Early Stage Endometrial Cancer

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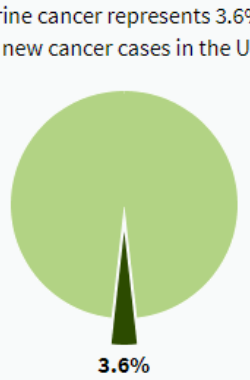
Case: Intro

- HPI:
  - 56 y.o. female, G0P0, with 4 yr hx of irregular menses, thought to be perimenopausal
  - Bleeding accompanied by worsening abdominal pain, led to transvaginal US
  - Pelvic US showed enlarged uterus, large polypoid mass in endometrial cavity, 25.4 mm endometrial stripe (normal < 5 mm)
  - CT A/P showed nodular enhancing masses in endometrium, suspicious for cancer
  - Bx showed high-grade adenocarcinoma

Epidemiology

- Uterine cancer: most common GYN malignancy
  - Cases per year: 65,620
  - Deaths per year: 12,590
- 5 year Relative Survival: 81.2%
- Median Age at Diagnosis: 63

	Common Types of Cancer	Estimated New Cases 2020	Estimated Deaths 2020
1.	Breast Cancer (Female)	276,480	42,170
2.	Lung and Bronchus Cancer	228,820	135,720
3.	Prostate Cancer	191,930	33,330
4.	Colorectal Cancer	147,950	53,200
5.	Melanoma of the Skin	100,350	6,850
6.	Bladder Cancer	81,400	17,980
7.	Non-Hodgkin Lymphoma	77,240	19,940
8.	Kidney and Renal Pelvis Cancer	73,750	14,830
9.	**Uterine Cancer**	**65,620**	**12,590**
10.	Leukemia	60,530	23,100



Risk Factors

- Phenotypic
  - Continuous unopposed estrogen stimulation
  - Obesity
  - Tamoxifen
  - Cirrhosis
  - Nulliparity
  - Diabetes
- Genotypic (3%)
  - Lynch Syndrome (HNPCC) – most commonly from germline mutations of MMR proteins (MLH1, MSH2, MSH6, or PMS2)

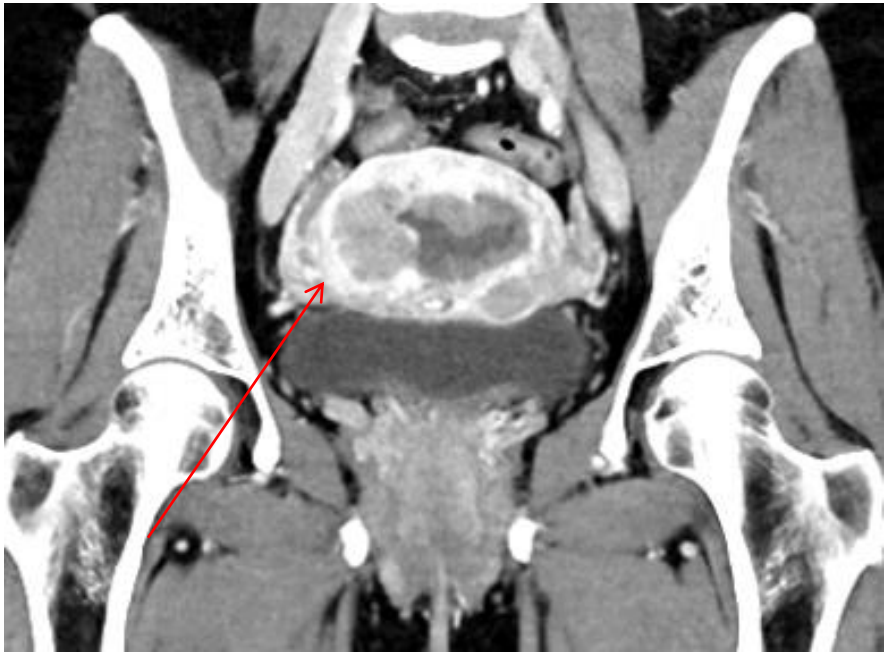
Classification

- Type I
  - Endometrioid
  - Associated with obesity, increased estrogen exposure
  - Better prognosis (overall survival of 85% at 5 years)
- Type II
  - Non-endometrioid
  - Considered high grade
  - Serous, clear cell, grade 3 endometrioid histologies
  - Associated with TP53 mutation
  - Worse prognosis (overall survival of 55% at 5 years)

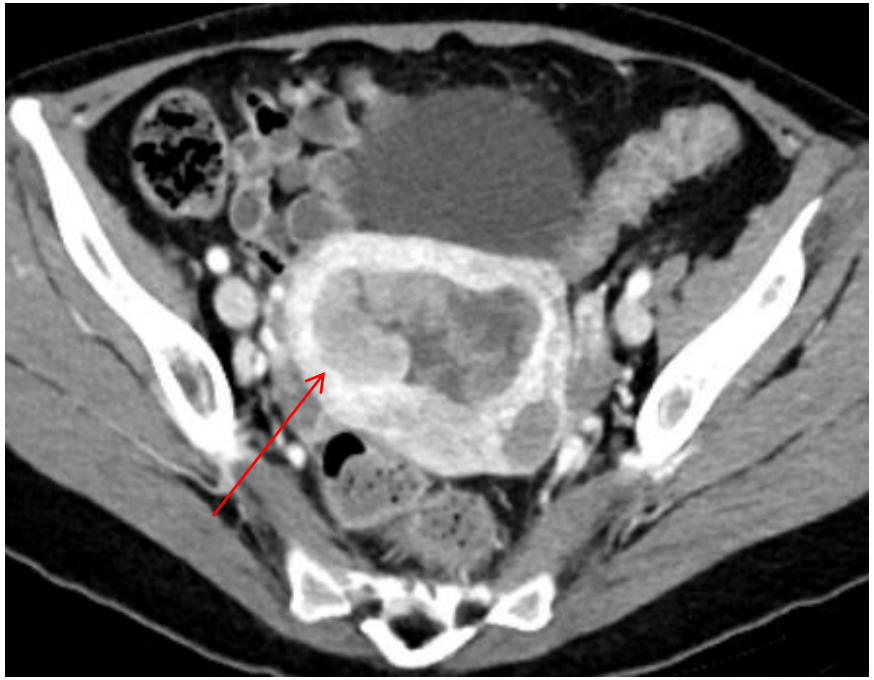
Workup & Evaluation

- Common presenting symptoms: Postmenopausal vaginal bleeding, menorrhagia, metrorrhagia, abdominal pain abdominal distension
- History and Physical
  - Physical exam should include inspection of external genitalia, vagina, cervix + pelvic exam, and rectal exam
- Labs: CBC (can consider LFT, renal function, chemistry profile)
- Imaging: Can consider Vaginal Ultrasound, CT c/a/p, Pelvic MRI, and PET
- Biopsy: Endometrial sampling (D&C if EMBx is negative)

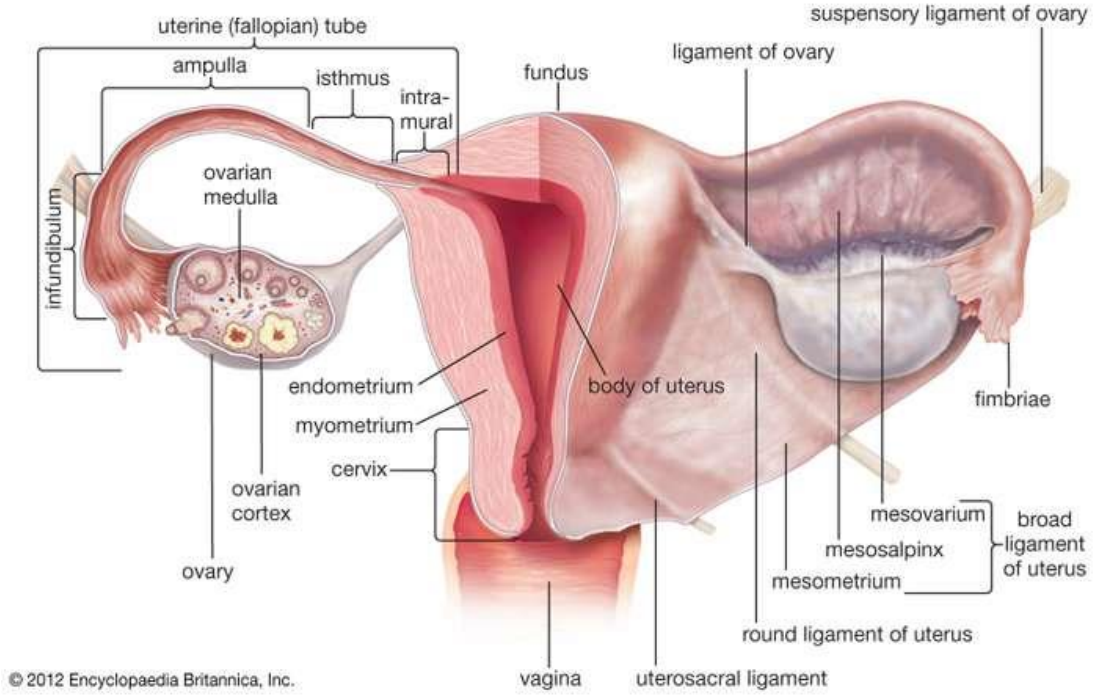
Case: Imaging



Pre-op CT of the pelvis: nodular enhancing masses centered in the endometrium with suspected myometrial invasion at > 50% in thickness on the right, concerning for invasive endometrial carcinoma



Anatomy


uterine (fallopian) tube
ampulla
isthmus
intra-mural
fundus
ligament of ovary
suspensory ligament of ovary
ovarian medulla
infundibulum
endometrium
myometrium
cervix
body of uterus
fimbriae
ovarian cortex
ovary
mesovarium
mesosalpinx
mesometrium
broad ligament of uterus
round ligament of uterus
vagina
uterosacral ligament
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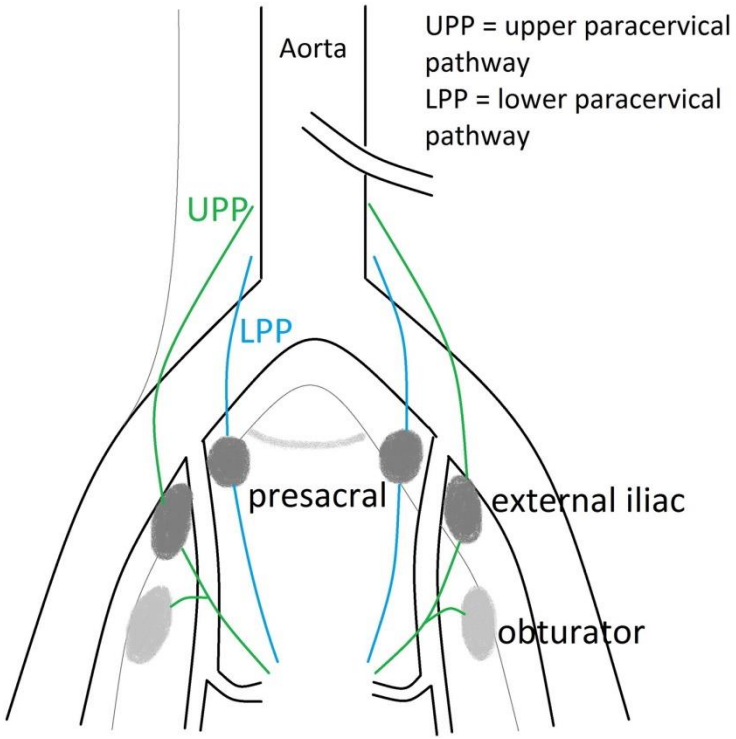

Aorta
UPP = upper paracervical pathway
LPP = lower paracervical pathway
UPP
LPP
presacral
external iliac
obturator

Staging

Current Staging as of 2009

Stage	Description
I	Tumor confined to the uterus
IA	<50% invasion of the myometrium
IB	≥50% invasion of the myometrium
II	Tumor invades the cervical stroma but does not extend beyond the uterus
III	Local or regional spread of tumor
IIIA	Serosal or adnexal invasion
IIIB	Vaginal or parametrial involvement
IIIC	Metastasis to pelvic or paraaortic lymph nodes
IIIC1	Pelvic lymph node involvement
IIIC2	Paraaortic lymph node involvement (with or without pelvic nodes)
IV	Extension to the pelvic wall, lower one-third of the vagina, or hydronephrosis or nonfunctioning kidney
IVA	Invasion of bladder or bowel mucosa
IVB	Distant metastases, including abdominal, or involvement of inguinal lymph nodes

Prior Staging from 1989

Stage

IA G123 Tumour limited to endometrium
IB G123 Invasion to <1/2 myometrium
IC G123 Invasion to >1/2 myometrium
IIA G123 Endocervical glandular involvement only
IIB G123 Cervical stromal invasion

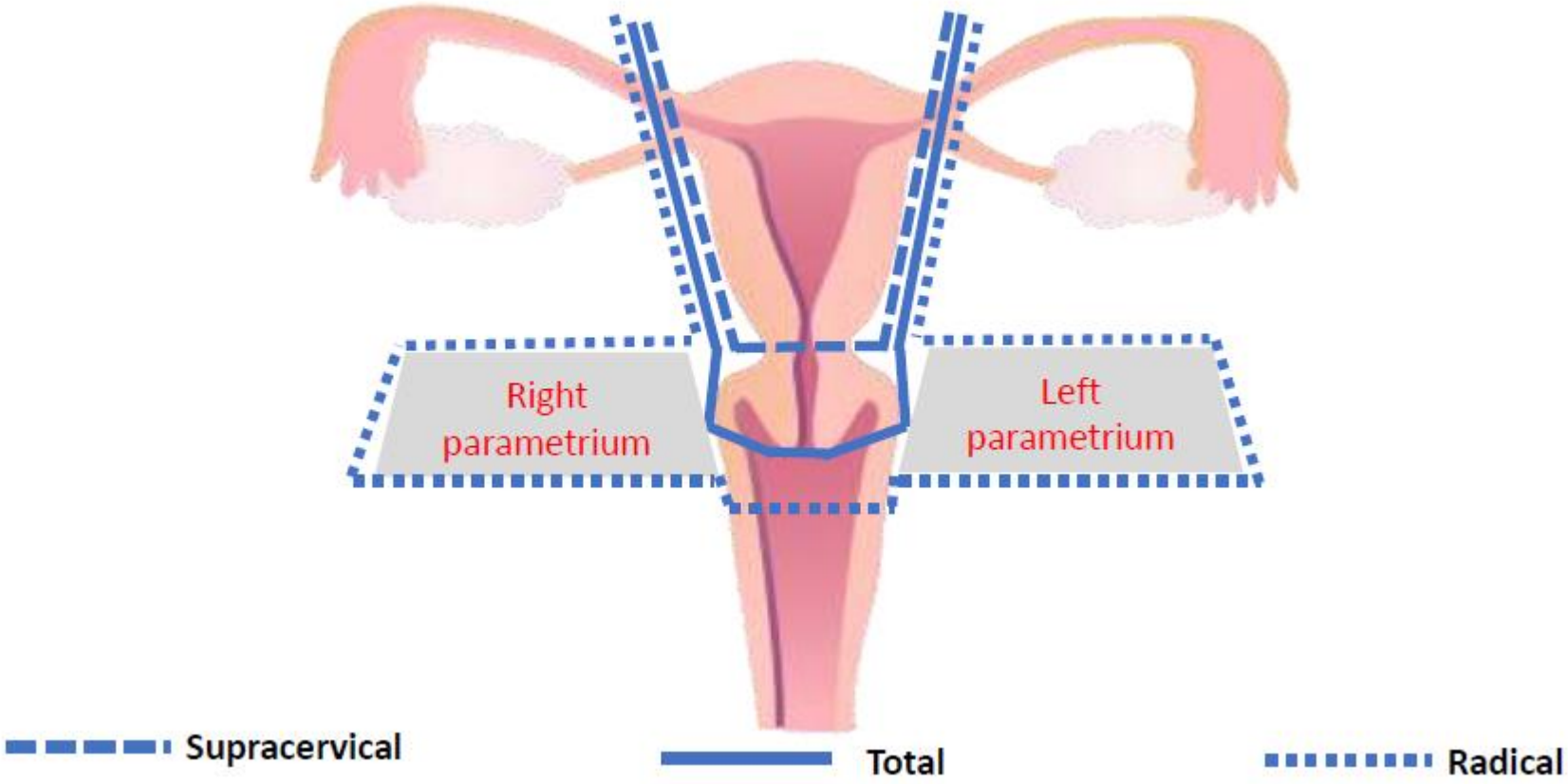
IIIA G123 Tumour invades serosa and/or adnexa and/or positive peritoneal cytology
IIIB G123 Metastases to pelvic and/or paraaortic lymph nodes
IVA G123 Tumour invasion of bladder and/or bowel mucosa
IVB Distant metastases including intra-abdominal and/or inguinal lymph nodes

Surgical Management

- TAH/BSO for apparent stage I disease
- Radical Hysterectomy for gross cervical invasion/uncertainty of endocervical vs endometrial
- Omental and peritoneal biopsies for high-risk disease
- Variable recs for surgical LN evaluation
  - SLNB slowly becoming standard of care

Surgical Management

Types of hysterectomy



Case: Path Findings

- Patient underwent robot assisted TAH/BSO/SLNB
- Path: endometrioid carcinoma, 6 cm in greatest dimension, FIGO grade 3, 72% myometrial invasion, LVSI -, no cervical stromal involvement, margins negative, 0/3 LN
- Final stage: **FIGO stage IB (pT1bN0M0) endometrioid adenocarcinoma**

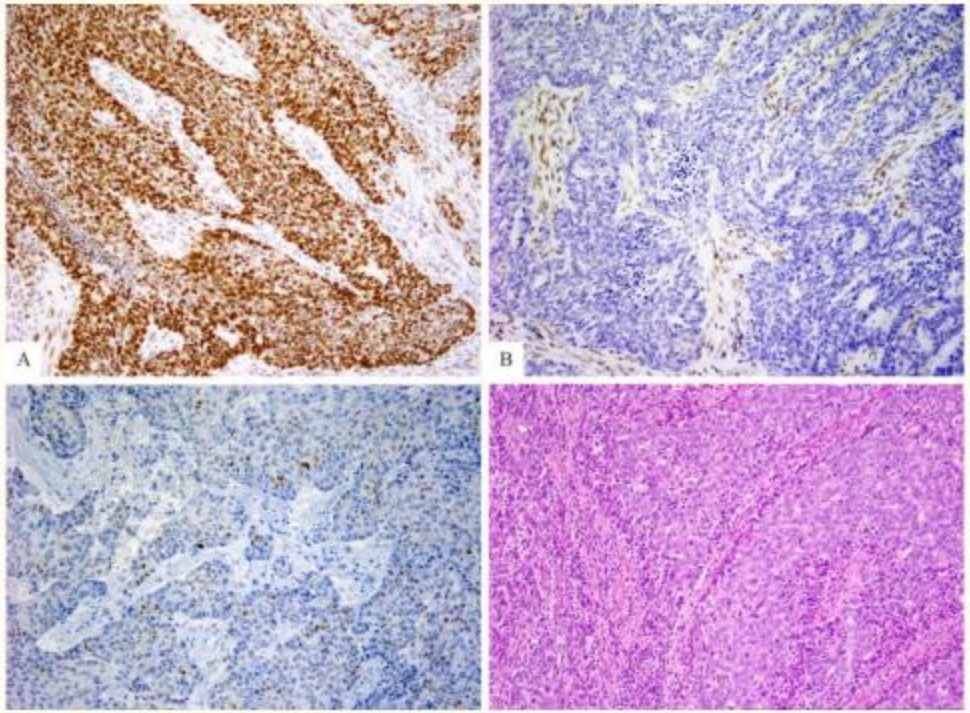


Figure 1

Use of immunohistochemistry for molecular subgroup assignment (A) FIGO grade 3 endometrioid carcinoma with p53 overexpression (p53abn subgroup). (B) FIGO grade 3 endometrioid carcinoma with loss of MLH1 expression (MMRd subgroup). (C) FIGO grade 3 endometrioid carcinoma with normal expression p53 staining, no DNA MMR abnormalities (not shown) and no POLE hotspot mutation (NSMP subgroup). (D) FIGO grade 3 endometrioid carcinoma lacking immunohistochemical abnormalities. *POLE* hotspot mutation identified (*POLE* subgroup).

Adjuvant Treatment Recs

High-Intermediate Risk

- Stage IA, grade I or II, endometrioid histology, no LVSI = consider observation
- Stage IA, grade III or stage IB, grade I-II = consider vaginal cuff brachytherapy
- **Stage IB, grade III = pelvic EBRT**
- Stage II = pelvic EBRT + vaginal cuff brachy boost
- Stage III-IV = definitive or adjuvant chemoRT, chemo alone, or RT alone +/- brachy

High-Intermediate Risk

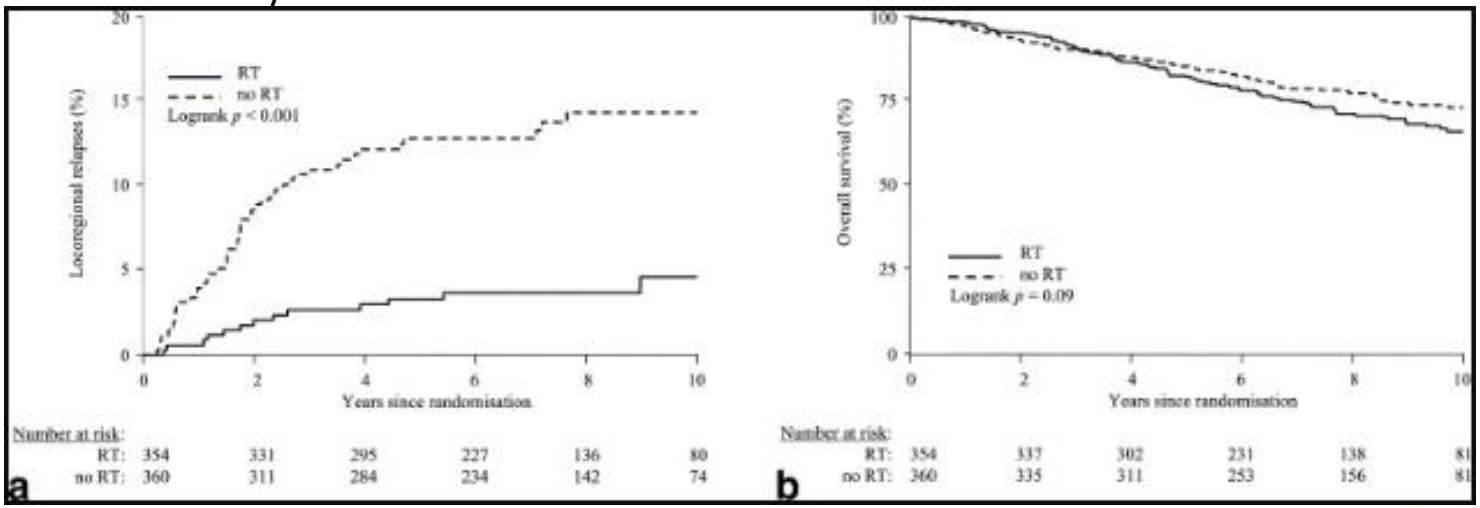
High-Intermediate Risk are stage I endometrial cancer patients who require adjuvant treatment

Common risk factors include:

- GOG99 HIR: age ≥70 with 1 risk factor, ≥50 with 2 risk factors, or any age with 3 risk factors. **Factors are grade 2-3, LVI, or IC**
- PORTEC-1: HIR group requires 2/3 factors: **age >60, invasion >50%, and/or grade 3**
- PORTEC-2: HIR: **age >60 and IC grade 1-2, or IB grade 3. Stage IIA any age, (grade 3 and >1/2 invasion excluded)**
- GOG249: HIR defined as: age ≥70 + 1 risk factor, age ≥50 + 2 risk factors, age ≥18 + 3 factors. Risk factors: **grade 2 or 3, LVSI, >50% myometrium**

Support for Adjuvant Recommendations

- Stage IA, grade I or II, endometrioid histology, no LVSI = <u>consider observation</u>
  - PORTEC-1: 715 pts, stage I (excluded stage IC with grade 3 and stage IB with grade 1), randomized to 46 Gy WPRT vs observation
    - 5 yr LRR 4% for WPRT vs 14% for obs
    - 5 yr LRR for HIR Group 4% for WPRT vs 23% for obs
    - **<u>10 yr OS of 66% for WPRT vs 73% for obs (p=0.09)</u>**
  - HIR Group requires 2 of following 3: age >60, invasion > 50% , or grade 3
  - **<u>Observation after surgery reasonable for low risk patients</u>**
  - Confirmed by GOG99

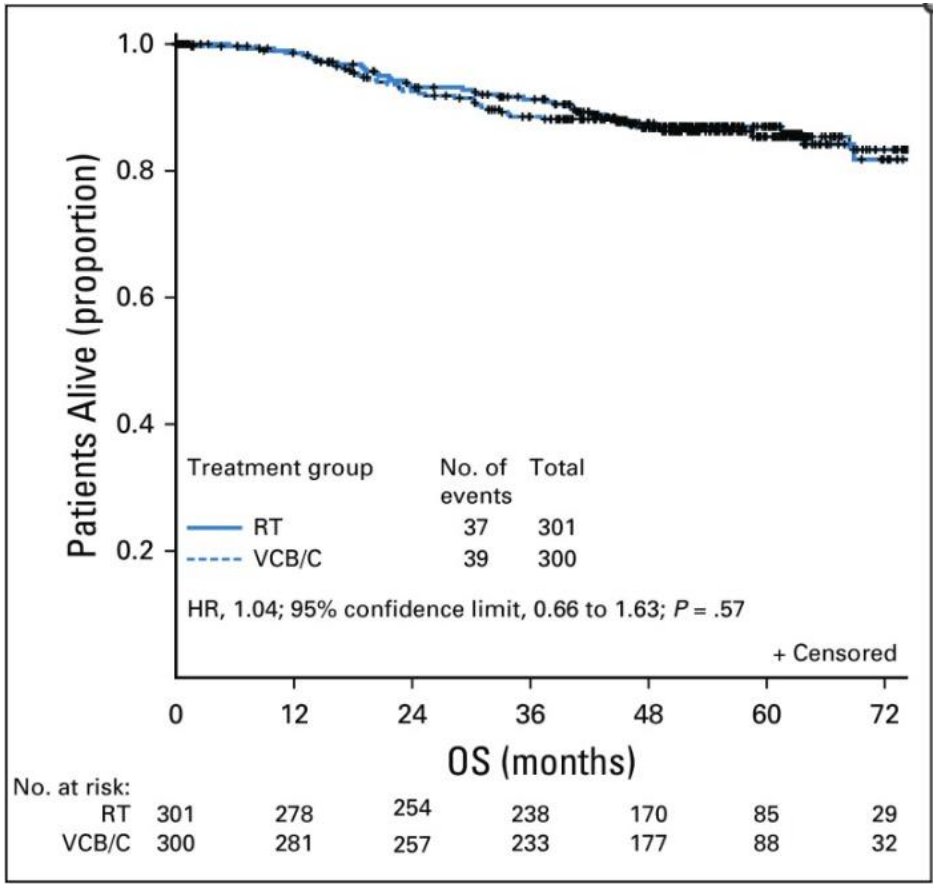


Support for Adjuvant Recommendations

- Stage IA, grade III or stage IB, grade I-II = <u>consider vaginal cuff brachytherapy</u>
  - PORTEC-2: 427 pts, HIR stage I and stage IIA (excluded grade 3 with greater than 50% invasion), randomized to 46 Gy WPRT vs vaginal cuff brachy 7 Gy x 3 HDR or 30 Gy LDR
  - 5 yr vaginal recurrence 1.6% WPRT vs 1.8% VCB
  - 5 yr pelvic recurrence 0.5% vs 3.8%
  - 5 yr OS 85% WPRT vs 80% VCB (NS)
  - Vaginal cuff brachy had lower rates of grade 1&2 GI toxicity
  - **<u>Vaginal cuff brachy non-inferior to WPRT on this study</u>**

Support for Adjuvant Recommendations

- Stage IB, grade III - Stage II = **pelvic EBRT +/- vaginal cuff brachy boost**
  - GOG249: 601 pts, stage I HIR, stage II (included serous or clear cell histology), randomized to WPRT (+ VCB boost for stage II) vs VCB then 3 cycles carbo/paclitaxel
    - **5 yr OS of 87% for WPRT vs 85% for VCB + CHT (NS)**
    - 5 yr RFS of 76% in both arms
    - Higher pelvic and para-aortic node failures with VCB + CHT (4% vs 9%)
    - **Increased acute toxicity with VCB + CHT**

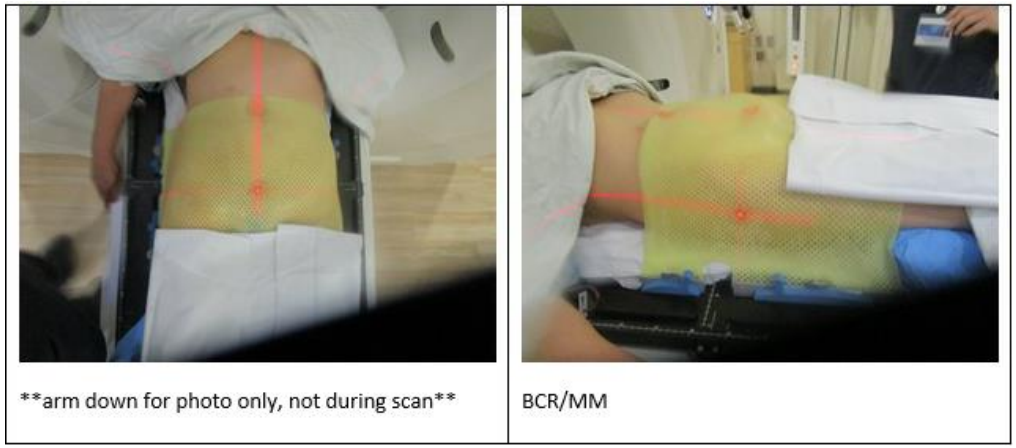


Case: Treatment Recommendations

- Patient's High-Intermediate risk factors included grade 3 disease and >50% myometrial invasion (See slide 12)
- Recommended adjuvant radiation to 45 Gy in 25 fx with SIB boost to vaginal CTV to 50 Gy in 25 fx (Boost without cervical stromal involvement is controversial)

Radiation Simulation

- Position: Supine with arms up or on chest
  - CT with IV contrast
  - Full and empty bladder scans
  - Consider:
    - pelvic thermoplastic mask and/or Vac-lok device
    - fiducial markers at vaginal apex
    - rectal balloon
    - Vaginal contrast



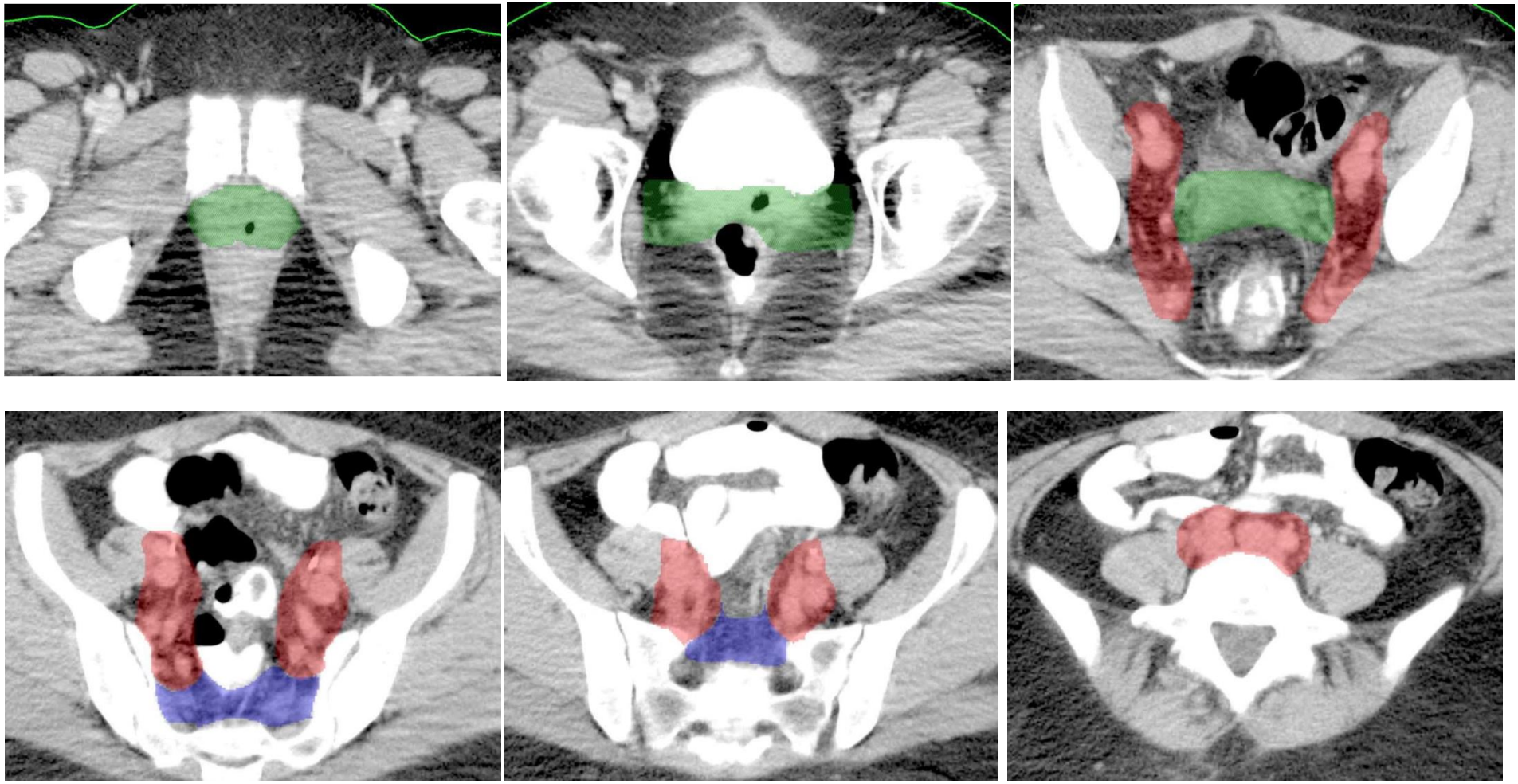
arm down for photo only, not during scan

BCR/MM

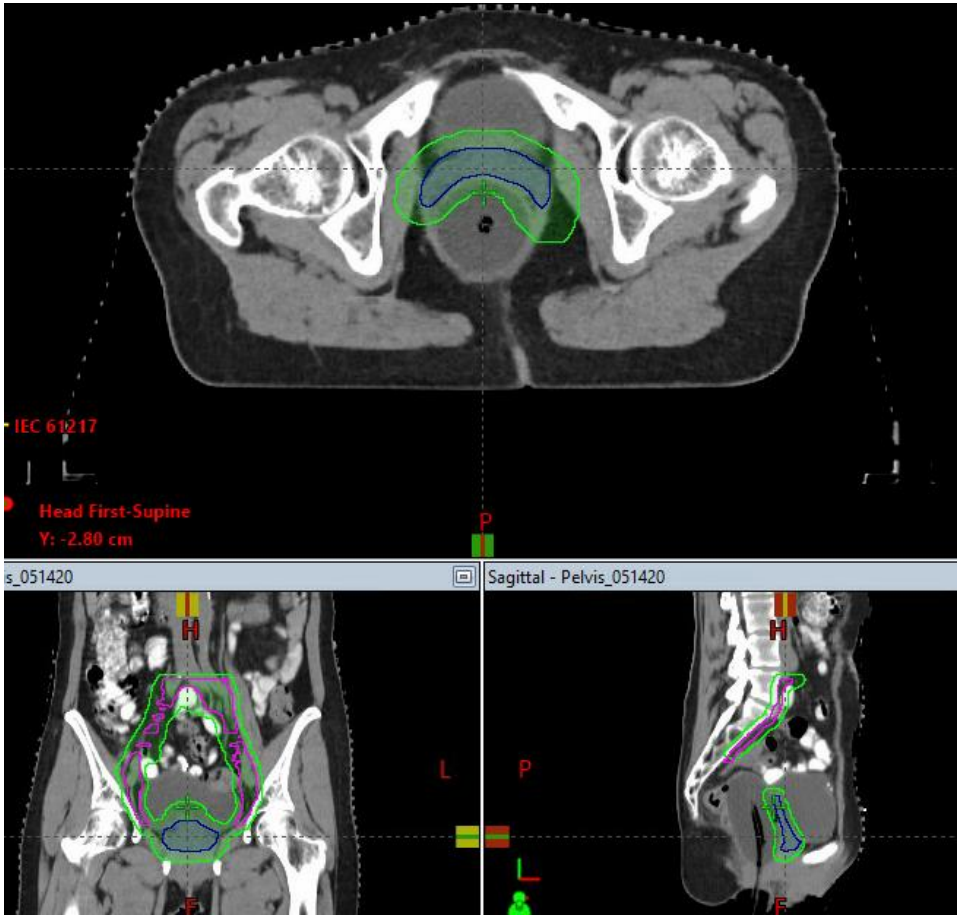
Radiation Contouring

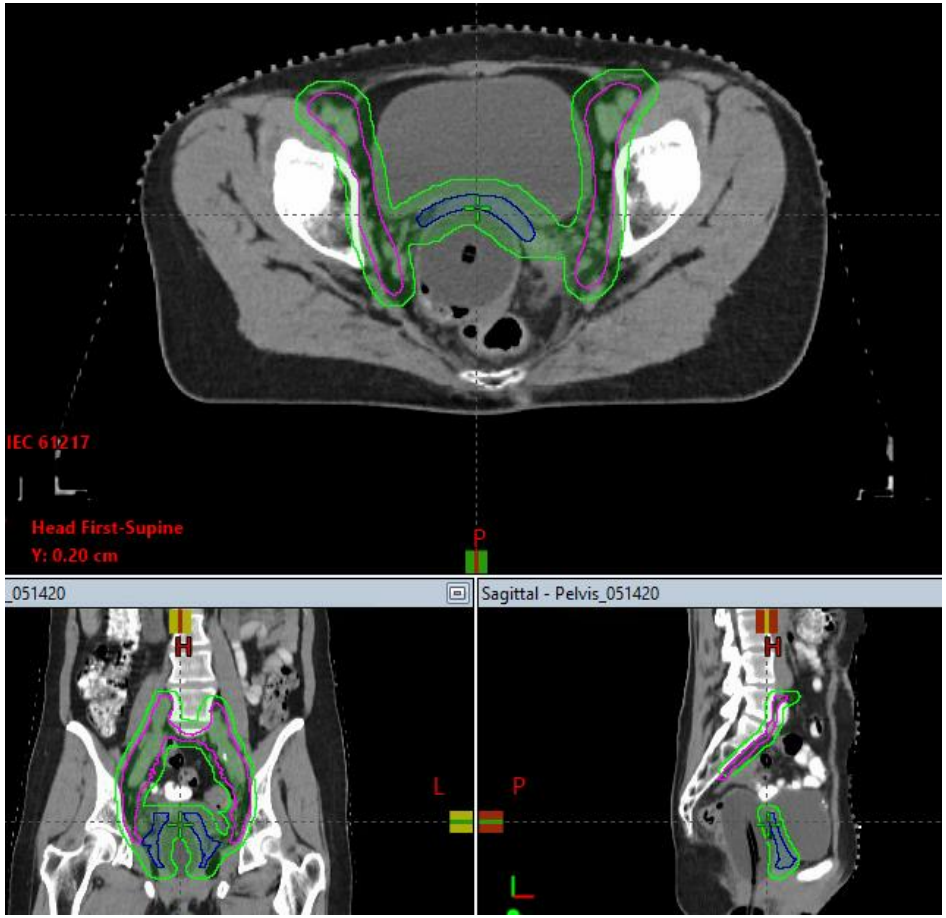
- CTV vagina/paravaginal
  - Upper 4.0 cm of vagina or to mid obturator foramen + paravaginal soft tissue lat to vagina
- ITV vagina/paravaginal
  - Merged CTV vagina from full and empty bladder scans, rectal balloon improves immobilization
- CTV lymph nodes
  - 0.7 cm margin around internal (hypogastric/obturator), external and common iliac nodes
  - presacral(1-2 cm anterior to S1-3) always should be included for patients with cervix involvement
- PTV total
  - Additional 0.5-0.7 cm margin from ITV and CTV nodal volume

Contouring: Consensus Guidelines



Case Contours





Green = combined vaginal and LN PTV to 4500 cGy,
Magenta = CTV LN to 4500 cGy, Blue = CTV vaginal/paravaginal to 5000 cGy

Radiation Technique

- Post-operative RT with IMRT/VMAT
- Prescription
  - 45 Gy in 1.8 Gy/fraction to PTV lymph node
  - SIB boost to 50 Gy in 2 Gy/fraction to PTV vagina
- 50.4 Gy in 1.8 Gy fractions is also an option

Key Dose Constraints

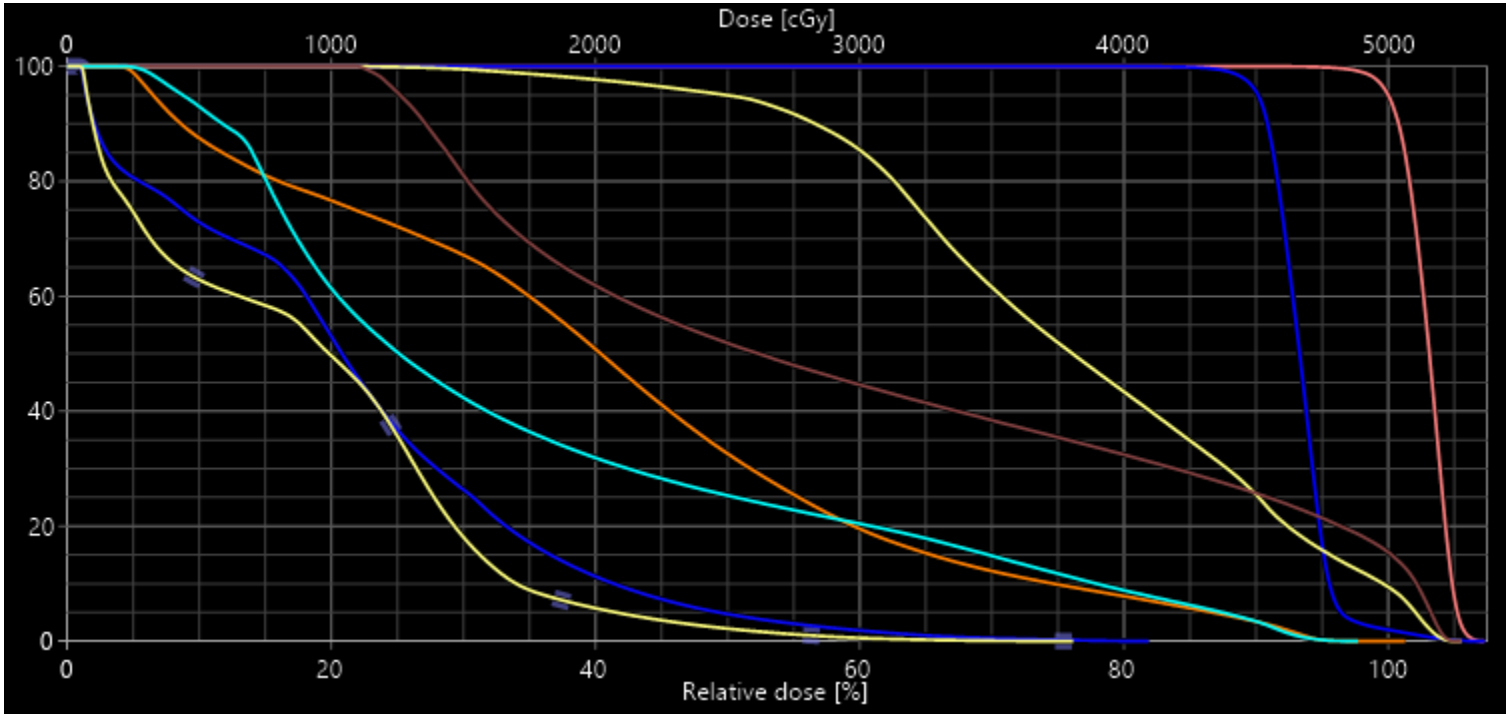
- Per RTOG 0418
  - Small bowel <30% to receive ≥ 40 Gy
  - Rectum <60% to receive ≥ 30 Gy, minor deviation 35% to 50 Gy
  - Bladder <35% to receive ≥ 45 Gy, minor deviation 35% to 50 Gy
  - Femoral heads ≤ 15% to receive ≥ 30 Gy, minor deviation 20% to 30 Gy

Key Dose Constraints

- QUANTEC

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)[†]	Endpoint	Dose (Gy), or dose/volume parameters[†]	Rate (%)	Notes on dose/volume parameters
Rectum	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V50 <50%	<15 <10	Prostate cancer treatment
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V60 <35%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V65 <25%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V70 <20%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V75 <15%	<15 <10	
Bladder	Whole organ	3D-CRT	Grade ≥ 3 late RTOG	Dmax <65	<6	Bladder cancer treatment. Variations in bladder size/shape/ location during RT hamper ability to generate accurate data
	Whole organ	3D-CRT	Grade ≥3 late RTOG	V65 ≤50 % V70 ≤35 % V75 ≤25 % V80 ≤15 %		Prostate cancer treatment Based on current RTOG 0415 recommendation
Small bowel	Individual small bowel loops	3D-CRT	Grade ≥ 3 acute toxicity[§]	V15 <120 cc	<10	Volume based on segmentation of the individual loops of bowel, not the entire potential peritoneal space
	Entire potential space within peritoneal cavity	3D-CRT	Grade ≥ 3 acute toxicity[§]	V45 <195 cc	<10	Volume based on the entire potential space within the peritoneal cavity

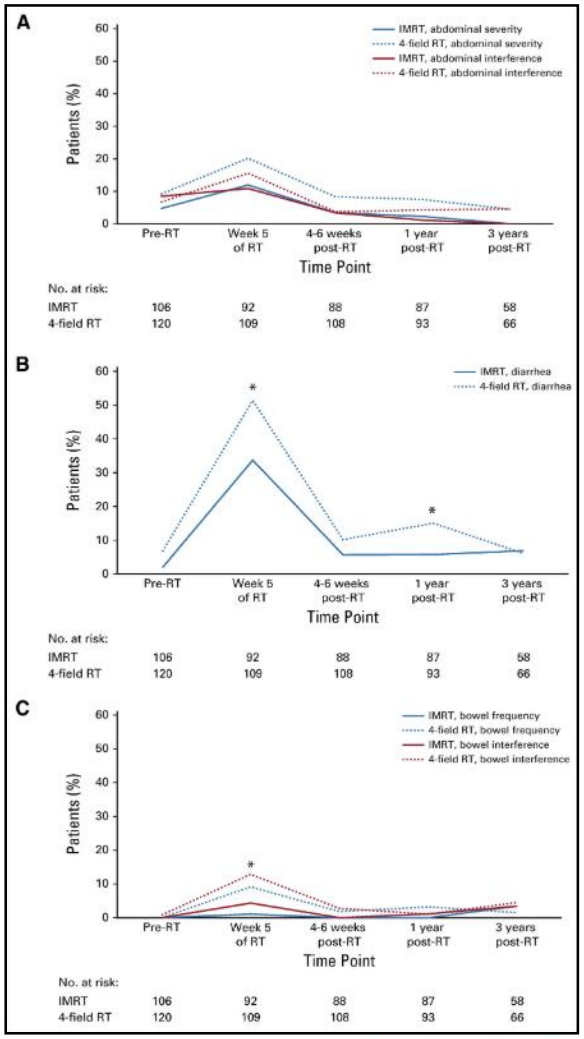
Case: Dose Volume Histogram



PTV Vagina
PTV LN
Bladder
Rectum
Large Bowel
Small Bowel
Right Femur
Left Femur

Acute & Late Side Effects

- RTOG 1203 (TIME-C): IMRT vs 3D Conformal
  - IMRT led to decrease in following patient reported events:
    - Diarrhea at 5 weeks (33.7% vs 51.9%, p=.01)
    - Fecal Incontinence at 5 weeks (1.1% vs 9.3%, p=.04)
    - Diarrhea at 1 yr (5.8% vs 15.1%, p=0.4)
    - Antidiarrheal medication at 1 yr (4.6% vs 13%, p=.03)



Treatment Side Effects

- Acute:
  - Diarrhea
  - Abdominal pain
  - Fatigue
  - Dysuria
  - Urinary frequency
  - Myeolosuppression
- Late:
  - Vaginal stenosis
  - Vaginal dryness
  - Rare incidences of cystitis, proctitis, sacral insufficiency fractures, bowel obstruction, fistula

Follow-up

- Physical Exam every 3-6 months for 2-3 yrs then every 6 months for 5 years then annually
- Imaging as clinically indicated
- Patient education including sexual health and use of dilator and lubricants
  - Dilator use recommendations vary, consider 1-3 x week for 10 minutes, can be less frequent if sexually active

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