Chapter 30
Endometrial Cancer

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PEARLS

- Most common gynecological cancer in the U.S; fourth most common malignancy in women after breast, lung, and colorectal.
- Risk factors: unopposed estrogen, postmenopausal (median age at diagnosis is 61 years), nulliparity, early menarche, late menopause, obesity, tamoxifen (7.5×), oral contraceptives use.
- Grade is determined by percentage of dedifferentiated solid growth pattern: Grade 1: ≤5%, Grade 2: 5–50%, Grade 3: >50%.
- Seventy-five percent of tumors are endometrioid endometrial adenocarcinomas, which are estrogen-dependent tumors that commonly present with postmenopausal bleeding and are frequently preceded by endometrial hyperplasia.
- Rate of progression to invasive cancer from simple hyperplasia is rare (<2%) with progression to carcinoma in patients with simple and complex hyperplasia with atypia being more common (30–40%).
- Twenty percent of endometrial carcinomas are nonendometrioid including papillary serous (UPSC), clear cell, and mucinous.
- Papillary serous and clear cell carcinomas are often diagnosed with more advanced disease and have a poorer prognosis.
- Up to 5% of uterine cancers are sarcomas, including carcinosarcoma (most common), leiomyosarcoma, and endometrial stromal sarcomas.
- Prognostic factors = stage (#1), cell type, grade, LVSI, depth of invasion, cervical extension, and patient age.
- Primary lymphatic drainage is to pelvic LN (internal and external iliac, obturator, common iliac, presacral, parametrial); direct spread may occur to paraaortic LN.
- ~1/3 of patients with + pelvic LN have + paraaortic LN.

WORKUP

- H&P with attention to uterine size, cervical and vaginal involvement, ascites, nodes.

- Labs: CBC, blood chemistries, LFTs, CA-125 (elevated in 60%), UA.
- 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.
- Pap smear has limited sensitivity (as low as 40%).
- Imaging: CXR, CT, or MRI of abdomen and pelvis or transvaginal ultrasound to evaluate symptomatic disease.
- Cystoscopy and/or sigmoidoscopy as clinically indicated.

STAGING (AJCC 6TH ED., 2002/FIGO 1988 PATHOLOGIC STAGING): ENDOMETRIAL CANCER

TX:	Primary tumor cannot be assessed
T0:	No evidence of primary tumor
Tis/0:	Carcinoma in situ
T1/I:	Tumor confined to corpus uteri
T1a/IA:	Tumor limited to endometrium
T1b/IB:	Tumor invades less than one-half of the myometrium
T1c/IC:	Tumor invades one-half or more of the myometrium
T2/II:	Tumor invades cervix, but does not extend beyond uterus
T2a/IIA:	Tumor limited to glandular epithelium of endocervix. There is no evidence of connective tissue stromal invasion
T2b/IIB:	Invasion of the stromal connective tissue of the cervix
T3/III:	Local and/or regional spread as defined below
T3a/IIIA:	Tumor involves serosa and/or adnexa (direct extension or metastasis) and/or cancer cells in ascites or peritoneal washings
T3b/IIIB:	Vaginal involvement (direct extension or metastasis)
T4/IVA:	Tumor invades bladder mucosa and/or bowel mucosa (bullous edema not sufficient to classify tumor as T4)
NX:	Regional lymph nodes cannot be assessed
N0:	No regional lymph node metastasis
N1/IIIC:	Regional lymph node metastasis to pelvic and/or paraaortic nodes
MX:	Distant metastasis cannot be assessed
M0:	No distant metastasis
M1/IVB:	Distant metastasis (includes metastasis to abdominal lymph nodes other than paraaortic, and/or inguinal lymph nodes; excludes metastasis to vagina, pelvic serosa, or adnexa)

A small number of patients may be treated with primary radiation. Such patients should be staged with the clinical staging system adopted by FIGO in 1971 (Int J Gynaecol Obstet 1971;9:172)

STAGING (AJCC 7TH ED., 2010/FIGO 2008)

Editors' note: All TNM stage and stage groups referred to elsewhere in this chapter reflect the 1988 FIGO/2002 AJCC staging nomenclature unless otherwise noted as the new system below was published after this chapter was written.

SUMMARY OF CHANGES

- The FIGO 1988 Stage IA and IB have been combined, so that Stage IA now involves the endometrium and/or less than one-half myometrial invasion, and IB is now equal to or greater than the outer one-half of the myometrium (previously IC).
- Stage II no longer has a subset A and B. Involvement of the endocervical glandular portion of the cervix (previously IIA) is now considered stage I. Previous stage IIB is now simply stage II.
- Stage IIIC pelvic and paraaortic node involvement have been separated, rather than combined in a single substage. As a result, stage IIIC is now categorized as IIIC1 (indicating positive pelvic nodes) and IIIC2 (indicating positive paraaortic nodes with or without positive pelvic nodes).
- A separate staging schema for uterine sarcoma has been added.

UTERINE CARCINOMAS

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)

**Note*: FIGO no longer includes Stage 0 (Tis).
**Endocervical glandular involvement only should be considered Stage I and not Stage II.

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

continued

Distant metastasis (M)

TNM Categories	*FIGO Stages*	
M0		No distant metastasis
M1	IVB	Distant metastasis (includes metastasis to inguinal lymph nodes intraperitoneal disease, or lung, liver, or bone. Excludes metastasis to paraaortic lymph nodes, vagina, pelvic serosa, or adnexa)

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

*Carcinosarcomas should be staged as carcinoma.
**Note: FIGO no longer includes Stage 0 (Tis).

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LEIOMYOSARCOMA, ENDOMETRIAL STROMAL SARCOMA

Primary tumor (T)

TNM Categories	*FIGO Stages*	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor limited to the uterus
T1a	IA	Tumor 5 cm or less in greatest dimension
T1b	IB	Tumor more than 5 cm
T2	II	Tumor extends beyond the uterus, within the pelvis
T2a	IIA	Tumor involves adnexa
T2b	IIB	Tumor involves other pelvic tissues
T3	III*	Tumor infiltrates abdominal tissues
T3a	IIIA	One site
T3b	IIIB	More than one site
T4	IVA	Tumor invades bladder or rectum

Note: Simultaneous tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.
*Lesions must infiltrate abdominal tissues and not just protrude into the abdominal cavity.

Regional lymph nodes (N)

TNM Categories	*FIGO Stages*	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis

continued

Distant metastasis (M)

TNM Categories	*FIGO stages*	
M0		No distant metastasis
M1	IVB	Distant metastasis (excluding adnexa, pelvic, and abdominal tissues)

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ADENOSARCOMA

Primary tumor (T)

TNM Categories	*FIGO stages*	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	I	Tumor limited to the uterus
T1a	IA	Tumor limited to the endometrium/endocervix
T1b	IB	Tumor invades to less than half of the myometrium
T1c	IC	Tumor invades more than half of the myometrium
T2	II	Tumor extends beyond the uterus, within the pelvis
T2a	IIA	Tumor involves adnexa
T2b	IIB	Tumor involves other pelvic tissues
T3	III*	Tumor involves abdominal tissues
T3a	IIIA	One site
T3b	IIIB	More than one site
T4	IVA	Tumor invades bladder or rectum

Note: Simultaneous tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.
*In this stage lesions must infiltrate abdominal tissues and not just protrude into the abdominal cavity

Regional lymph nodes (N)

TNM Categories	*FIGO stages*	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIC	Regional lymph node metastasis

Distant metastasis (M)

TNM Categories	*FIGO stages*	
M0		No distant metastasis
M1	IVB	Distant metastasis (excluding adnexa, pelvic and abdominal tissues)

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UTERINE SARCOMA

Anatomic stage/prognostic groups

I:	T1 N0 M0
IA*:	T1a N0 M0
IB*:	T1b N0 M0
IC**:	T1c N0 M0
II:	T2 N0 M0
IIIA:	T3a N0 M0
IIIB:	T3b N0 M0
IIIC:	T1, T2, T3 N1 M0
IVA:	T4 Any N M0
IVB:	Any T Any N M1

**Note*: Stages IA and IB differ from those applied for leiomyosarcoma and endometrial stromal sarcoma.
***Note*: Stage IC does not apply for leiomyosarcoma and endometrial stromal sarcoma.

TREATMENT RECOMMENDATIONS

2002 Stage	Recommended treatment
All patients	■ All medically operable patients should have surgery. Perform TAH/BSO or radical hysterectomy if cervical stromal involvement and obtain peritoneal cytology. Generally, exploratory laparotomy with inspection and palpation ± biopsy of the omentum, liver, peritoneal surfaces, and adnexae is performed. Consider selective pelvic and paraaortic LN dissection for myometrial invasion or if grade 2–3, and include nodes from paraaortic, common iliac, external iliac, internal iliac, and obturator chains. Adjuvant treatment as below:
IA, IB	■ Observation, or if grade 2–3 and adverse features present (age >60 years, LVSI, large tumor size, lower uterine involvement), pelvic RT and/or vaginal cuff brachytherapy (VC)
IC	■ Observation, or if other adverse features present (grade 2–3, advanced age >50–70 years, LVSI, large tumor size, lower uterine segment involvement) pelvic RT and/or vaginal cuff brachytherapy (VC). Consider chemotherapy for grade 3
IIA, IIB	■ Consider pelvic RT ±VC. Consider chemotherapy for grade 3
IIIA	■ Positive cytology only: Observation for grade 1–2, chemotherapy for grade 3. Consider pelvic RT and/or VC. All other IIIA: Chemotherapy and/or tumor-directed RT

continued

Stage III-IV	■ Surgery → chemotherapy and/or tumor-directed RT
Medically inoperable	■ Tumor-directed EBRT to uterus, cervix, upper vagina, pelvic LN, and other involved areas (~45–50.4 Gy), followed by intracavitary brachytherapy boost (e.g., 6 Gy × 3 HDR to uterine serosal surface). Consider dose-escalation to gross disease using image-guided brachytherapy or IMRT with CT or MRI planning
Recurrence	■ If no prior RT → EBRT and IC or IS brachytherapy boost to total dose 60–70 Gy. Consider IS salvage brachytherapy for select previously irradiated patients
Papillary serous/clear cell	■ Surgery. For stage IA, consider chemotherapy and/or tumor-directed RT. For stage IB, IC, II, and debulked stage III-IV, give chemotherapy ± tumor-directed RT.
Sarcomas, carcinosarcoma [malignant mixed mesodermal (Mullerian) tumor]	■ Surgery. Post-op RT for high-grade sarcomas, leiomyosarcomas, and carcinosarcomas to improve LC. Pelvic RT ± VC for stages I–II and tumor-directed RT for stages III–IV. Consider chemotherapy for high-grade undifferentiated sarcoma and leiomyosarcoma

VIII

STUDIES

LYMPHADENECTOMY

- *MRC ASTEC* (2009): 1,408 women thought preoperatively to have corpus confined disease randomized to surgery (TAH/BSO/washings/PALN palpation) ± lymphadenectomy. With adjustment for baseline characteristics and pathology, lymphadenectomy provided no significant OS or RFS.

ADJUVANT RADIOTHERAPY

- *GOG 99* (Keys et al. 2004): Three hundred and ninety-two patients with IB (60%), IC (30%), and occult II (10%) treated with TAH/BSO, pelvic and PALN sampling, and peritoneal cytology with 6-year F/U. Patients randomized to observation vs. post-op WP RT (50.4 Gy). Two-third of patients had low–intermediate risk disease and one-third of patients were high-intermediate risk (G2-3, outer 1/3 involvement, and LVSI or age >50 years + 2 factors, or age >70 years + 1 factor). WP RT improved LRR (12→3%), mostly among high-intermediate risk patients

(26→6%) compared to low–intermediate risk patients (6→2%). No difference in OS (86→92%), but not powered to detect OS change. Majority of pelvic recurrences were in the vaginal cuff.

- *PORTEC-1* (Creutzberg et al. 2000; Scholten et al. 2005): Seven hundred and fourteen patients with IB G2–3 or IC G1–2 treated with TAH/BSO randomized to observation vs. WP RT (46 Gy). No LN dissection (only sampling of suspicious LN). Ninety percent of patients had G1–2 and 40% were IB. WP RT decreased LRR (14→4%), with 75% of failures occuring in the vaginal vault. No difference in OS (81 vs. 85%) or DM (8 vs. 7%). Update with 10-year f/u and central pathology review for 80% of patients confirmed WP RT continued to reduce LRR (14→5%) without an OS benefit (66 vs. 73%), even after excluding IB grade 1 patients. Patients with 2 or more risk factors (age ≥60 years, grade 3, and ≥50% myometrial invasion) had greatest LRR benefit with RT (23→5%).
- *ASTEC EN.5* (2009): Nine hundred and nine patients with IA/B grade 3, IC any grade, or I-II papillary serous or clear cell histology randomized after surgery to observation or WP RT (40–46 Gy). However, vaginal cuff brachytherapy was used in 51% of patients randomized to the observation arm. There was no difference in 5-year OS (84%) or DSS (89–90%). WP RT reduced isolated pelvic or vaginal recurrences (6.1→3.2%), and increased acute toxicity (27→57%) and late severe toxicity (3→7%).
- Aalders et al. (1980): Five hundred patients with IB-IC any grade treated with TAH/BSO without LN sampling. Sixty-five percent of patients had IB G1-2 Randomized to VC vs. VC → WP RT. VC = LDR 60 Gy to surface. WP RT = 2/40 Gy with central shielding at 20 Gy. Addition of WP RT decreased pelvic and vaginal recurrences (7→2%), but did not change OS (90%) because more DM in WP RT arm. On subset analysis, most improvement in LRR with IC G3 (20→5%). Poor prognostic factors = IC, G3, LVSI, age >60 years.
- *PORTEC 2* (Nout 2008 – abstract only): Four hundred and twenty-seven patients with high-intermediate risk (age >60 years and IC grade 1–2 or IB grade 3; any age and IIA grade 1–2 or grade 3 with <50% invasion) randomized to WP RT (46 Gy) or VC brachytherapy (21 Gy HDR in 3 fx or 30 Gy LDR). Although WP RT reduced pelvic relapse (3.6→0.7%), there was no significant difference in 3-year VC relapse (0.9% VC vs. 2% WP), OS (90–91%), or RFS (89–90%). Patient-reported quality of life was better with VC brachytherapy.
- *Metaanalyses* (Johnson 2007; Kong et al., 2007) suggest that pelvic EBRT may improve DFS for high-risk patients, such as those with IC grade 3 disease.

- *SEER* (Lee et al. 2006). Review of 21,249 patients with stage I disease treated with (19.2%) or without (80.8%) adjuvant RT. Adjuvant RT improved OS and RFS for IC grade 1 and IC grade 3–4 patients, similar to results among patients who had a surgical LN examination.

ROLE OF CHEMOTHERAPY

- *GOG 122* (Randall et al. 2006): Three hundred and ninety-six patients with III/IV disease treated with surgery with maximal residual disease ≤2 cm randomized to WART (30 Gy + 15 Gy pelvic boost + 15 Gy paraaortic boost if pelvic LN+ or no sampling of pelvic and paraaortic LN) vs. chemo (doxorubicin + cisplatin every 3 weeks × 7c → cisplatin × 1c). 21% of patients had UPSC in each arm. Chemo improved 5-year OS (42→55%) and DFS (38→50%), but increased grade 3–4 hematologic, gastrointestinal, and cardiac toxicity.
- *Ontario Canada group* (Lupe et al. 2007): Thirty-three patients with III/IV disease treated with carboplatin/paclitaxel every 3 weeks × 4c, then pelvic RT 45 Gy, then 2 more cycles chemo. PA RT and/or VC HDR were optional. 2-year DFS and OS 55%, with only 3% pelvic relapse.
- *RTOG 9708* (Greven et al. 2006): Phase II trial of 46 patients with grade 2–3 disease with either >50% myometrial invasion and cervical stromal invasion or pelvic-confined extrauterine disease treated with WP RT (45 Gy) and cisplatin on days 1 and 28. Four-year pelvic, regional, and distant recurrence rates were 2%, 2%, and 19%, respectively. Four-year OS and DFS were 85% and 81%, respectively. There were no recurrences for stages IC, IIA, or IIB.
- *Italian* (Maggi et al. 2006): Three hundred and forty-five patients with IC G3, II G3 with >50% myometrial invasion, and IIIA-IIIC randomized to pelvic RT 45–50 Gy vs. CAP chemo (cyclophosphamide/doxorubicin/cisplatin) monthly × 5c. Note 64% of the patient had stage III disease. No difference in 7-year OS 62% or PFS 56–60%. RT delayed LF (11→7%) and chemo delayed DM (21→16%)
- *Japanese* (Susumu et al. 2008): 385 patients with stage IC-III with >50% myometrial invasion treated with surgery and pelvic LN dissection randomized to pelvic RT (45–50 Gy) vs. CAP chemo (cyclophosphamide, doxorubicin, cisplatin) every 4 weeks for 3c. Only 3% received brachytherapy. No difference in 5-year PFS (82–84%) or OS (85–87%). On subset analysis, no difference for ICG1-2 <70 years (low–intermediate risk), but chemo improved PFS (66→84%) and OS (74→90%) for

higher-risk group (ICG3 or IC >70 years or stage II or IIIA (+cytology)). Seven percent pelvic failures in each arm, but fewer vaginal recurrences in RT arm. No differences in extrapelvic recurrences (~15%).

- *NSGO-EC-9501/EORTC 55991* (Hogberg 2007 – abstract only): Three hundred and seventy-two patients with surgical stage I, II, IIIA (+cytology only), or IIIC (+pelvic LN only) randomized to pelvic RT (≥44 Gy) ± VC brachytherapy vs. chemotherapy before or after RT. Chemotherapy included options of doxorubicin/cisplatin, carboplatin/paclitaxel, or carboplatin/paclitaxel/epirubicin. Most patients had 2 or more risk factors of grade 3, deep myometrial invasion, or DNA nondiploidy. Patients with serous, clear cell, or anaplastic histology were eligible regardless of risk factors. Addition of chemotherapy to RT improved 5-year PFS by 7% (75→82%).

SARCOMA

- *EORTC 55874* (Reed et al. 2008): Two hundred and twenty-four women with stage I/II of all uterine sarcoma subtypes after TAH/BSO/washings with optional nodal sampling randomized to observation vs. post-op WP RT (50.4 Gy). RT reduced LRR (22% vs. 40%), but had no effect on OS, PFS, or DM. In subset analysis, WP RT increased LC for carcinosarcomas, but not leiomyosracomas.
- *GOG 150* (Wolfson et al. 2007): Two hundred and thirty-two patients with stage I-IV uterine carcinosarcoma ≤ 1 cm residual and/or no extraabdominal spread randomized to WART (whole abdomen 30 Gy/pelvis 49.8-50 Gy at 1 Gy bid or 1.5 Gy QD) vs. chemotherapy (cisplatin/ifosfamide/mesna × 3c). No significant difference in recurrence rate or survival between the two arms.

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Simulate patient supine with CT planning; administer presimulation enema.
- WP borders: superior = L5-S1; inferior = below obturator canal and including upper 1/2–2/3 of vagina; lateral = 2 cm lateral to pelvic brim; posterior = split sacrum to S3; anterior = pubic symphysis. Consider using IMRT (Fig. 30.1)
- EFRT borders: Extend superior border to top of L1 with CT planning to avoid kidneys. Recommend IMRT.

- If IMRT is used, careful attention to target delineation is necessary, and consider using internal target volume (ITV) or volume of vagina that is in both the empty and full bladder CT. Refer to RTOG CTV consensus guidelines (Small et al. 2008).

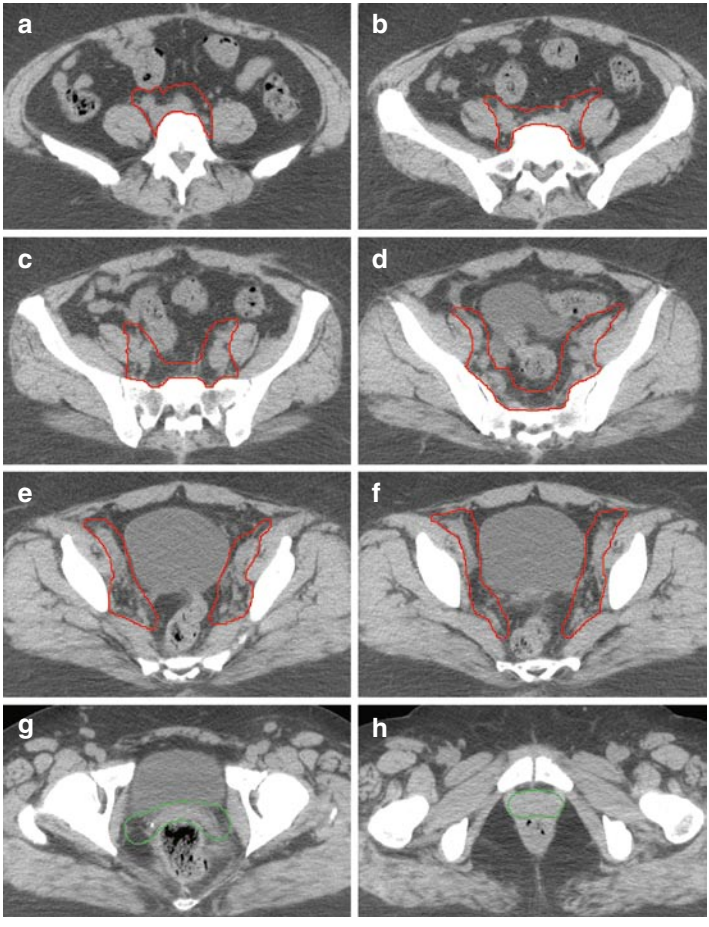

Fig. 30.1 Example pelvic nodal IMRT clinical tumor volumes on representative axial CT slices: (**a**) upper common iliacs, (**b**) midcommon iliacs and presacral area, (**c**) lower common iliacs and presacral area, (**d**) upper internal and external iliacs and presacral area, (**e** and **f**) internal and external iliacs, (**g**) vagina and parametrium, (**h**) vagina

- 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 two-third 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 their experience.
- Brachytherapy for intact uterus: Use Martinez-Y applicator or combination of tandem and cylinder with interstitial catheters. Consider using US guidance and 3D image-guided brachytherapy. Use tandem with ring or ovoids for pre-op stage II.
- WART = Use CT or fluoroscopy to determine 1 cm above diaphragmatic dome. Consider using IMRT (Fig. 30.1).

DOSE PRESCRIPTIONS

- Post-op
  - WP: 1.8 Gy/fx to 45–50.4 Gy.
  - VC boost: 6 Gy × 3 at vaginal surface (HDR) or 20 Gy at vaginal surface (LDR).
  - VC alone: 6 Gy × 5–6 or 10–10.5 Gy × 3 at vaginal surface (HDR) or 50–60 Gy at vaginal surface (LDR).
- Pre-op: WP 1.8 Gy/fx to 45 Gy and T&R or T&O 6 Gy × 3 (HDR).
- Vaginal extension: WP 45 Gy plus interstitial implants 6–7 Gy × 3 (HDR).
- Paraaortic LN+: EFRT to 45–50 Gy, enlarged unresectable nodes should be boosted to 60 Gy. IMRT recommended. Consider IORT at surgery.
- WART: 1.5 Gy/fx to 30 Gy to whole abdomen → boost paraaortic LN and WP to 45 Gy. Consider IMRT to improve target coverage and marrow sparing.
- Inoperable: WP 45–50 Gy and 6–7 Gy × 3 (HDR).

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 WART, use blocks to restrict kidneys <15 Gy, liver block to shield R lobe of liver after 25 Gy.

COMPLICATIONS

- TAH/BSO complications – mortality (<1%), infection, wound dehiscence, fistula, bleeding
- Frequency and urgency of urine and/or stool
- Vaginal stenosis – use dilators
- Thrombocytopenia with WART

FOLLOW-UP

- Physical exam every 3 months × 2 years, then every 6 months × 3 years, then annually. Vaginal cytology every 6 months for 2 years, then annually. CA-125 optional. Annual chest X-ray. CT/MRI as clinically indicated.

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