disease[a,b]			
	Preferred Regimens	**Other Recommended Regimens**	**Useful In Certain Circumstances**
Systemic therapies[a,b]	• Carboplatin/paclitaxel (category 1 for carcinosarcoma)[1] • Carboplatin/paclitaxel/trastuzumab[c] (for stage III/IV or recurrent HER2-positive uterine serous carcinoma)[2]	• Carboplatin/docetaxel[d] • Cisplatin/doxorubicin[3] • Cisplatin/doxorubicin/paclitaxel[e,f,3] • Carboplatin/paclitaxel/bevacizumab[e,g,4] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[5] • Albumin-bound paclitaxel[h] • Topotecan • Bevacizumab[g,i,6] • Temsirolimus[7] • Docetaxel[d] (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[8] • Cisplatin/ifosfamide (for carcinosarcoma)	N/A
Biomarker-directed systemic therapy for second-line treatment	N/A	N/A	• Lenvatinib/pembrolizumab[j,k,9] • Pembrolizumab[l] (for TMB-H[10] or MSI-high [MSI-H]/MMR deficient [dMMR] tumors[m,11]) • Nivolumab[n,12] • Larotrectinib or entrectinib for *NTRK* gene fusion-positive tumors (category 2B)[e]

128. In women with advanced or recurrent serous endometrial cancer, 30% of tumors will over-express:

A. EGFR.
B. HER2.
C. PDL1.
D. ROS1.

Key: B

Rationale:

In a multicenter, randomized phase II trial for patients with stage III or IV or recurrent HER2/neu-positive endometrial cancer, addition of trastuzumab to carboplatin-paclitaxel was well tolerated and increased progression-free survival. https://ascopubs.org/doi/full/10.1200/JCO.2017.76.5966.

Reference:

Fader, N. (2018). Randomized Phase II Trial of Carboplatin-Paclitaxel Versus Carboplatin-Paclitaxel-Trastuzumab in Uterine Serous Carcinomas That Overexpress Human Epidermal Growth Factor Receptor

consultation.

- **Estrogen receptor (ER) testing is recommended in the settings of stage III, IV, and recurrent disease.**
- **HER2 immunohistochemistry (IHC) testing (with reflex to HER2 fluorescence in situ hybridization [FISH] for equivocal IHC) is recommended for possible treatment of advanced stage or recurrent serous endometrial carcinoma.[4]**
- **Morphologic evaluation of endometrial carcinoma to determine histologic type—especially in high-grade cancers—is challenging and issues exist regarding diagnostic reproducibility.[5,6]**

Cervical Involvement

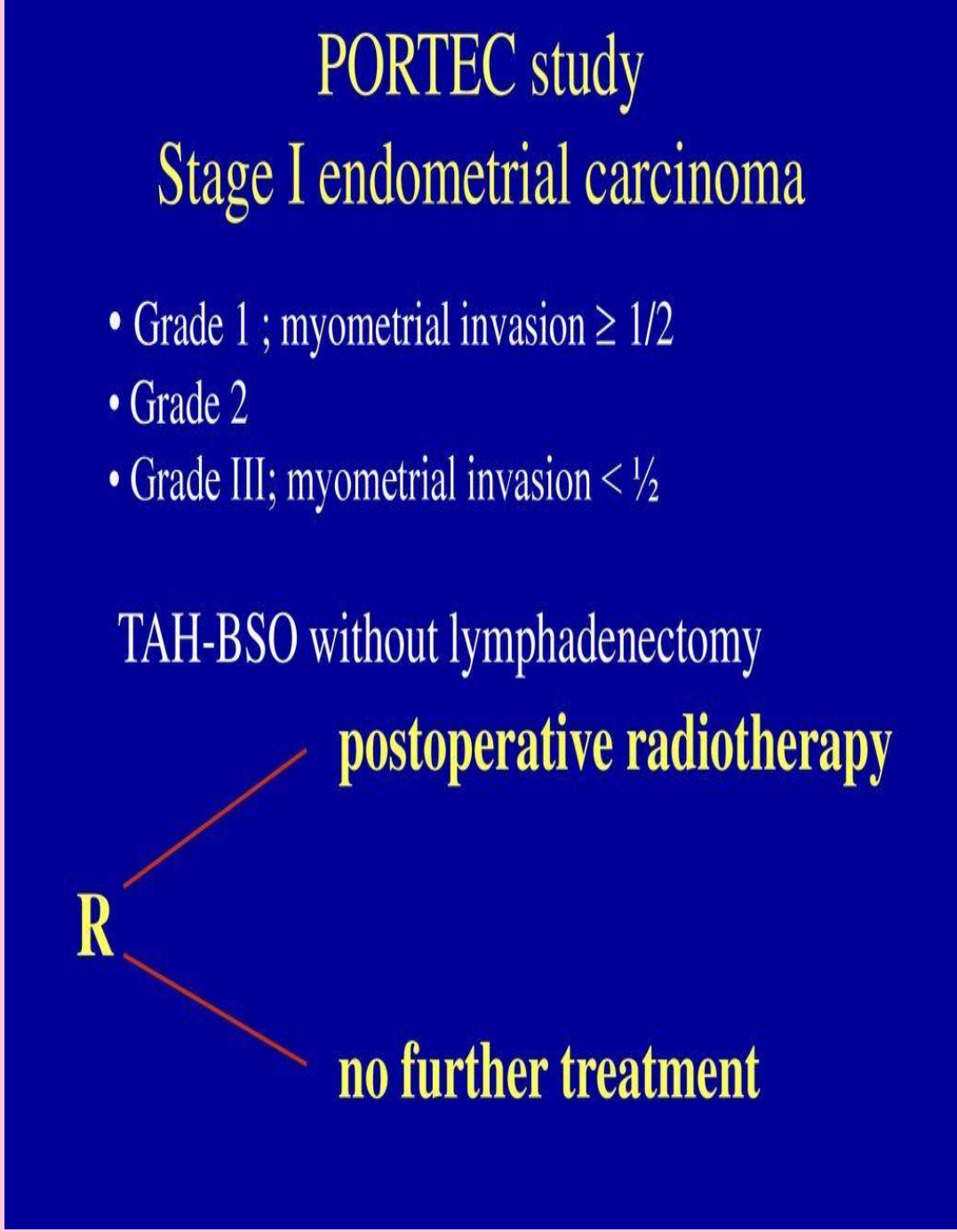
Gross cervical involvement increases the risk of parametrial extension as well as spread to pelvic lymph nodes in a fashion similar to primary cervical cancer. Such patients could undergo radical hysterectomy and pelvic lymph node dissection or preoperative radiation including pelvic radiation and intracavitary brachytherapy followed by simple hysterectomy

For patients with cervical stromal invasion grade 1 and 2 and the depth of cervical stromal invasion less than 50% intravaginal RT could be offered if they underwent adequate surgical lymph node assessment. For those with grade 3 or deep cervical stromal invasion, pelvic RT is recommended irrespective of lymphadenectomy

PORTEC-1

714 pts grade 1 with ≥50% myometrial invasion, grade 2 with any invasion, or grade 3 less than 50% myometrial invasion underwent TAH/BSO with washings with no lymphadenectomy and were randomized to adj EBRT (46 Gy) vs. observation.

EBRT reduced LRR from 14% to 5% at 10 yrs. 74% of LRs were in the vaginal vault (improved local control rate). There was no difference in 10- yr OS. Note that with pelvic EBRT is associated with long term urinary and bowel symptoms leading to lower physical functioning even 15 years after treatment



80. According to PORTEC-1, which outcome is associated with adjuvant EBRT over observation?

a. Improved overall survival
b. Decreased distant metastases
c. Improved physical functioning scores
d. Increased incontinence for urine

Key: D

Rationale: PORTEC-1 was a randomized study that compared adjuvant external beam radiotherapy to observation for select endometrioid adenocarcinomas. While local control was improved in the EBRT arm, long term follow up shows no improvement of survival by EBRT. Toxicity outcomes for EBRT are markedly worse.

References: Nout RA, J Clin Oncol, 2011 May 1, 29(13):1692-700.

110. As demonstrated in the PORTEC-1 study, what is the absolute improvement in local control at 5 years with the addition of RT to stage I intermediate risk endometrial cancer patients?

A. 0%
B. 10%
C. 20%
D. 30%

Key: B
Domain: 7.1

Citations: Creutzberg CL, et. al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomized trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000; 355 (9213): 1404-11.

Rationale: The 5-year actuarial locoregional recurrence rates were 4% in the radiotherapy group and 14% in the control group ($p<0.001$). There was no difference in OS.

PORTEC-2

randomized 427 pts with intermediate-high–risk endometrial cancer defined as:

1. Age >60 yrs and inner 1/3 (IA) myometrial invasion and grade 3

2. Age >60 yrs and outer 2/3 (IB and IC) myometrial invasion and grades 1–2

3. Invasion of cervical glandular epithelium and grades 1–2 except grade 3 with > 1/2 myometrial invasion.

All pts were s/p TAH/BSO without pelvic LND and were randomized to EBRT (46 Gy) vs. VBT alone (21 Gy in 3 fx or 30 Gy).

At median f/u at 3.8 yrs, VBT was similar to EBRT with respect to 5-yr outcomes:

vaginal relapse (1.8% vs. 1.6%)

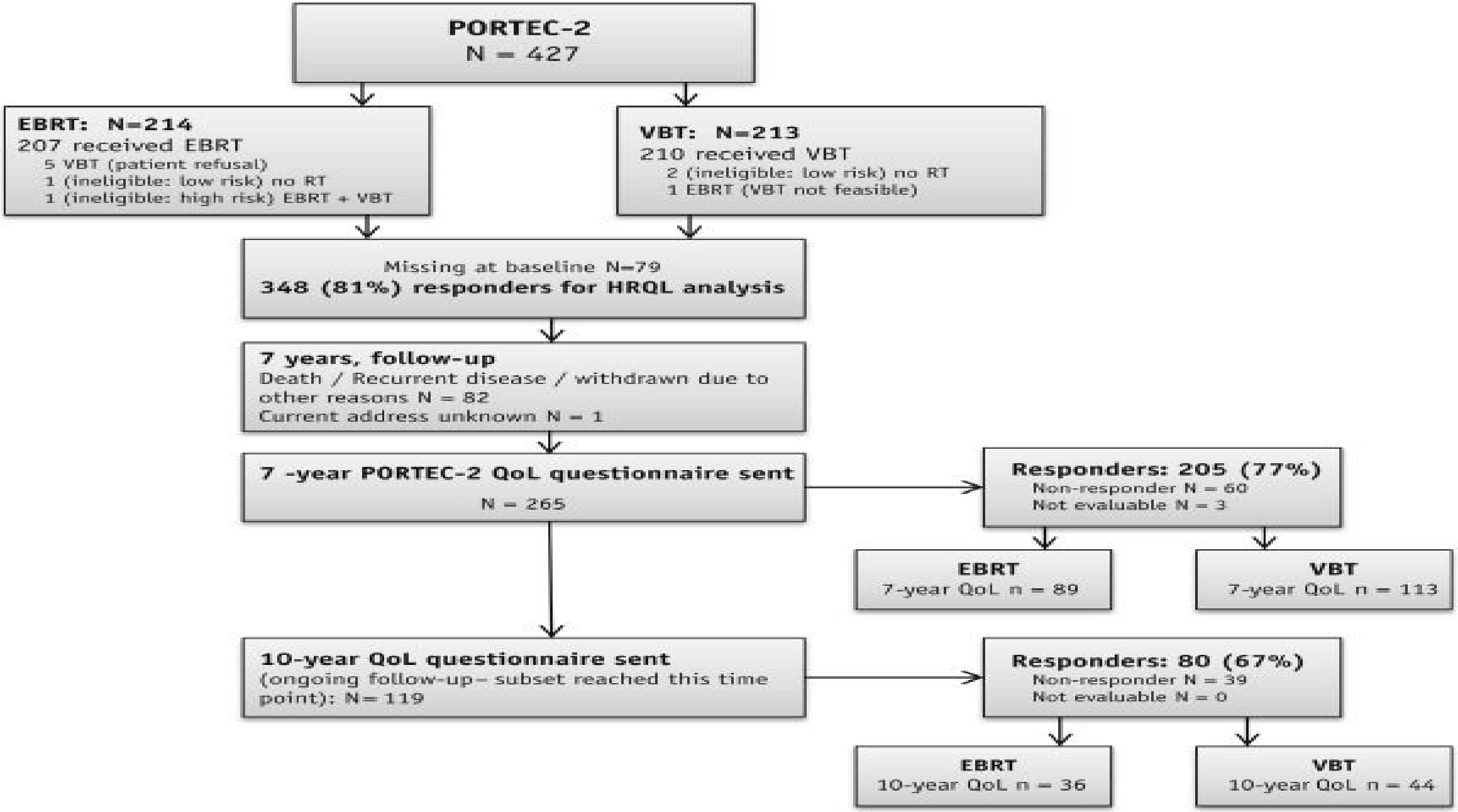
isolated pelvic relapse (1.5% vs. 0.5%)

LRR (5.1% vs. 2.1%)

OS (85% vs. 80%)

However, there were significantly higher rates of acute grades 1–2 GI toxicity in the EBRT group.

The authors concluded that VBT should be standard in intermediate-high–risk endometrial cancer. (Nout RA et al., Lancet 2010)


PORTEC-2
N = 427
EBRT: N=214
207 received EBRT
5 VBT (patient refusal)
1 (ineligible: low risk) no RT
1 (ineligible: high risk) EBRT + VBT
VBT: N=213
210 received VBT
2 (ineligible: low risk) no RT
1 EBRT (VBT not feasible)
Missing at baseline N=79
348 (81%) responders for HRQL analysis
7 years, follow-up
Death / Recurrent disease / withdrawn due to other reasons N = 82
Current address unknown N = 1
7 -year PORTEC-2 QoL questionnaire sent
N = 265
Responders: 205 (77%)
Non-responder N = 60
Not evaluable N = 3
EBRT
7-year QoL n = 89
VBT
7-year QoL n = 113
10-year QoL questionnaire sent
(ongoing follow-up– subset reached this time point): N= 119
Responders: 80 (67%)
Non-responder N = 39
Not evaluable N = 0
EBRT
10-year QoL n = 36
VBT
10-year QoL n = 44

60. Per PORTEC-2 (Postoperative Radiation Therapy in Endometrial Carcinoma), what is the same for EBRT and vaginal brachytherapy?

a. Long-term QoL
b. Pelvic recurrence
c. Vaginal cuff recurrence
d. Acute grade 1–2 GI toxicity

Key: C

Rationale: PORTEC-2 was a randomized study that compared adjuvant external beam radiotherapy to vaginal cuff brachytherapy for patients with intermediate-risk endometrioid adenocarcinomas. While pelvic relapses were more frequent in the brachytherapy arm, vaginal recurrence rates were comparably low in both arms. The toxicity measures strongly favored brachytherapy.

References: Nout RA, Lancet, 2010 Mar 6, 375(9717): 816-23.

PORTEC-3 trial comparing pelvic RT vs. Pelvic RT + chemo in high-risk pts.

686 high-risk pts randomized to RT alone (48.6 Gy) vs. chemoRT (2 cycles concurrent cisplatin and 4 adjuvant cycles of carboplatin + paclitaxel).

Inclusion criteria :

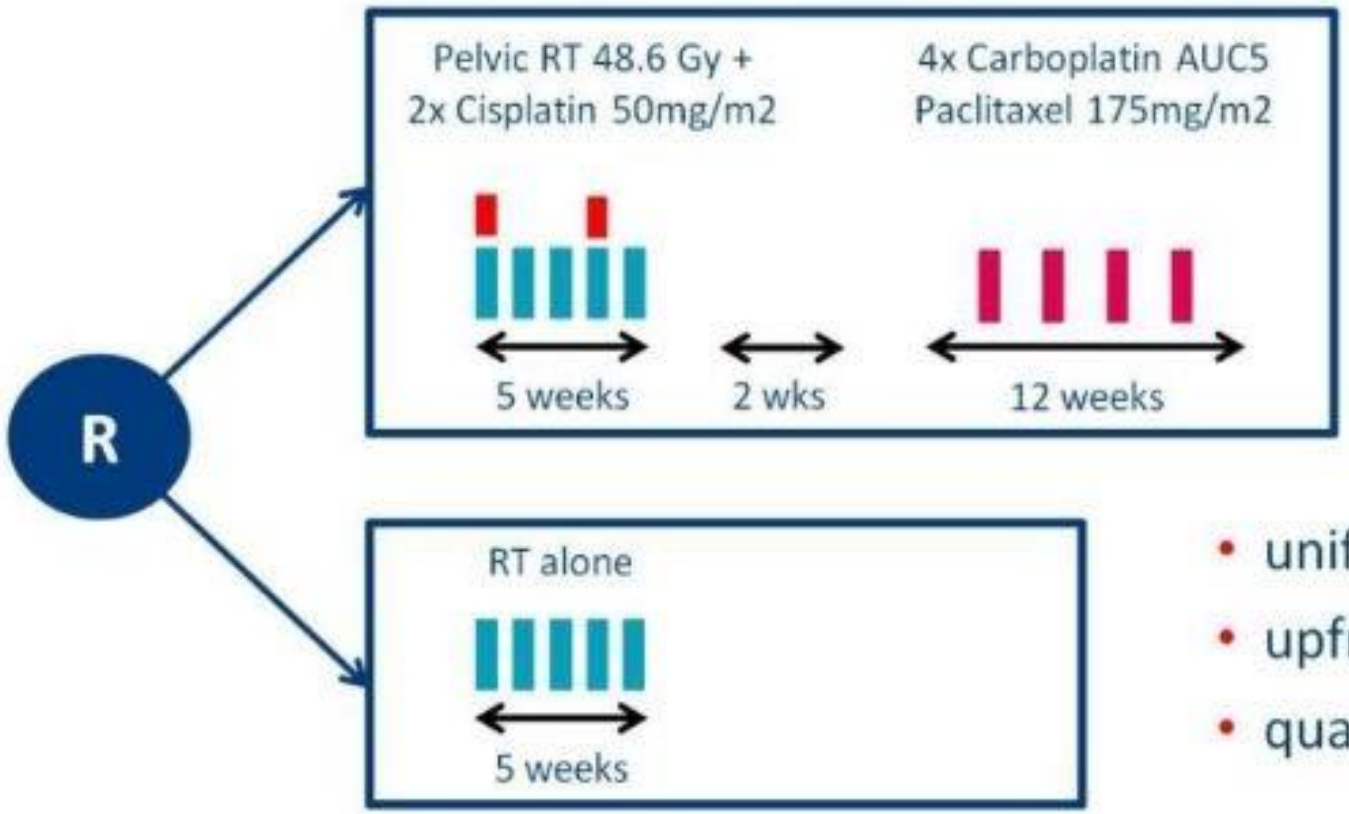
High risk endometrial ca FIGO 1(endometroid type ,grade3, with deep endometrial invasion or LVSI)

Clear or serous types stage (1-3)

Parametrial involvement

PORTEC-3 trial design

- **High risk Endometrial Cancer (HREC)**



- uniform treatment schedule
- upfront pathology review
- quality of life analysis

Conclusions

CTRT vs RT for high-risk endometrial cancer:

- Trend for improved 5-year FFS
  - Risk reduction of 7% (FFS) and 5% (OS)
- Significant 11% FFS benefit with CTRT for stage III disease
- Significantly more toxicity with CTRT in the first 12 months
- OS analysis may need longer follow-up

177. Based on the results of PORTEC-3 (LANCET Oncol 2018), what adjuvant therapy is appropriate for a 55-year-old female with pathologic Stage IB grade 3 endometrioid adenocarcinoma of the uterus with LVSI?

A. Vaginal brachytherapy

B. Vaginal brachytherapy + chemotherapy

C. Pelvic radiation therapy

D. Pelvic radiation with chemotherapy

Key: C

Citations: de Boer SM, Powell ME, Mileshkin L, Katsaros D, et al., Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial; 2018 Lancet Oncol. 295-309.

Rationale: Based on PORTEC-3, combined adjuvant chemotherapy and radiotherapy cannot be recommended as a new standard of care for patients with stage I–II endometrial cancer because no survival differences were found and pelvic control was high with radiotherapy alone. 5-year failure-free survival for stage I–II patients was 80·8% (74·1–86·0) in the chemoradiotherapy group versus 76·6% (69·5–82·2) in the radiotherapy group (0·85, 0·54–1·33; p=0·47).

107. In the subset analysis of PORTEC-3 trial, patients with which histology MOST benefited from the addition of chemotherapy to RT?

A. Endometrioid
B. Carcinosarcoma
C. Clear cell
D. Serous

Key: D
Domain: 7.1

Citations: De Boer SM, Powell ME, Mileshkin L, Katsaros D, et. al. Adjuvant Chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): Patterns of Recurrence and Post-hoc Survival Analysis of a Randomised Phase 3 Trial. Lancet Oncol 20(9):1273-1285, 2019

Rationale: Chemotherapy is the mainstay of adjuvant treatment for advanced serous carcinomas. PORTEC-3 was a phase III study of radiotherapy alone vs. chemoradiation for advanced, resected endometrial cancers. When comparing serous cancers with all other histologies in a post-hoc exploratory subgroup analysis, women with serous cancers had significantly lower overall survival and failure-free survival than did those with other histologies, irrespective of treatment received. After adjusting for stratification factors, significant improvements in overall survival and failure-free survival were observed for serous cancers treated with chemoradiotherapy versus radiotherapy alone: 5-year overall survival was 71·4% (95% CI 60·1–84·7) with chemoradiotherapy versus 52·8% (40·6–68·6) with radiotherapy alone (HR 0·48 [95% CI 0·24–0·96]; p=0·037), and 5-year failure-free survival was 59·7% (95% CI 45·1–71·6) with chemotherapy versus 47·9% (33·9–60·6) with radiotherapy alone (HR 0·42 [95% CI 0·22–0·80]; p=0·008).

108. If postoperative concurrent chemoradiation is given for endometrial cancer, what is the MOST common dose of cisplatin?

A. 20 mg/m^2
B. 30 mg/m^2
C. 40 mg/m^2
D. 50 mg/m^2

Key: D
Domain: 7.1

Citations: De Boer SM, Powell ME, Mileshkin L, Katsaros D, et. al. Adjuvant Chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): Patterns of Recurrence and Post-hoc Survival Analysis of a Randomised Phase 3 Trial. Lancet Oncol 20(9):1273-1285, 2019.

Rationale: The role of concurrent chemoradiation after hysterectomy for stage III-IV endometrial cancer remains under investigation. In the PORTEC-3 study, in the chemoradiotherapy group, women received two cycles of cisplatin 50 mg/m2 administered intravenously in the first and fourth week of external-beam radiotherapy, followed by four cycles of carboplatin AUC5 and paclitaxel 175 mg/m2 administered intravenously at 21-day intervals. This schedule has initially been evaluated in phase II RTOG studies.

GOG 249

comparing EBRT alone vs. VBT + carbo/taxol in early stage high intermediate–risk pts.

Initial reports show similar rates of RFS, PFS, and OS with higher toxicity and poorer QOL in the VB + chemo arm. (59 th Annual ASTRO Meeting presentation, 2017)

GOG 258:

Randomized phase III trial of cisplatin + tumor volume directed irradiation followed by carboplatin + paclitaxel vs. chemo alone (carboplatin + paclitaxel) for optimally debulked, advanced endometrial carcinoma. Awaiting results.

81. In the GOG-249 randomized trial of patients with high-intermediate and high risk early stage endometrial cancer, which of the following was associated with the experimental (brachytherapy and chemotherapy) arm?

A. Improved OS
B. Improved nodal relapse rate
C. Worse acute toxicity
D. Less fatigue

Key: C

Rationale:
GOG 249 enrolled 610 patients randomly assigned to the typical pelvic irradiation or the combination of chemotherapy and vaginal brachytherapy. Most patients had the G1-2 endometrioid histology. Standard EBRT resulted in lower nodal relapse rate, better acute toxicities, and lower patient-reported fatigue levels while maintaining the same OS and RFS as the experimental treatment.

Reference:
Randall, M. E., et. al. Adjuvant Pelvic Radiation Therapy Versus Vaginal Brachytherapy Plus Paclitaxel/ Carboplatin in High-Intermediate and High-Risk Early Stage Endometrial Cancer. *Journal of Clinical Oncology*. JCO, 2019.

TIME-C trial

Time-C trial compared 3D vs. IMRT for postop endometrial and cervical pts evaluating GU and GI outcomes. Initial reports show improved GI and GU toxicity with IMRT. (58 th Annual ASTRO Meeting presentation, 2016)

RTOG 1203

A RANDOMIZED PHASE III STUDY OF STANDARD VS. IMRT PELVIC RADIATION FOR POST-OPERATIVE TREATMENT OF ENDOMETRIAL AND CERVICAL CANCER (TIME-C)

SCHEMA

STRATIFY		RANDOMIZE	
	XRT Dose 1. 45 Gy 2. 50.4 Gy **Chemotherapy** 1. No Chemotherapy 2. 5 cycles of weekly cisplatin at 40mg/m2 **Disease Site** 1. Endometrial 2. Cervix		**Arm 1** IMRT pelvic radiation treatment
			Arm 2 4-field pelvic radiation treatment

See Section 5.0 for pre-registration requirements, Section 6.0 for details of radiation therapy, and Section 7.0 for details of drug therapy.

Patient Population: (See Section 3.0 for Eligibility)
Pathologically proven diagnosis of endometrial and cervical cancer who require post-operative radiation or chemoradiation; Zubrod performance status of 0–2.

Required Sample Size: 281 patients

71. In the randomized TIME-C (RTOG 1203) trial comparing IMRT vs 3D for pelvic radiotherapy after hysterectomy, what was LESS frequent in the IMRT arm?

A. Use of urinary tract analgesics
B. Use of anti-diarrheals
C. Witnessed emesis
D. Silver sulfadiazine application

Key: B

Rationale:
Patients with cervical and endometrial cancer who received pelvic radiation postoperatively were stratified by dose (45 or 50.4 Gy), use of chemotherapy (none or 5 cycles of weekly cisplatin at 40 mg/m2), and disease site, and then randomly assigned to standard 4-field radiation or IMRT. The primary endpoint was a change in acute gastrointestinal (GI) toxicity from baseline to 5 weeks measured by the bowel domain of Expanded Prostate Cancer Index Composite (EPIC). 20.4% of women on the standard RT arm took 4 or more antidiarrheal medications daily, as compared to 7.8% of women on the IMRT arm (P = 0.04). GI toxicity was not different between 2 arms and 4-6 weeks after RT completion.

Reference:
Klopp AH, et al. Patient-Reported Toxicity During Pelvic Intensity-Modulated Radiation Therapy: NRG Oncology-RTOG 1203. J Clin Oncol. 2018 Aug 20; 36(24):2538-2544. doi:10.1200/JCO.2017.77.4273.

158. Regarding TIME-C (RTOG 1203) and RTOG 0724 trials for gynecologic malignancies, what is the recommended small bowel dose constraint when treating with adjuvant pelvic IMRT?

A. V40 < 10%

B. V40 < 20%

C. V40 < 30%

D. V40 < 40%

Key: C

Citations: Klopp A, Yeung A, Gil K, et al. 3-16-2015. NRG Oncology 1-79. RTOG 1203 a randomized phase III study of standard vs. IMRT pelvic radiation for post-operative treatment of endometrial and cervical cancer (time-c). Jhingran A, Gray H, Weidhaas J, et al. 12-29-2010. RTOG 1-72. RTOG 0724/GOG-0724 phase III randomized study of concurrent chemotherapy and pelvic radiation therapy with or without adjuvant chemotherapy in high-risk patients with early-stage cervical carcinoma following radical hysterectomy.

Rationale: This dose constraint is the only small bowel constraint utilized in the TIME-C (RTOG 1203) and RTOG 0724 trials utilizing IMRT for pelvic radiation therapy after hysterectomy.

259. The use of which medications was monitored when evaluating the primary endpoint of the TIME-C (RTOG 1203) trial that compared adjuvant pelvic IMRT to 3D techniques in cervical and endometrial cancers?

A. Urinary Analgesics

B. Anti-diarrheals

C. Anti-emetics

D. Silver Sulfadiazine

Key: B

Citations:

Ref 1 Page: Yeung AR, Pugh SL, Klopp AH, Gil KM, et al. Clinicians Underreport Adverse Events in NRG Oncology's Radiation Therapy Oncology Group 1203: The Importance of Using Patient-Reported Outcomes in Oncology Clinical Trials. 2016. Intl J Radiat Oncol Biol Phys S125.

Rationale: Patients with cervical and endometrial cancer who received pelvic radiation postoperatively were stratified by dose (45 or 50.4 Gy), use of chemotherapy (none or 5 cycles of weekly cisplatin at 40 mg/m2), and disease site, and then randomly assigned to standard 4-field radiation or IMRT. The primary endpoint was change in acute gastrointestinal (GI) toxicity from baseline to 5 weeks measured by the bowel domain of Expanded Prostate Cancer Index Composite (EPIC). 20.4% of women on the standard RT arm took 4 or more antidiarrheal medications daily, as compared to 7.8% of women on the IMRT arm (P Z 0.04).

51. In the GOG-258 randomized trial of advanced endometrial carcinoma, what was the approximate 5-year incidence of pelvic/paraaortic nodal recurrence in the chemotherapy alone arm?

    A. 10%
    B. 20%
    C. 30%
    D. 40%

Key: B

Rationale:
Chemoradiotherapy was associated with a lower 5-year incidence pelvic and/or paraaortic lymph-node recurrence (11% vs. 20%; hazard ratio, 0.43; 95% CI, 0.28 to 0.66) than with chemotherapy alone. However, standard chemotherapy resulted in better severe acute toxicity, a higher rate of completion of treatment, a trend towards better distant control, and equivalent RFS.

Reference:
Matei, D. (2019), et al. Adjuvant Chemotherapy plus Radiation for Locally Advanced Endometrial Cancer. *N Engl J Med*, 2317-2326.

COG 33

According to GOG 33, the risk of LN involvement is less than 5 % for tumors limited to the endometrium (all grades) and 5%–10% for tumors invading the inner and middle 3 rd of the myometrium (all grades). For tumors invading the outer 3 rd of the myometrium, the risk is 10% for grade 1, 20% for grade 2, and 35% for grade 3. Note: imaging of Pelvis was not obtained in these pts. (Creasman WT et al., Cancer 1987)

In pts with +LVSI, 27% had +pelvic LNs and 19% had +P-A LNs.

Substantial LVSI is the strongest independent prognostic factor for LR, DM, and OS based off pooled analysis of PORTEC 1 and 2. Only EBRT reduced the risk of pelvic recurrence. (Bosse T et al., Eur J Cancer 2015)

165. According to GOG 33 (Creasman et al), what is the estimated risk of pelvic lymph node metastases for FIGO grade I adenocarcinoma of the endometrium, invading the deep third of the myometrium?

a. 3 %
b. 10 %
c. 20 %
d. 30 %

Key: B

Rationale: Results of GOG33 may be used to estimate probability of nodal dissemination in endometrial cancer, complimented by more modern studies.

References: Creasman WT, Cancer 1987 Oct 15, 60(8 Suppl):2035-41.

Radiation technique

EBRT

Patients are simulated in the supine position. Immobilization of the upper and lower body is recommended. Patients should be simulated with a (comfortably) full bladder. At some centers, two scans are performed (full bladder and empty bladder) and the two scans are fused to generate an integrated target volume (ITV)

Since the patient's vasculature serves as a surrogate for the lymph nodes, it is helpful to perform a contrast-enhanced CT simulation.

Treatment consists of upfront surgery, consisting of a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO). Radiation therapy is delivered following surgery in women with adverse pathologic features including high-grade disease, deep myometrial invasion, cervical stromal extension, and regional lymph node involvement

Table 20.1 Target volumes used in endometrial cancer patients undergoing postoperative pelvic IMRT

Target volumes	Definition and description
GTV	Not applicable
CTV_1	Vaginal cuff Include any fat and soft tissue anterior and posterior to the vaginal cuff between the bladder and rectum
CTV_2	Paravaginal/parametrial tissues, proximal vagina (excluding the cuff)
CTV_3	Includes common iliac,[a] external and internal iliac nodal regions In patients with cervical stromal involvement, the presacral region is also included The common iliac and external and internal iliac regions are defined by including the pelvic vessels plus a 7-mm expansion (excluding bone, muscle, and bowel) as well as all suspicious lymph nodes, lymphoceles, and pertinent surgical clips Soft tissues between the internal and external iliac vessels along the pelvic sidewall are included The presacral area consists of the soft tissues anterior (minimum 1.0 cm) to the S1–S2 vertebrae Upper extent: 7 mm inferior to L4–5 interspace Lower extent: superior aspect of femoral head (lower extent of external iliacs) and paravaginal tissues at level of vaginal cuff (lower extent of internal iliacs)
PTV_1	$CTV_1 + 15$ mm
PTV_2	$CTV_2 + 10$ mm
PTV_3	$CTV_3 + 7$ mm

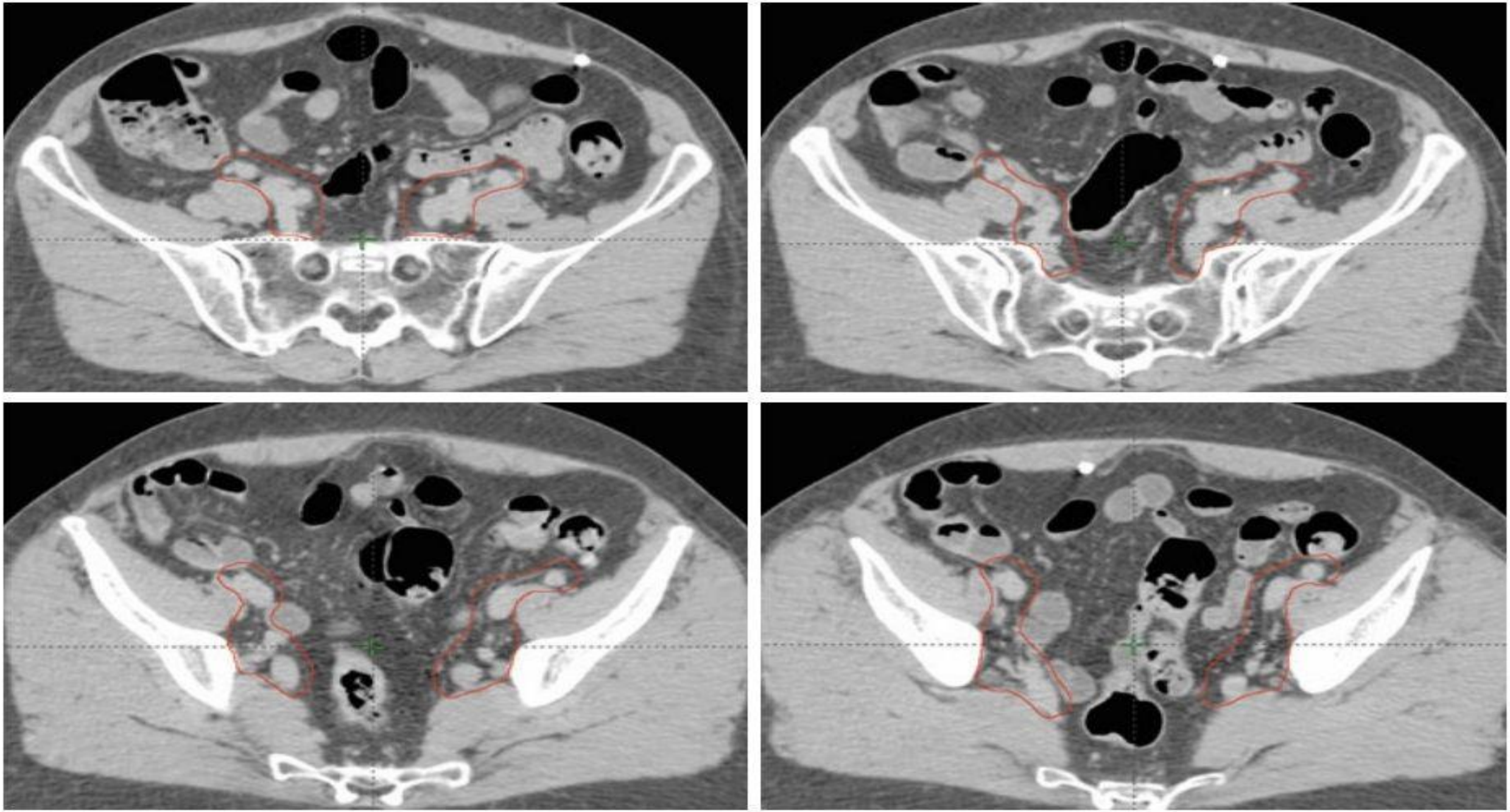
The final PTV is then generated by the union of the PTV_1, PTV_2, and PTV_3: $PTV = PTV_1 \cup PTV_2 \cup PTV_3$

IMRT intensity-modulated radiation therapy, *GTV* gross tumor volume, *CTV* clinical target volume, *PTV* planning target volume

[a]To the level of L4–5 which will not include the entire common iliac nodal region in many patients

Table 20.2 Organs at risk (OAR)

Organ	Definition and description
Bowel	Outermost loops of bowel from the level of the L4–5 interspace to the sigmoid flexure Includes the sigmoid colon and ascending/descending colon present in the pelvis In patients with intact cervical cancer, bowel loops posterior to the uterus in the lower pelvis within the PTV are not included
Rectum	Defined by the outer rectal wall from the level of the sigmoid flexure to the anus
Bladder	Defined by the outer bladder wall
Bone marrow	The pelvic bones serve as a surrogate for the pelvic bone marrow Regions included are the os coxae, L5 vertebral body, entire sacrum, acetabulae, and proximal femora superior extent: superior border of L5 or the iliac crest (whichever is more superior) Inferior extent: ischial tuberosities
Femoral heads	Entire femoral head excluding the femoral neck

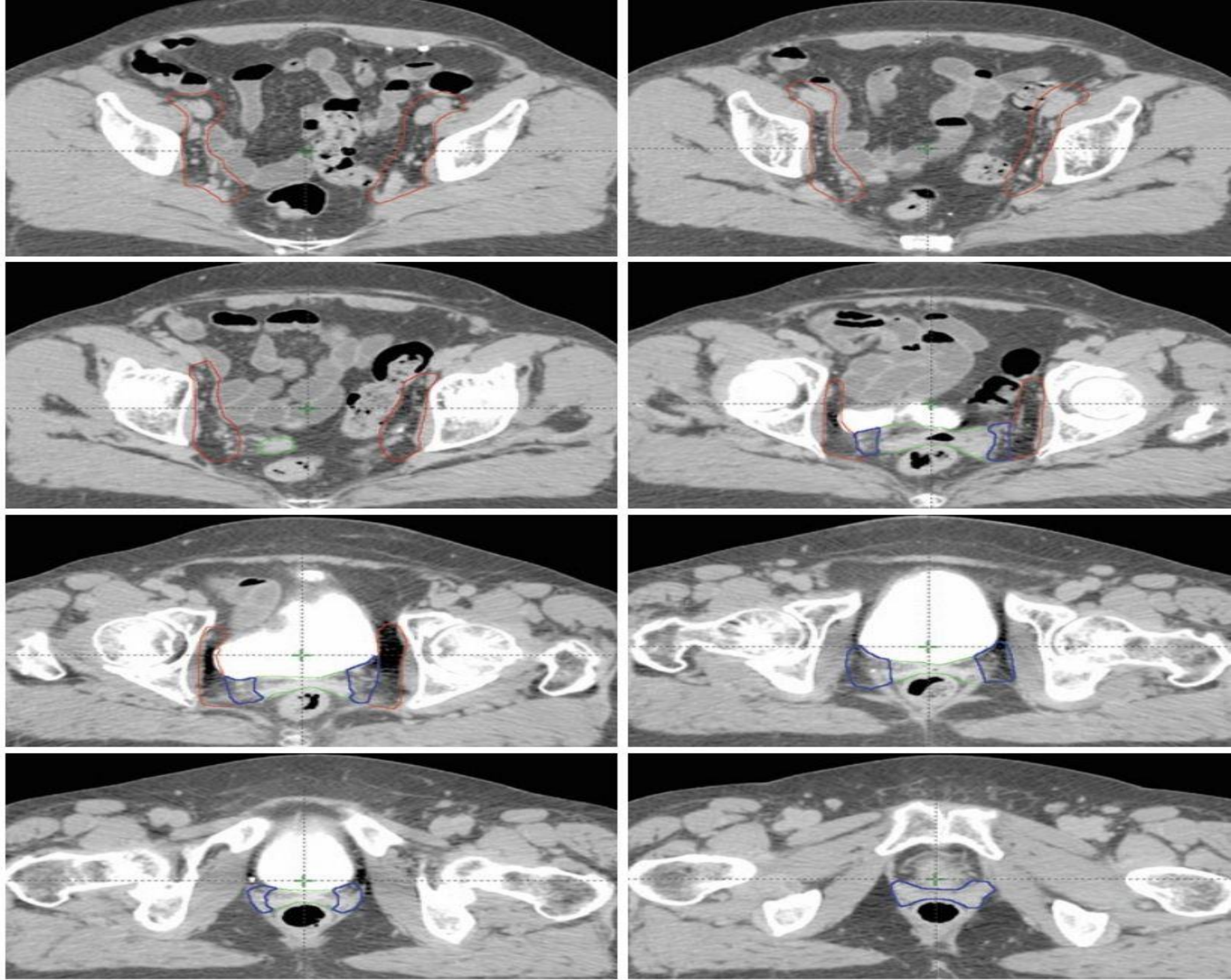


A patient with stage IB endometrial cancer undergoing adjuvant pelvic radiation theraphy. Three clinical target volumes (CTV) are shown:

CTV 1 (green) consists of the vaginal cuff including fat and soft tissues anterior and posterior to the vaginal cuff between the bladder and rectum

CTV 2 (blue) includes the paravaginal/parametrial tissues and proximal, vagina (excluding the cuff)

CTV 3 (orange) consists of the common, external and internal iliac lymph node regions. In this patient, the pre-sacral region is not included



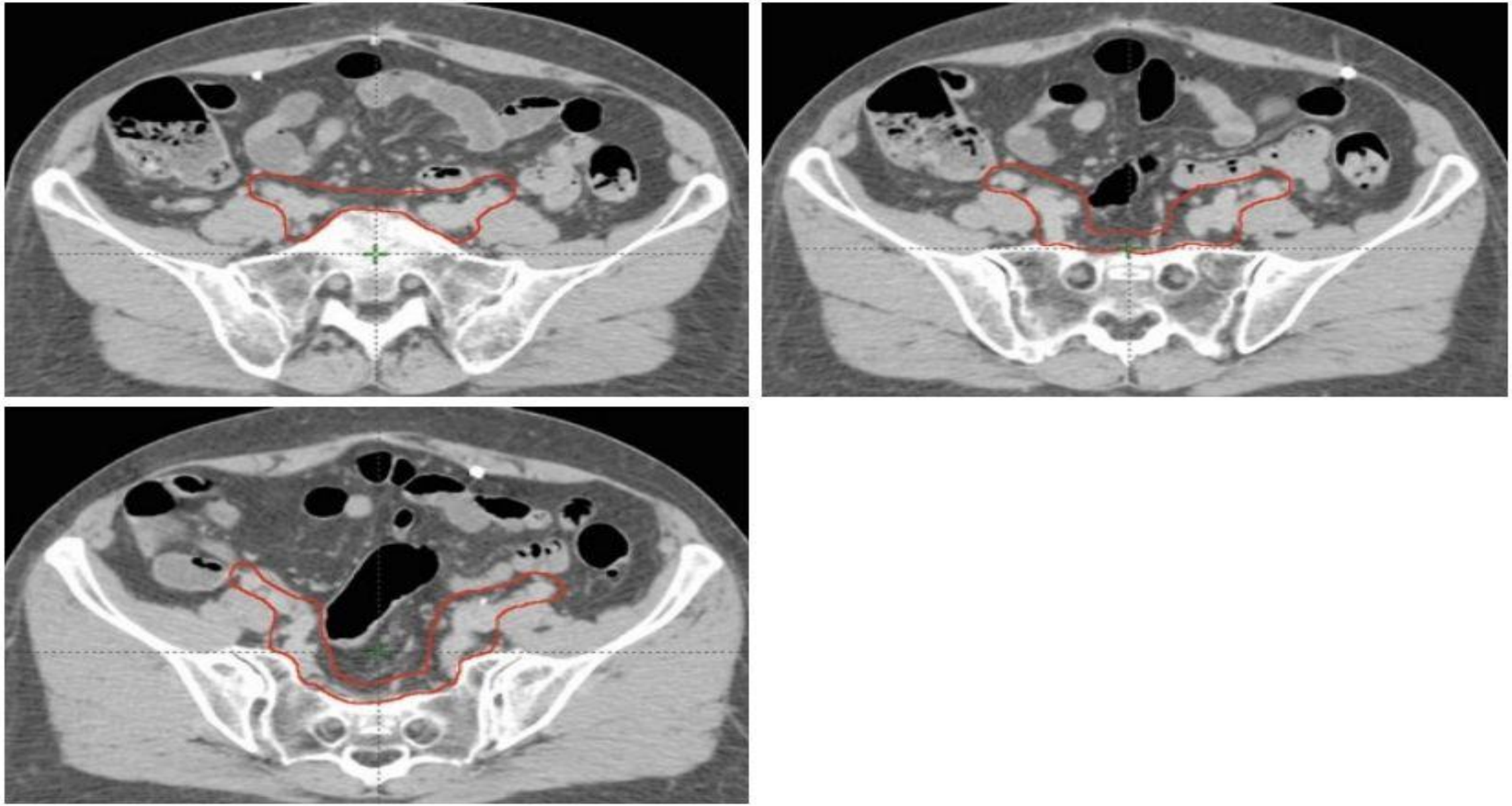


Fig. 20.2 The clinical target volume-3 (CTV_3) (*orange*) is modified in endometrial cancer patients with cervical stromal invasion to include the pre-sacral region

16. Which pathologic feature of endometrial cancer would prompt inclusion of the presacral lymphatics in the CTV for adjuvant RT?

    A. Extensive LVI

    B. Deep myometrial invasion

    C. Uterine fundal involvement

    D. Cervical stromal involvement

Key: D

Citations: Uterine Neoplasms. NCCN Guidelines in Oncology 5/25/18. National Comprehensive Cancer Network 1-103.

References: Per NCCN guidelines, pelvic radiotherapy should target the gross disease (if present), the lower common iliacs, external iliacs, internal iliacs, parametria, upper vagina/para-vaginal tissue, and presacral lymph nodes (in patients with cervical involvement.

IMRT may decrease risk of bowel, bladder, rectal toxicity.

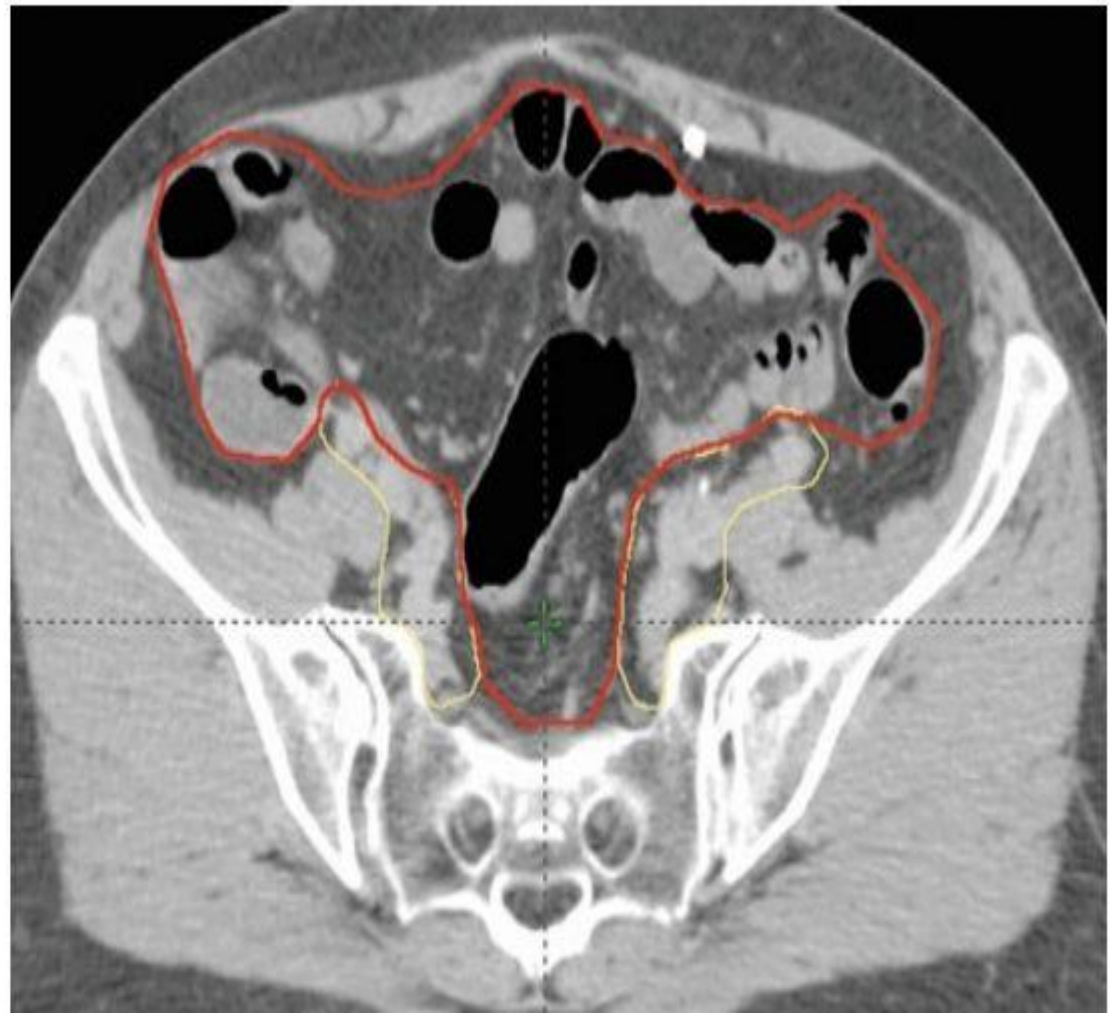


Fig. 20.4 Bowel contours (*red*) on a representative computed tomography (CT) slice in the patient described in Figure 1. The clinical target volume0-3 (CTV_3) is shown in *yellow*

brachytherapy

Initiate brachytherapy as soon as the vaginal cuff is healed preferably (6-8)weeks after surgery but in general 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 third of vagina ,in cases of extensive LVSI or positive margin, a longer segment of brachytherapy may be treated

For medically inoperable uterine cancer ,brachytherapy doses for definitive therapy are individualized based on clinical situations .when available , image guided therapy should be used .based on the best available evidence ,an 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 EQD2 more than 80 GY

122. When using brachytherapy alone for medically inoperable Stage I endometrial cancer, the ABS consensus statement recommends that the D90 of the CTV receive an EQD2 of at least

A. 24 Gy

B. 32 Gy

C. 40 Gy

D. 48 Gy

$$EQD\,2 = D\left(\frac{d + \alpha/\beta}{2 + \alpha/\beta}\right)$$

D90 =percentage of the prescribed dose

Key: D

Citations: Consensus statement for brachytherapy for the treatment of medically inoperable endometrial cancer. Schwartz, 2015, 587-599, Brachytherapy 14.

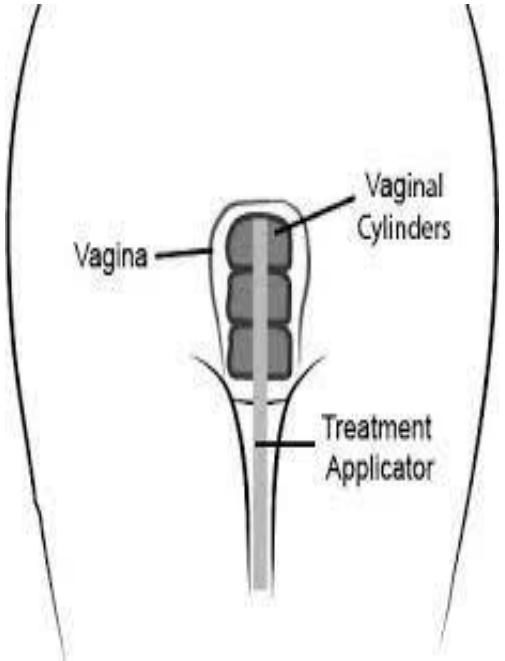
Rationale: Based on best available evidence, the panel recommends that patients with Stage I endometrial cancer should receive an EQD2 of at least 48 Gy for brachytherapy alone and at least 65 Gy for the combination of EBRT + brachytherapy to 90% of the (D90)CTV volume encompassing the entire uterus, dependent on tumor and patient specific factors.

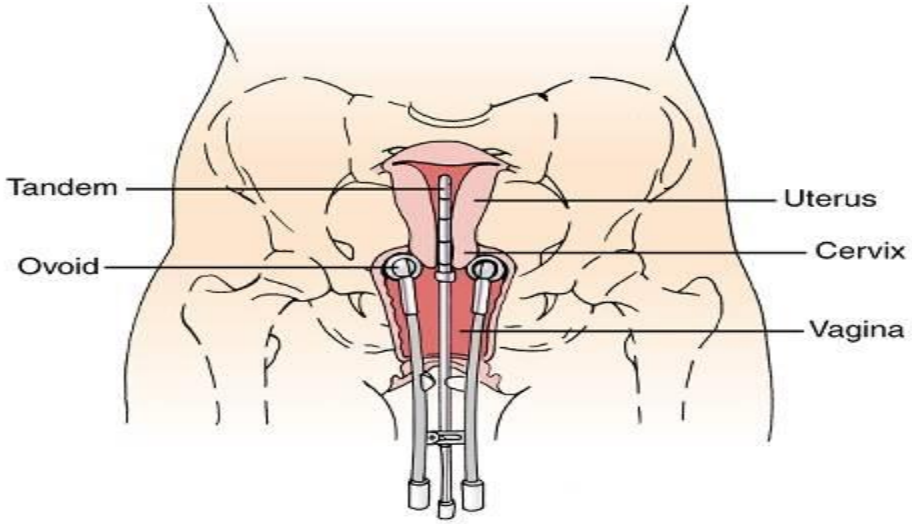
INTERSTITIAL BRACHYTHERAPY

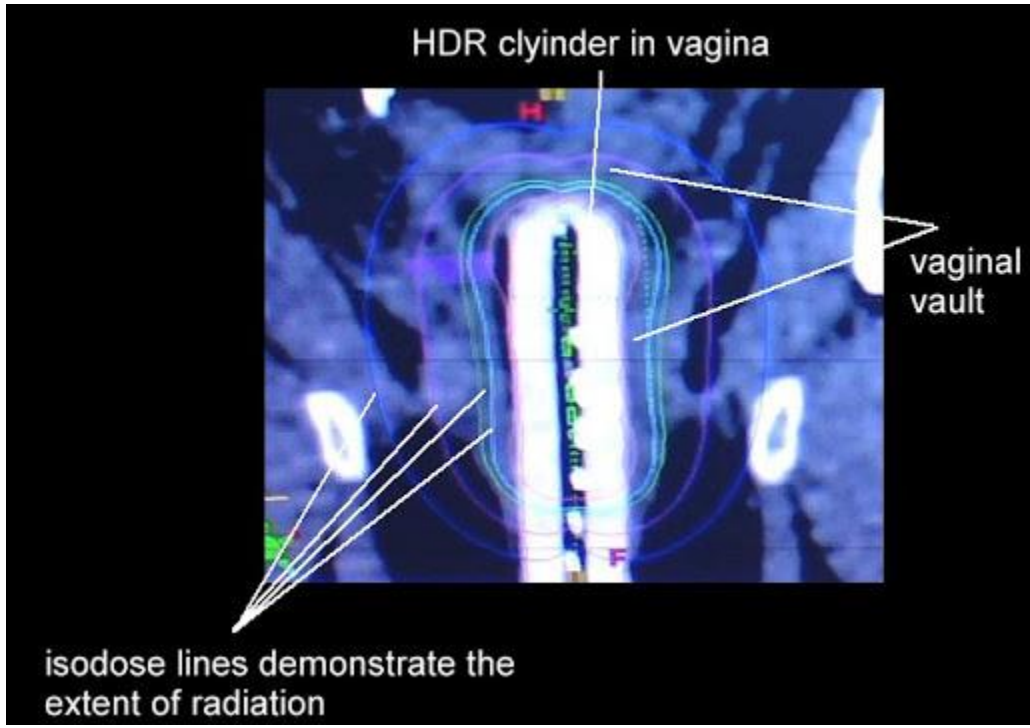
Is an advanced technique where multiple needles /catheters are inserted in the gross disease /target .interstitial brachytherapy may be preferred to maximize dose to the target and minimize dose to the OARS for cases where intracavitary brachytherapy is not possible .3D planning allows delineation on CT . dose and fractionation depend on prior RT dose ,target volume and OARs doses .

Vaginal brachytherapy

Place two marker seeds in vaginal cuff at both ends of hysterectomy scars. Use largest vaginal cylinder possible (2.5–3.5 cm). Target upper 2/3 of vaginal cuff. Consider CT planning. We recommend prescribing dose to vaginal surface because it represents the Dmax of normal tissue. However, some institutions prescribe to 0.5 cm, and dose and fractionation should be modified based on institutional experience







Brachytherapy for intact uterus

Use Martinez-Y applicator or combination of tandem and cylinder +/− interstitial catheters. Consider US guidance and 3D image-guided brachytherapy. Use tandem with ring or ovoids for pre-op stage 2

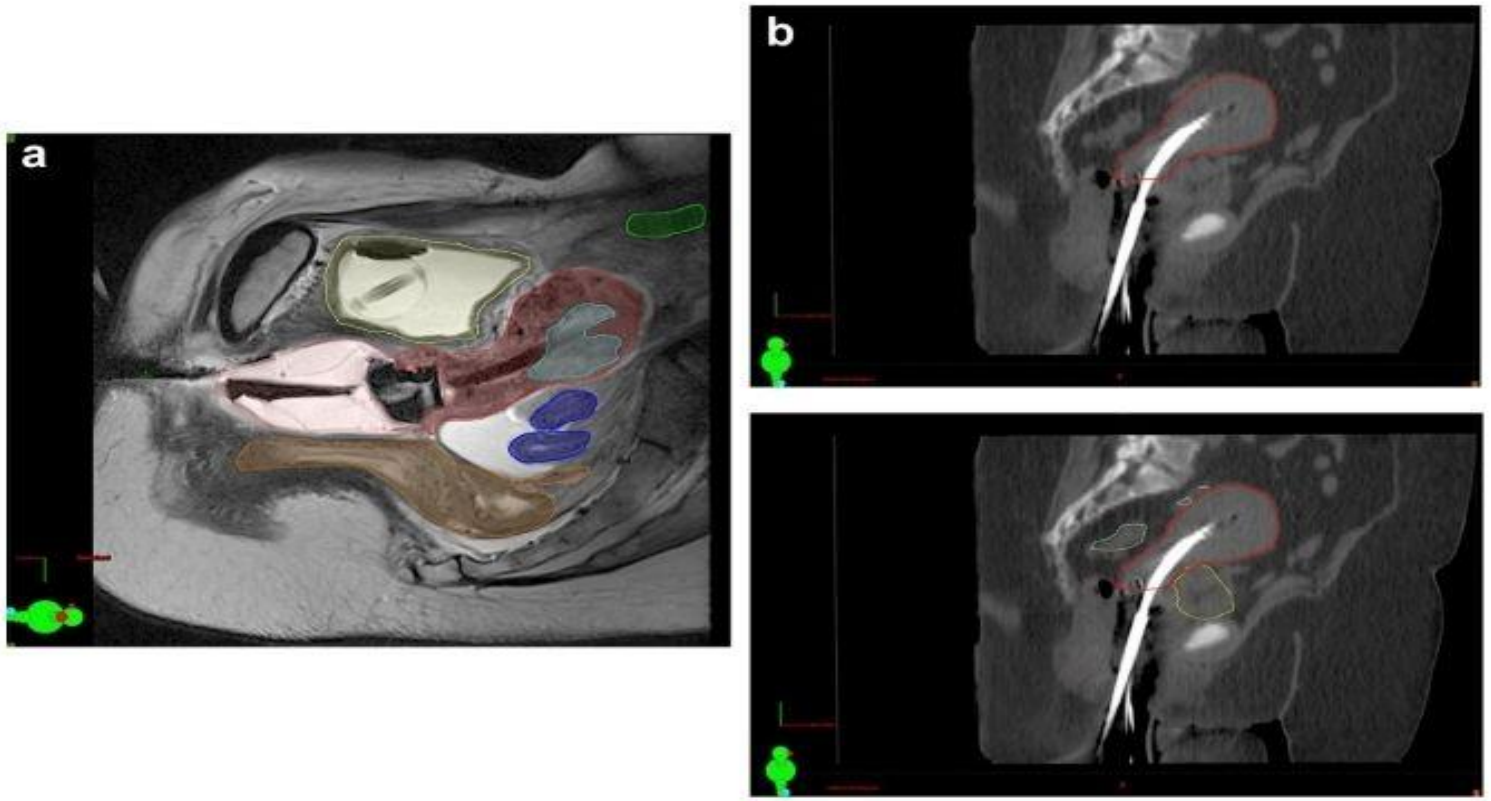


Fig. 1. Contouring for medically inoperable endometrial cancer using intraoperative magnetic resonance imaging (MRI) or computer tomography (CT). (a) Sagittal slices of T2-weighted MRI showing gross tumor volume (light blue) and clinical target volume including uterus, cervix, and upper vagina (red) with adjacent sigmoid colon (dark blue), rectum (orange), bowel (green), and bladder (yellow). (b) Sagittal view from a CT image data set displaying the uterus (red) for a tandem and ovoid implant with Heyman capsules displayed without and with the surrounding organs at risk, that is, sigmoid (light green), bladder (yellow), and rectum (brown).

DOSE PRESCRIPTIONS

- Post-op (see ASTRO guideline, Klopp, PRO 2014; ABS guideline, Small, Brachytherapy 2012).
  - VC alone:
    - HDR: 10.5 Gy x 3 (UCSF), 6 Gy x 5, 4 Gy x 6 at vaginal surface.
    - LDR: 50–60 Gy at vaginal surface.
  - Pelvic LN: 1.8 Gy/fx to 45–50.4 Gy.
  - VC brachytherapy boost:
    - HDR: 6 Gy x 3 at vaginal surface.
    - LDR: 20 Gy at vaginal surface.
  - Paraaortic LN+: EFRT to 45-50 Gy and boost enlarged unresectable nodes up to 65 Gy (sequential) or 54 Gy/25 fx with simultaneous integrated boost (SIB) using IMRT/IGRT."
- Inoperable: Follow ABS guidelines (Schwarz, Brachytherapy 2015).
  - HDR alone for selected MRI Stage I Grade 1–2 with limited myometrial invasion: 6 Gy × 6, 8.5 Gy × 4, 5 Gy × 9–10.
  - Tumor-directed EBRT 45-50 Gy and boost involved nodes up to 65 Gy (sequential) or 54 Gy/25 fx (SIB) with IMRT/IGRT.
  - HDR boost examples: 6.5 Gy × 3, 5 Gy × 5, 8.5 Gy × 2.

DOSE LIMITATIONS

- Upper vaginal mucosa 150 Gy, midvaginal mucosa 80–90 Gy, lower vaginal mucosa 60–70 Gy.
- Ovarian failure with 5–10 Gy. Sterilization with 2–3 Gy.
- Small bowel <45–50.4 Gy, rectal point dose <70 Gy, bladder point <75 Gy based on 2D planning.
- For IMRT: small bowel <30% to receive 40 Gy; rectum <60% to receive 30 Gy; bladder <35% to receive 45 Gy; femoral head ≤15% to receive 30 Gy, bone marrow ≤37% to receive 40 Gy (RTOG 0418, Jhingran, IJROBP 2012; Klopp, IJROBP 2013).

181. What two factors result in highest risk of a pelvic insufficiency fracture after IMRT in treating gynecologic cancers (IJROBP 2017)?

A. Age and smoking

B. Age and tumor location

C. Tumor location and postmenopausal status

D. Age and postmenopausal status

Key: D

Citations: IJROBP 2017.

73. An HDR plan was created using a source activity before a source exchange, but it will be delivered after a source exchange. What MUST be adjusted in the plan to deliver the intended dose?

a. Increase the source dwell times
b. Decrease the source dwell times
c. Increase the source step size
d. Decrease the source step size

Key: B

Rationale: The dose scales with the source activity and dwell times. With a higher activity same total dose with the same dose distribution as the plan, but with a higher activity source be reduced. If the step sizes changed, the dose distribution would change.

References: Khan. The Physics of Radiation Therapy. Lippincott Williams and Wilkins. 2014, 5th Ed., p. 345.

297. What happens if the applicator treatment length of an HDR treatment channel is entered incorrectly in the treatment plan?

A. The source will dwell at times that are different than intended
B. The source will move to a location different than intended
C. The source step size will be different than the plan
D. The source activity will be different than the plan

Key: B
Domain: 13.11

Citations: Kubo et al. High dose-rate brachytherapy treatment delivery: Report of the AAPM Radiation Therapy Committee Task Group N0. 59. Med. Phys. 25(4). 1998.

Rationale: The applicator treatment length in the HDR plan communicates to the afterloader the maximum distance the source can move to. Source dwell positions are then relative to this maximum distance. If the treatment length in the plan does not match the actual length of the applicator and transfer guide tube system, then the source will move to a position that doesn't match the intended anatomical treatment position.

63. In Grade 1-2 endometrioid carcinoma, what is the MOST common method to specify the target volume in single-modality postoperative vaginal cylinder brachytherapy?

A. Entire vagina
B. Entire vagina excluding the distal 1 cm
C. Vaginal cuff up to 2.5 cm in length
D. Proximal 4 cm length

Key: D

Rationale:
While the individual approaches vary, the most commonly used in U.S. prescription is one specifying a fixed vaginal length. Four centimeters length has been reported to be the most prevalent in practice. It is unclear if treating total or near-total vaginal length improves outcomes, but it increases the probability of side effects.

Reference:
M.Harkenrider, M., Grover, S., Erickson, B. A., Viswanathan, A. N., Small, C., Kliethermes, S., & Jr., W. S. (2016). Vaginal brachytherapy for postoperative endometrial cancer: 2014 Survey of the American Brachytherapy Society. *Brachytherapy*, 23-29.

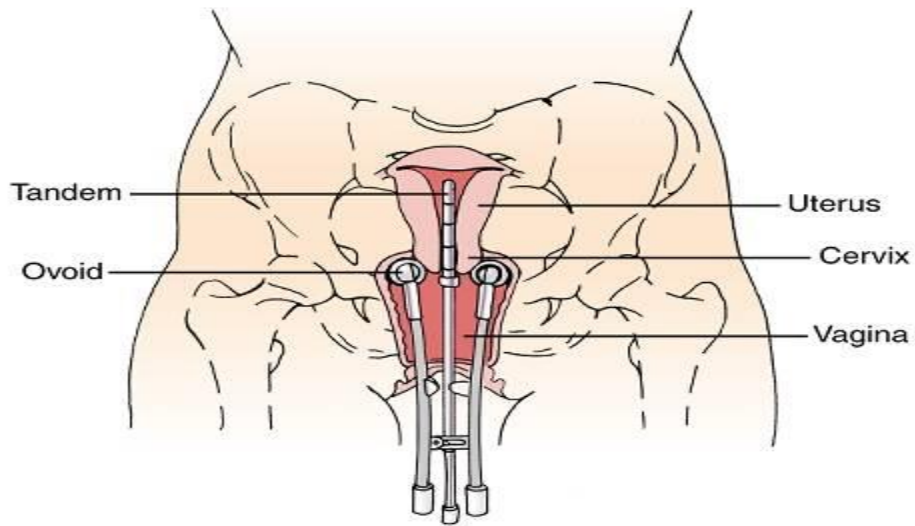
212. What is the HDR brachytherapy target volume for inoperable Stage I adenocarcinoma of the endometrium?

a. Uterus
b. Uterus and cervix
c. Uterus, cervix and upper 3-5 cm vagina
d. Uterus, cervix and entire vagina

Key: C

Rationale: The target volume is the entire uterus, cervix, and upper 3-5 cm of vagina. The required length of the vagina to be treated cannot be encompassed by ovoids. The use of ovoids should be limited to cases with lower uterine segment involvement or Stage II disease where the medial parametrium is a part of the target volume.

References: Nag, The American Brachytherapy Society Recommendations for High-Dose-Rate Brachytherapy for Carcinoma of the Endometrium, 2000, IJROBP, Vol 48 (3), 779-790.



UTERINE CARCINOSARCOMA

Uterine carcinosarcoma (UCS) is no longer considered a uterine sarcoma. By strict definition, Carcinosarcoma, malignant mixed müllerian tumor (MMMT), is not considered to be a sarcoma, but rather an epithelial malignancy (carcinoma). The epithelial component predicts for lymphatic spread and the sarcomatous component predicts for local spread.

MMMT: vaginal bleeding

The main treatment is surgery, and these patients should undergo comprehensive surgical staging similar to that with serous cancer. Pelvic nodal metastasis is seen in 21.1%, and in para-aortic node in 15.2% of patients.

With regard to the role of adjuvant radiation, the EORTC performed a prospective, randomized trial addressing the role of postoperative pelvic RT in stages I to II uterine sarcomas. There were a total of 224 patients in the trial who underwent TAH/BSO, and 166 who had peritoneal washings. Lymphadenectomy was optional. There were 91 carcinosarcomas included in that study; the rate of pelvic recurrence only was 4% in the pelvic RT arm compared to 24% for the surgery-alone arm. The corresponding rates for any local recurrence were 24% and 47%, respectively, for this subset of patients.

Adjuvant chemotherapy has been evaluated mainly in carcinosarcoma

GOG-150 is a phase III randomized study of whole abdominal RT versus three cycles of cisplatin, ifosfamide, and mesna (CIM). Eligible patients (n = 206) included those with stages I to IV UCS, no >1-cm postsurgical residuum, and/or no extraabdominal spread. Stage distribution was as follows: I, 64 (31%); II, 26 (13%); III, 92 (45%); and IV, 24 (12%). The estimated crude probability of recurring within 5 years was 58% for chemotherapy and 52% for RT. Adjusting for stage and age, the recurrence rate was 21% lower for chemotherapy patients than for RT patients (RH, 0.789; 95% CI = 0.530 to 1.176; P = .245, two-tailed test). The estimated death rate was 29% lower in the chemotherapy group

The conclusion was that there was not a statistically significant advantage in recurrence rate or survival for adjuvant chemotherapy over RT in patients with UCS

At MSKCC, patients with surgical stage I or II carcinosarcoma are treated with intravaginal RT and chemotherapy. Most stage III patients are treated in a similar fashion with few exceptions when extrauterine disease is limited to nodal disease. Then, consideration is given to concurrent pelvic RT/cisplatin followed by carboplatin/paclitaxel.

Sarcoma of the uterus

Sarcomas account for about 10% of uterine malignancy

Most common uterine sarcomas (From most common to least common):

1. Leiomyosarcoma (LMS)
2. Endometrial stromal sarcoma (ESS)
3. Adenosarcoma

Typical presentation:

LMS and ESS: similar Sx and signs as uterine fibroids—fullness, early satiety, etc.

incidence of nodal mets:

LMS: 8% (6.6%–9.1%), usually associated with extrauterine Dz ESS: traditionally thought to be low. (A recent study of 831 pts with ESS showed a 10% incidence.), patients with endometrial stromal sarcomas and adenosarcomas might benefit from lymph node sampling. On the other hand, for patients with leiomyosarcomas, the rate of nodal involvement is too low to justify routine lymphadenectomy

In general, uterine sarcomas have a higher rate of DM than endometrial cancer, the most common site of mets is the lung.

Grade is most important for ESS. Low-grade ESS is a hormone-sensitive low-grade malignancy with an indolent course, whereas high-grade ESS is characterized by an aggressive clinical course and is now considered a different Dz entity

Staging :

MMMT is still staged according to the FIGO system for endometrial adenocarcinoma

LMS and ESS staging: FIGO I: limited to uterus

FIGO IA: ≤5 cm

FIGO IB: >5 cm

FIGO II: extends beyond uterus within pelvis

FIGO IIA: adnexal involvement

FIGO IIB: involves other pelvic structures

FIGO III: invades abdominal tissues (not just protruding into abdomen)

FIGO IIIA: 1 abdominal site

FIGO IIIB: >1 abdominal site

FIGO IIIC: mets to pelvic LNs, para-aortic (P-A) LNs, or both

FIGO IVA: invades bladder or rectum

FIGO IVB: DM (excludes abdominal, pelvic, or adnexa tissue)

Serous carcinoma, clear cell carcinoma, carcinosarcoma, undifferentiated/ dedifferentiated carcinoma	Surgery. For IA: observe, chemo +/– vaginal brachy, or EBRT +/– vaginal brachy. For stage IB-IV: chemo +/– EBRT +/– vaginal brachy
Low-grade endometrial stromal sarcoma	Surgery. For stage I, observe or estrogen blockade. For stage II-IVA, estrogen blockade +/– EBRT. For stage IVB, estrogen blockade +/– palliative EBRT
High-grade endometrial stromal sarcoma, undifferentiated uterine sarcoma, uterine leiomyosarcoma	Surgery. If stage I, observe or consider systemic therapy. If stage II or III, consider systemic therapy and/or consider EBRT. If stage IVA, systemic therapy and/or EBRT. If stage IVB, systemic therapy +/– palliative EBRT

SYSTEMIC THERAPY FOR UTERINE SARCOMA[1]
(Clinical trials strongly recommended)

	Preferred Regimens	Other Recommended Regimens	Useful In Certain Circumstances
Systemic Therapies	• Doxorubicin	• Docetaxel/gemcitabine • Doxorubicin/ifosfamide • Doxorubicin/dacarbazine • Gemcitabine/dacarbazine • Gemcitabine/vinorelbine • Dacarbazine • Gemcitabine • Epirubicin • Ifosfamide • Liposomal doxorubicin • Pazopanib[2] • Temozolomide[2] • Trabectedin[3] • Eribulin (category 2B)[2]	N/A
Biomarker-Directed Systemic Therapy for Second-Line Treatment	N/A	N/A	• Pembrolizumab for TMB-H tumors[4] • Larotrectinib or entrectinib for *NTRK* gene fusion-positive tumors[2] (category 2B)

SYSTEMIC THERAPY FOR UTERINE SARCOMA[1]
(Clinical trials strongly recommended)

	Preferred Regimens	Other Recommended Regimens	Useful In Certain Circumstances
Anti-Estrogen Hormone Therapy for Low-Grade ESS or Hormone Receptor–Positive (ER/PR) uLMS[5]	• Aromatase inhibitors for low-grade ESS	• Aromatase inhibitors (for ER/PR-positive uLMS) • Fulvestrant • Megestrol acetate (category 2B for ER/PR-positive uLMS) • Medroxyprogesterone acetate (category 2B for ER/PR-positive uLMS) • GnRH analogs (category 2B for low-grade ESS and ER/PR-positive uLMS	N/A

treatment

Uterine sarcoma primary Tx modality: Type I hysterectomy and BSO is the mainstay. Ovarian preservation may be considered in young pts with early stage LMS and low-grade ESS. The role of RT, chemo, and HRT is still controversial.

Pelvic LND, P-A LND, or both for uterine sarcoma is considered controversial. They usually are recommended in MMMT and undifferentiated sarcoma. They usually are not recommended in LMS and ESS without extrauterine Dz.

The role of adj RT remains controversial. The issue has been addressed in at least 1 randomized trial and multiple retrospective studies. In general, the data suggest adj RT offers LC benefit with a limited, if any, OS benefit for MMMT. The role of adj RT in LMS, which has a high DM rate, is unclear but likely limited, if any.

For LMS patients, the rate of pelvic recurrence only was 2% in the pelvic RT compared to 14% in patients treated with surgery alone, and for any local recurrence, it was 20% versus 24%. The EORTEC study was not powered to detect a significant difference in PFS or OS.

Similar to epithelial cancers, pelvic irradiation is typically recommended for MMMT with deep myometrial involvement, cervical involvement, nodal involvement, or R1/2 resections. VBT alone may be given for FIGO IA pathology.

Although controversial, adj irradiation may be considered in pts with uterine LMS with an R1 or R2 resection, particularly in the context of a clinical trial

The RT volumes are essentially the same for uterine sarcoma and endometrial carcinoma. Although, for LMS, nodal volumes can be excluded

For patients with leiomyosarcomas, the main treatment is surgery, and the role of adjuvant treatment, whether RT or chemotherapy, is not well defined. The high rate of distant relapse in these patients overshadows any local control benefit attained with adjuvant RT.

These patients should be encouraged to participate in trials assessing the role of chemotherapy and/or targeted therapy. For patients with low-grade endometrial stromal sarcomas, observation is feasible, because most are hormonally sensitive and generally behave in an indolent manner, with long disease-free intervals. For those with undifferentiated endometrial sarcomas, adjuvant pelvic RT is reasonable. For patients with adenosarcomas, especially with sarcomatous overgrowth, adjuvant pelvic RT is also reasonable.