Management of Radiation Toxicities - Pelvis

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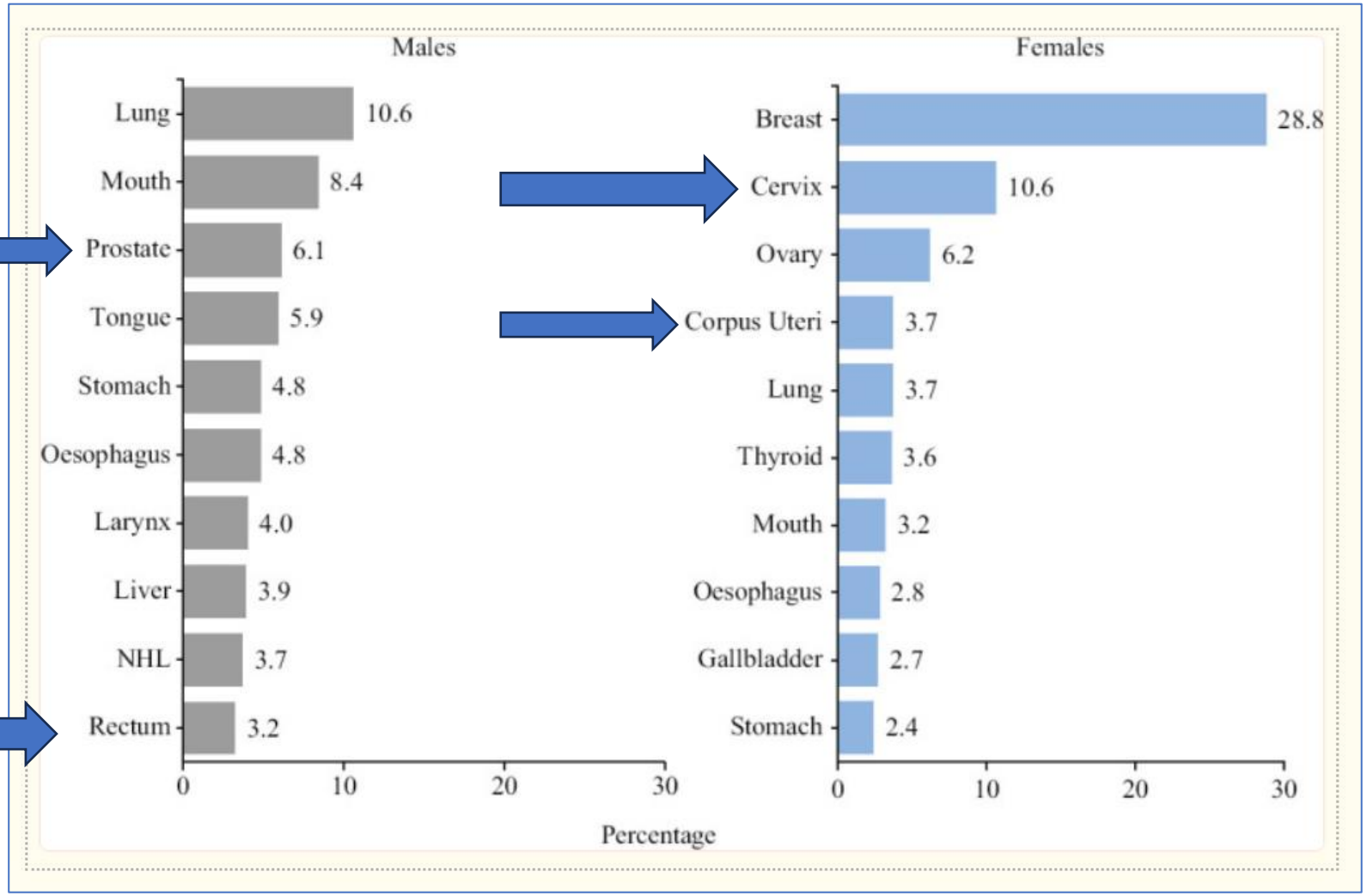
RTOG and EORTC

- Radiation toxicity
  - Acute - within the first 3 months after treatment
  - Late - occurs after 3 months.

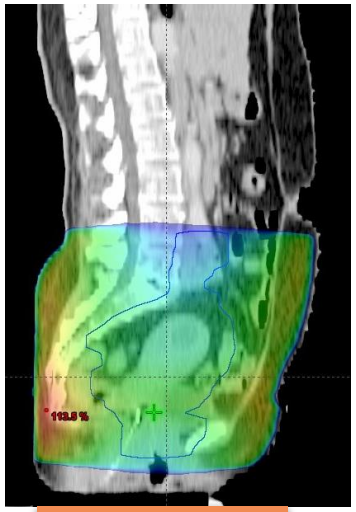
Estimated proportion of top 10 leading sites of cancer in India by sex – 2022



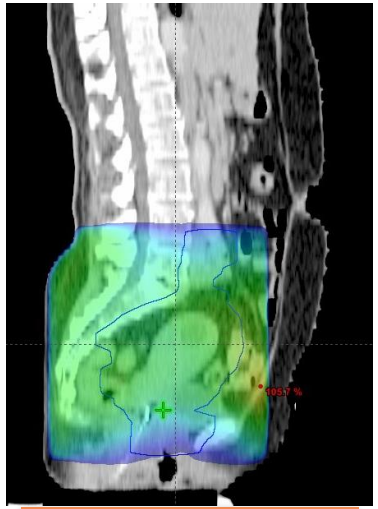
- With ⇧ in cancer survival, app. 20%–25% of pts develop chronic toxicities, affecting their quality of life.

- Overall, 50% of patients report that their GI symptoms affect their quality of life and 20%–40% say that this effect is moderate or severe. *Andreyev et al. Algorithm-based management of patients with gastrointestinal symptoms in patients after pelvic radiationtreatment (ORBIT): a randomised controlled trial. Lancet 2013*.

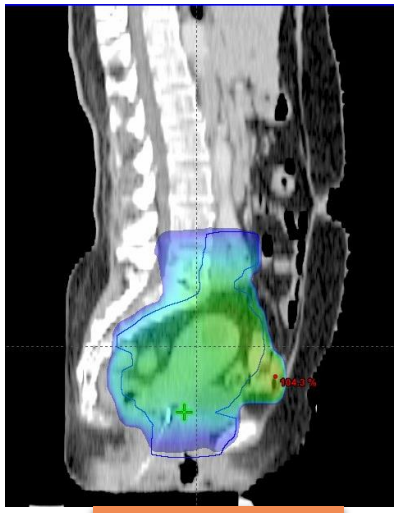
- Acute radiation proctitis - 2% to 39% with EBRT.
- Pts who develop acute radiation proctitis are more likely to develop chronic changes.
- The incidence of chronic radiation changes previously as high as 30%, but with recent advances in radiation techniques, estimates are only 1%–5%.



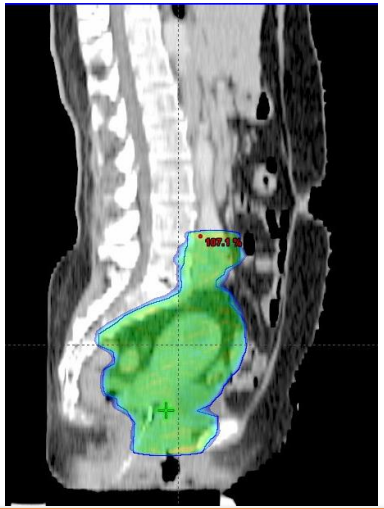
2D RT



4 FIELD RT



3DCRT



IMRT

ADVANTAGES OF MODERN RT TECHNIQUES

01

Reduction in acute bowel toxicity

02

Reduction in acute hematological toxicity

03

Reduction in long term anortectal, GI and GU dysfunction

04

Escalation of dose to nodes

05

For extended field RT

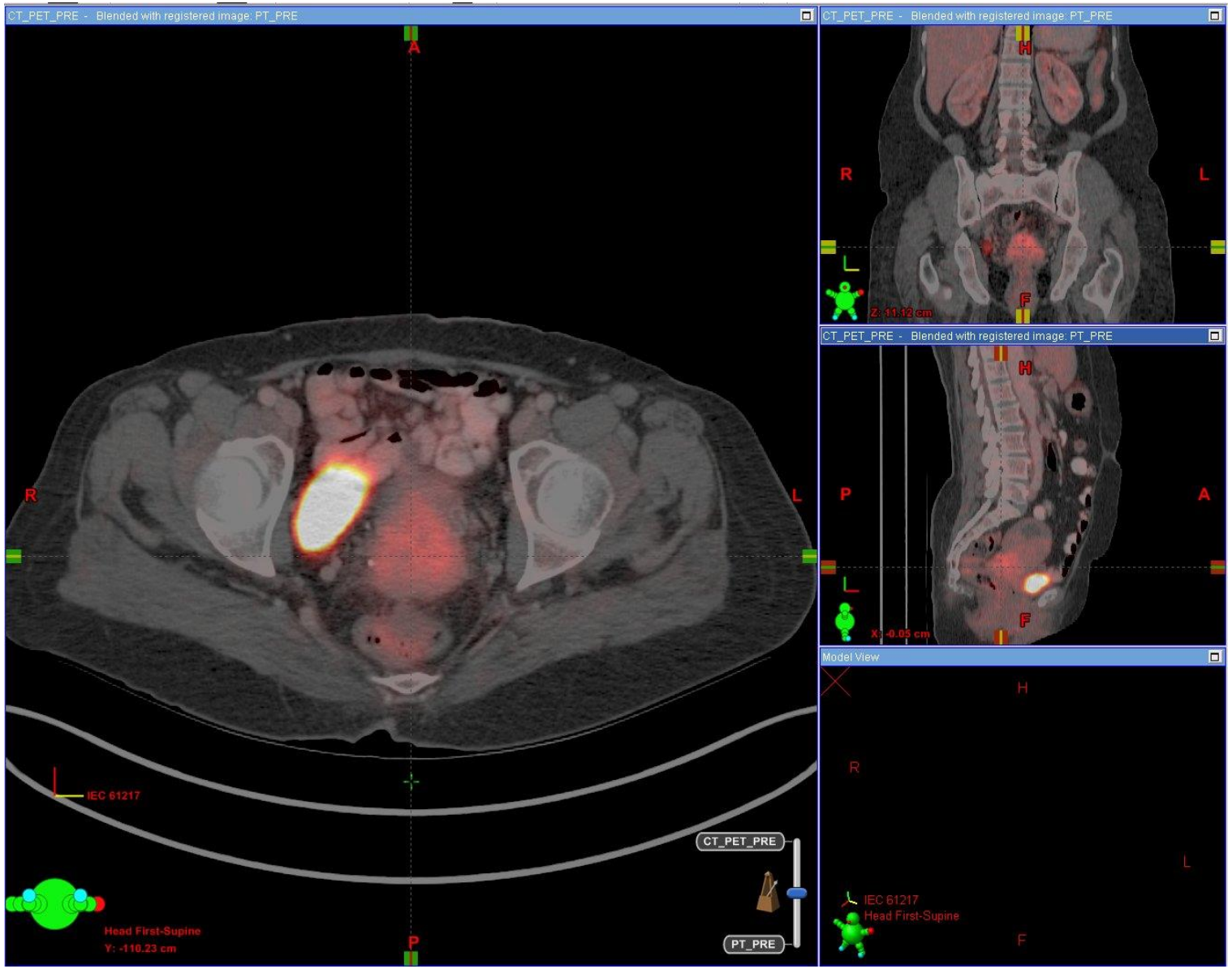
- A RCT evaluated the toxicity - locally advanced cervical cancer who received either whole-pelvis RT by 3DCRT or IMRT at a dose of 50.4 Gy in 28 fractions administered with concurrent cisplatin 40 mg/m2 followed by HDR intracavitary RT.

TOXICITY	3DCRT	IMRT	P
GRADE 2 GI	63.6%	31.8%	0.034
GRADE 3 GI	27.3%	4.5%	0.47
CHRONIC GI	50%	13.6%	0.011

- Dosimetric comparison demonstrated significantly less dose to the rectum and small bowel in IMRT as compared to 3DCRT.

Gandhi AK, et al. Int J Radiat Oncol Biol Phys. 2013;87:542-548.

CASE – D.A

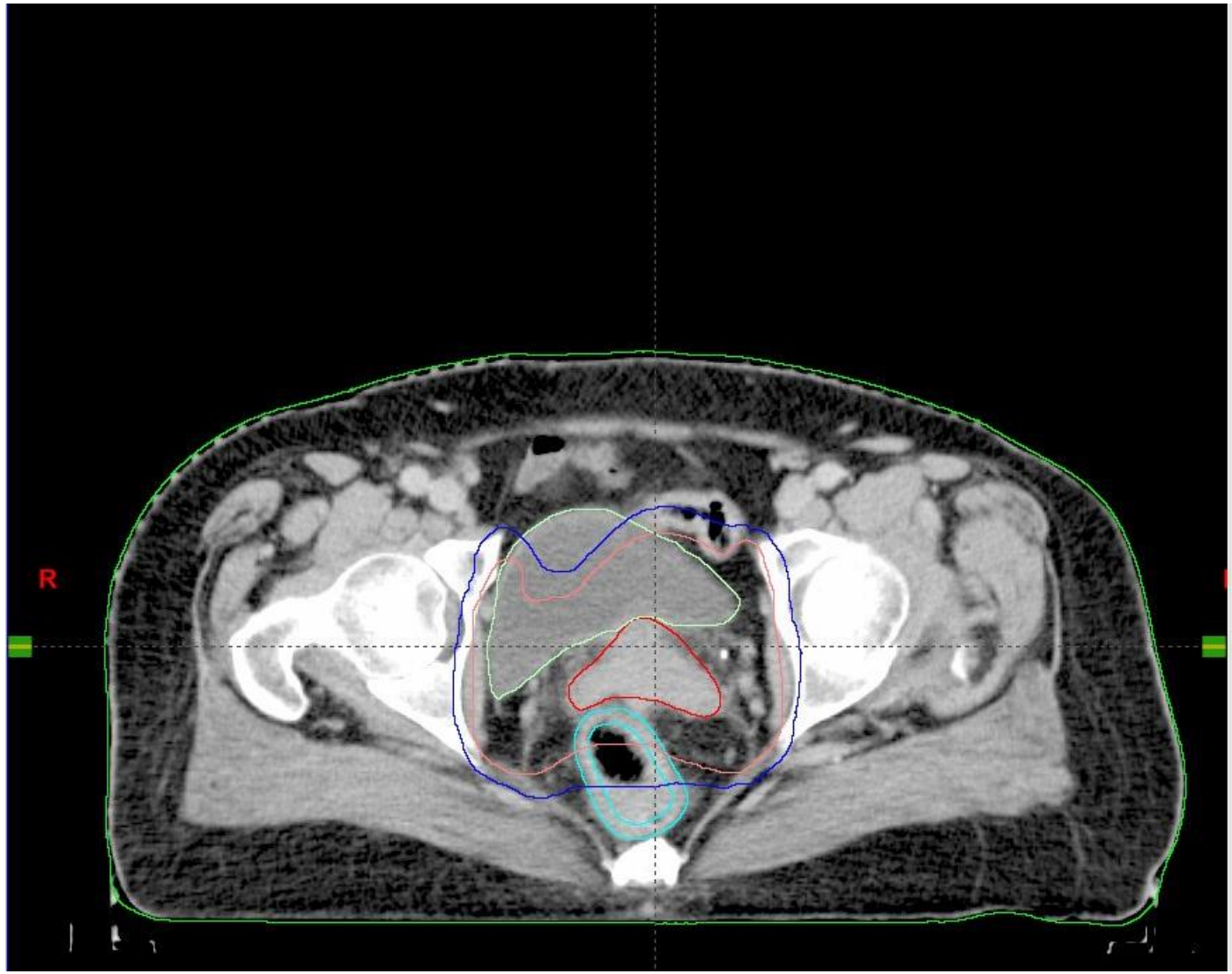


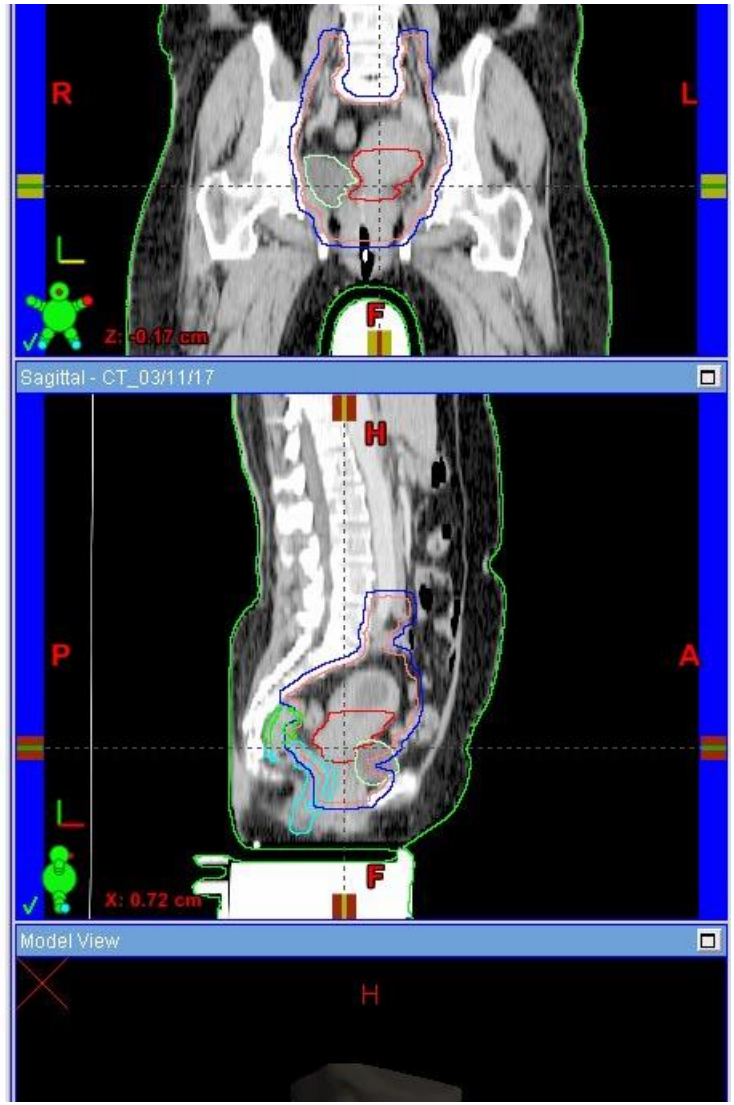
63 yr old female investigated for post menopausal bleeding of 6 mths duration

PET CT SCAN – showed a PET avid mass in cervix with no lymphadenopathy

HPR - M.D, Squamous cell carcinoma

Diagnosis - STAGE II B


R


R
L
L
F
Z: -0.17 cm
Sagittal - CT_03/11/17
H
P
A
L
F
X: 0.72 cm
Model View
H

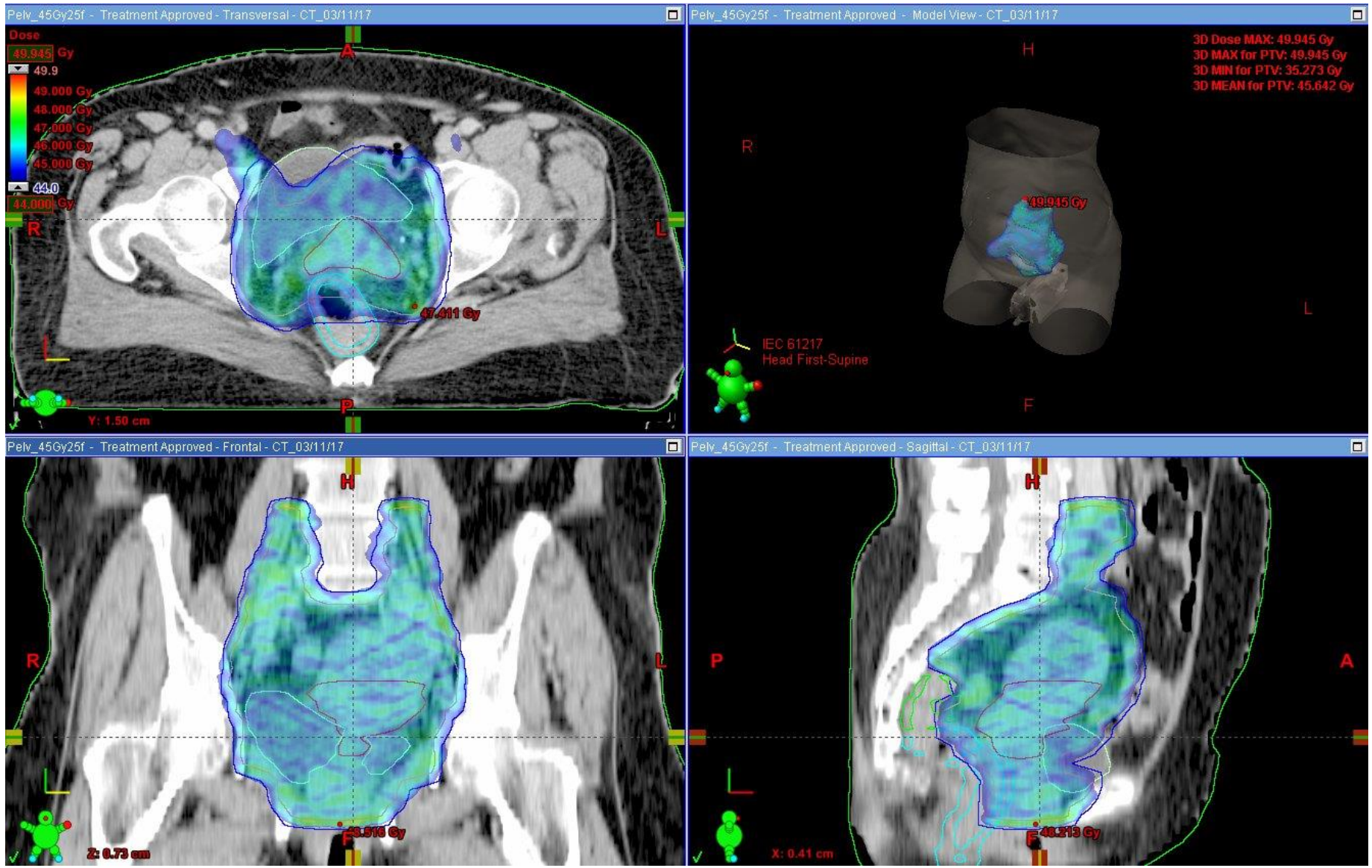

Pelv_45Gy25f - Treatment Approved - Transversal - CT_03/11/17
Dose
49.945 Gy
49.9
49.000 Gy
48.000 Gy
47.000 Gy
46.000 Gy
45.000 Gy
44.0
44.000 Gy
A
R
L
P
47.411 Gy
Y: 1.50 cm
Pelv_45Gy25f - Treatment Approved - Model View - CT_03/11/17
3D Dose MAX: 49.945 Gy
3D MAX for PTV: 49.945 Gy
3D MIN for PTV: 35.273 Gy
3D MEAN for PTV: 45.642 Gy
H
R
L
F
49.945 Gy
IEC 61217
Head First-Supine
Pelv_45Gy25f - Treatment Approved - Frontal - CT_03/11/17
H
R
L
F
Z: 0.73 cm
Pelv_45Gy25f - Treatment Approved - Sagittal - CT_03/11/17
H
P
A
F
X: 0.41 cm

IMAGE GUIDANCE - IGRT

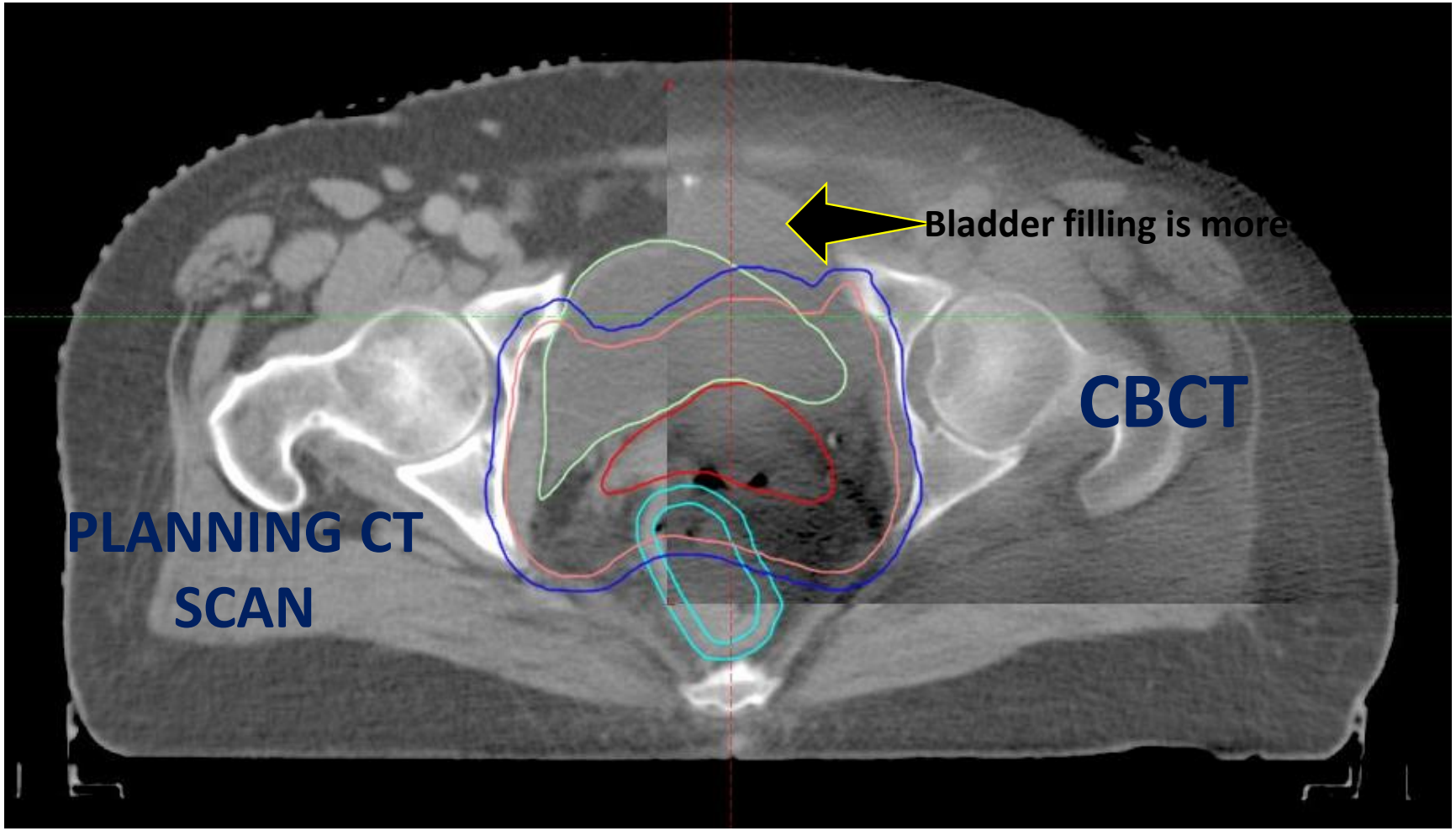
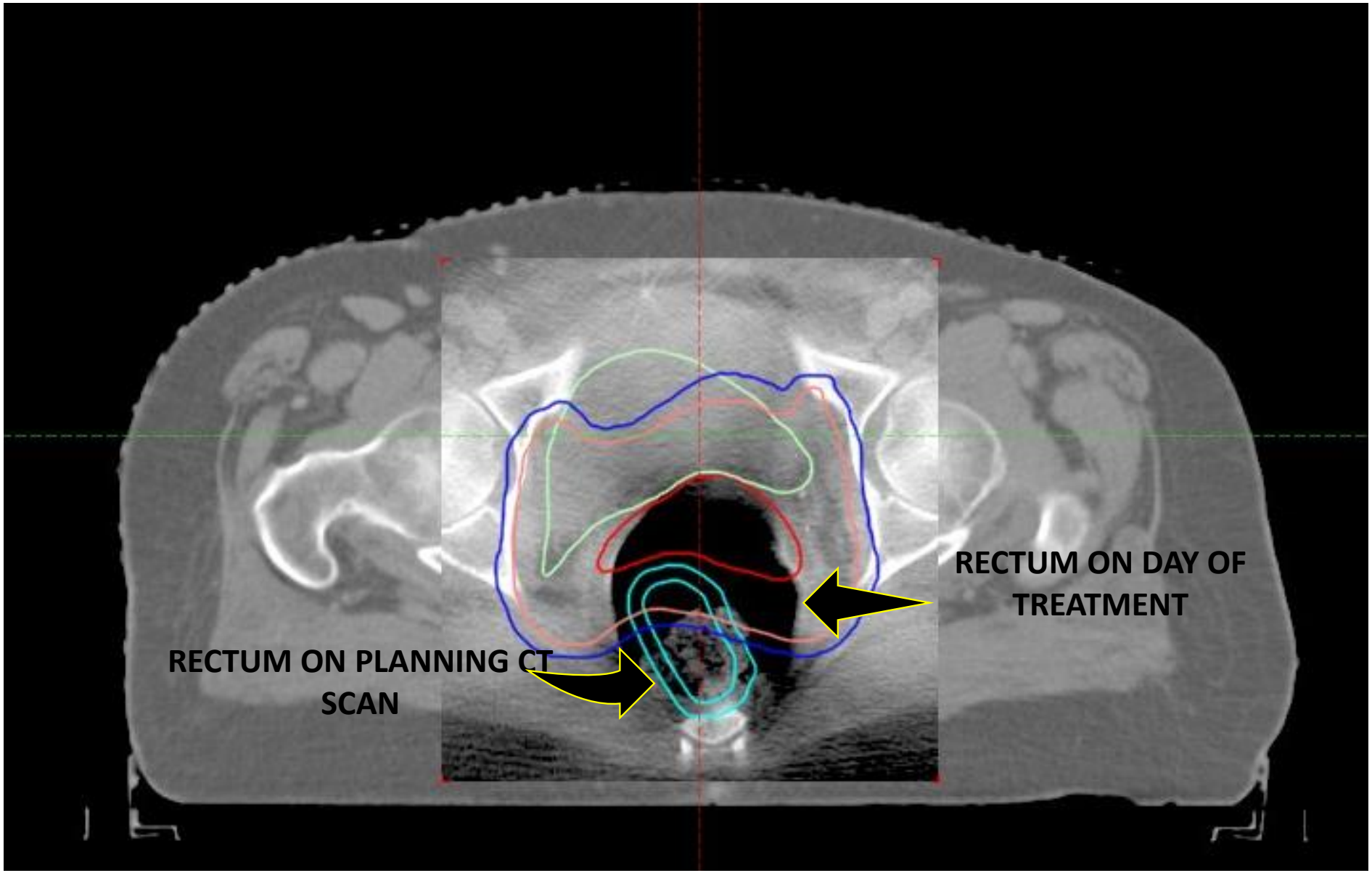
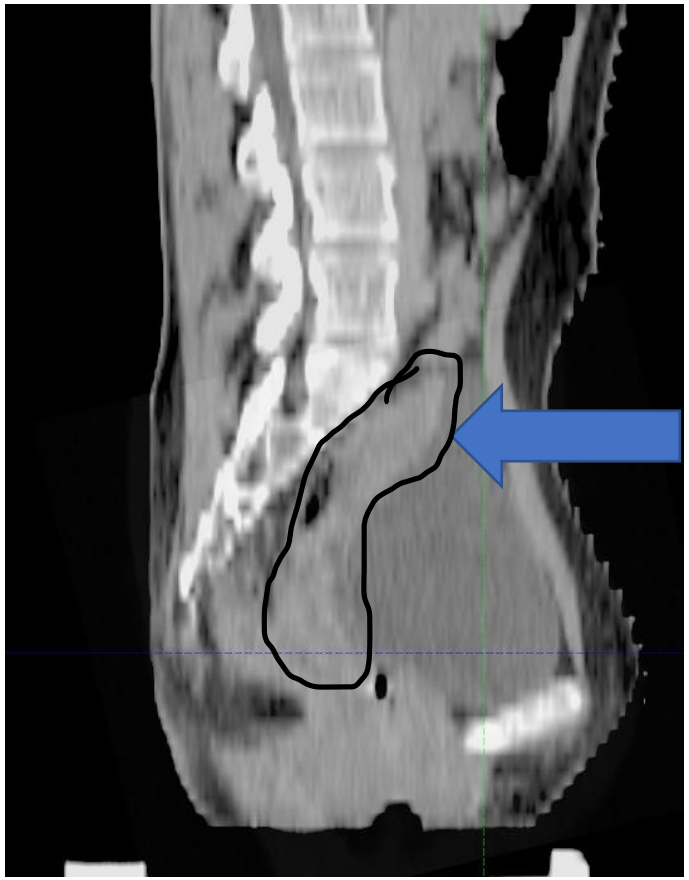
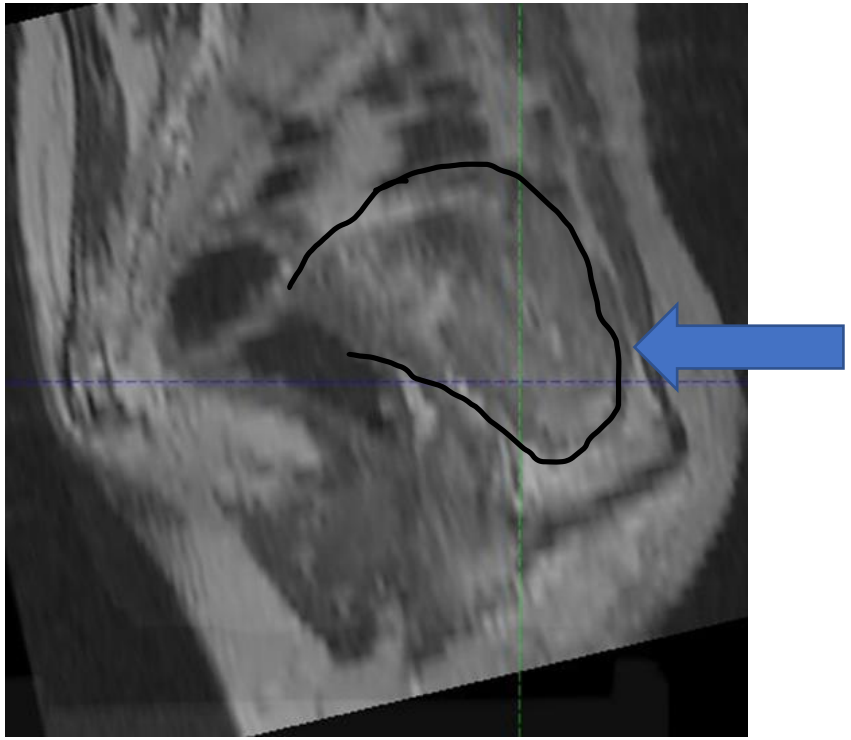


IMAGE GUIDANCE - IGRT





EFFECT OF BLADDER FILLING ON UTERUS\CERVIX



Factors associated with toxicity

Patient-related factors

- coexisting comorbidities
  - prior pelvic inflammatory disease
  - vascular disease because of diabetes or arteriosclerosis
  - CVD
  - IBD
- smoking history
- Low BMI < 22
- The use of anticoagulants -lead to higher rates of post-treatment bleeding

Treatment-related Factors

- Prior abdominal/pelvic surgery - increased risk of developing bowel obstructions
- Pts. who receive >50 Gray (Gy) of RT to the pelvis - lead to adhesions, which limit intestinal displacement
- cumulative radiation dose, treatment volume, radiation modality (EBRT, brachytherapy or both)

Toxicities associated with pelvic RT

- GI
- GU
- Sexual
- Hematological
- Bone
- Dermatological

GI toxicity

Patho-physiology

- Acute GI toxicity - is a response from therapy leading to epithelial inflammation. The symptoms –
  - self-limiting
  - improves with cessation of additional radiation
  - mitigated with medications or endoscopic therapies
- Late toxicity - Radiation proctitis/enteritis are misleading (improper treatment), because the injury is actually mediated by small vessel ischemia and not only by mucosal inflammation.
- Current management - stepwise escalation from medical Rx to endoscopic to surgical methods.

Acute toxicities - GI

TOXICITY	SYMPTOMS	DIAGNOSIS	TREATMENT
Enteritis	Diarrhea, tenesmus, mucus	If severe, CT; Consider C. diff testing	➢ Frequent loose stools, not watery: encourage oral fluids, probotics, low fiber diet ➢ for diarrhea– probiotics, racedrotil, Imodium/lomotil, check electrolytes, consider IV fluids ➢ for diarrhea (refractory)- Antibiotics, regular IV fluids, consider hospitalization
Proctitis	Rectal bleeding	Sigmoidoscopy or anoscopy	sucralfate enemas, 5-aminosalicylic acid, steroid enemas
Hemorrhoids		Physical examination with visual inspection	lidocaine topically; oral pain regimen, sitz bath

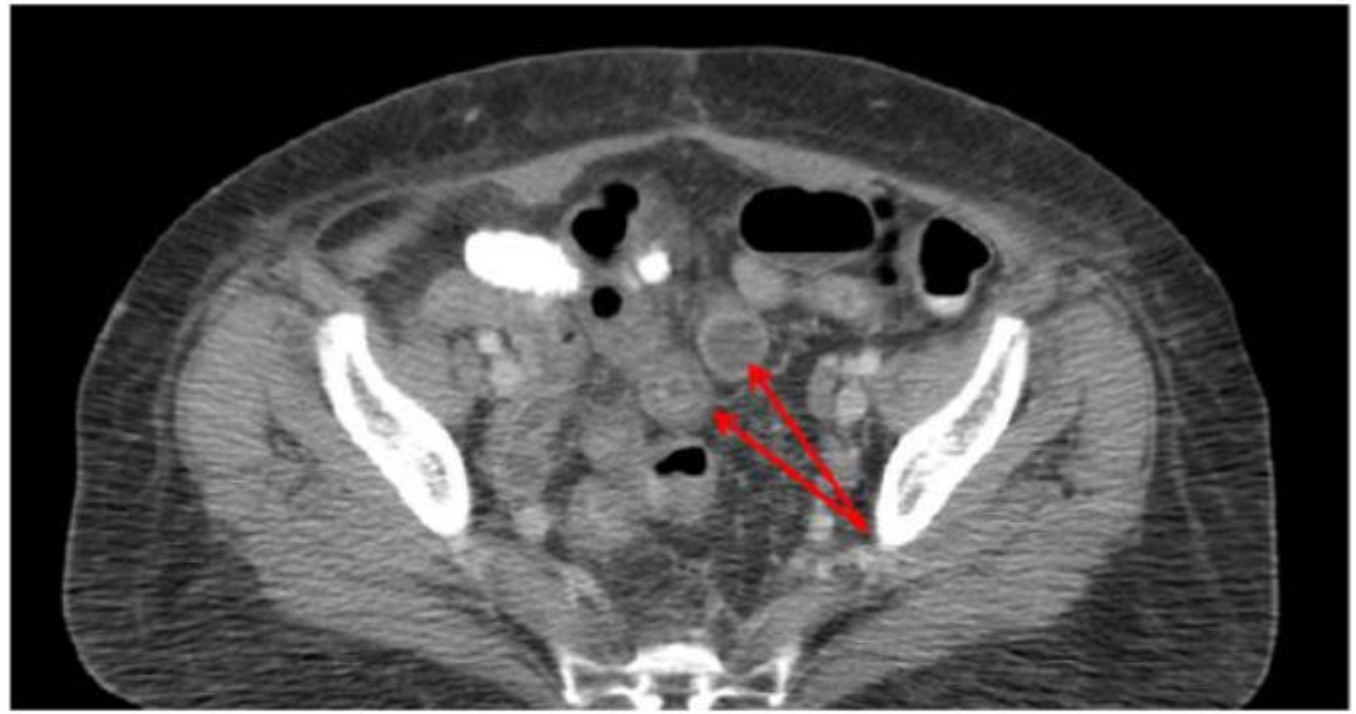


Figure 1. Acute radiation enteritis manifests as diffuse thickening, hyperemia, and hyper-enhancement (red arrows) of the small bowel wall in the pelvis on computerized tomography imaging.

Diagnosis of Chronic Radiation Proctitis

- Chronic radiation proctitis - as a diagnosis of exclusion
- Clinicians must rule out other common causes :
  - *inflammatory bowel disease*
  - *sexually transmitted infections*
  - *physical trauma*
  - *secondary or recurrent malignancy.*
- Pts. sigmoidoscopy or colonoscopy - Direct visualization of mucosa - shows pale friable mucosa, multiple telangiectasias
- Biopsies of the rectum - avoided , high risks of bleeding and the formation of fistulas. If malignancy is suspected, should be done from the posterior and lateral rectal walls
- Adjunctive imaging studies -assist in the detection of recurrence or fistula formation

Management of Chronic Radiation Proctitis

Medical

- Adequate hydration
- Avoid constipation
- 5-aminosalicyclic acid/Mesocol – oral tablets/enemas/suppository
- Steroid enemas
- Sucralfate enemas
- Metrogyl (oral)
- Anti oxidants – Vit A, C, E
- Hyperbaric oxygen

Non surgical

- Endoscopic coagulation (APC - 85-90% control rates)
- Nd:YAG laser, RFA – less effective than APC
- Formalin therapy – chemical cauterisation

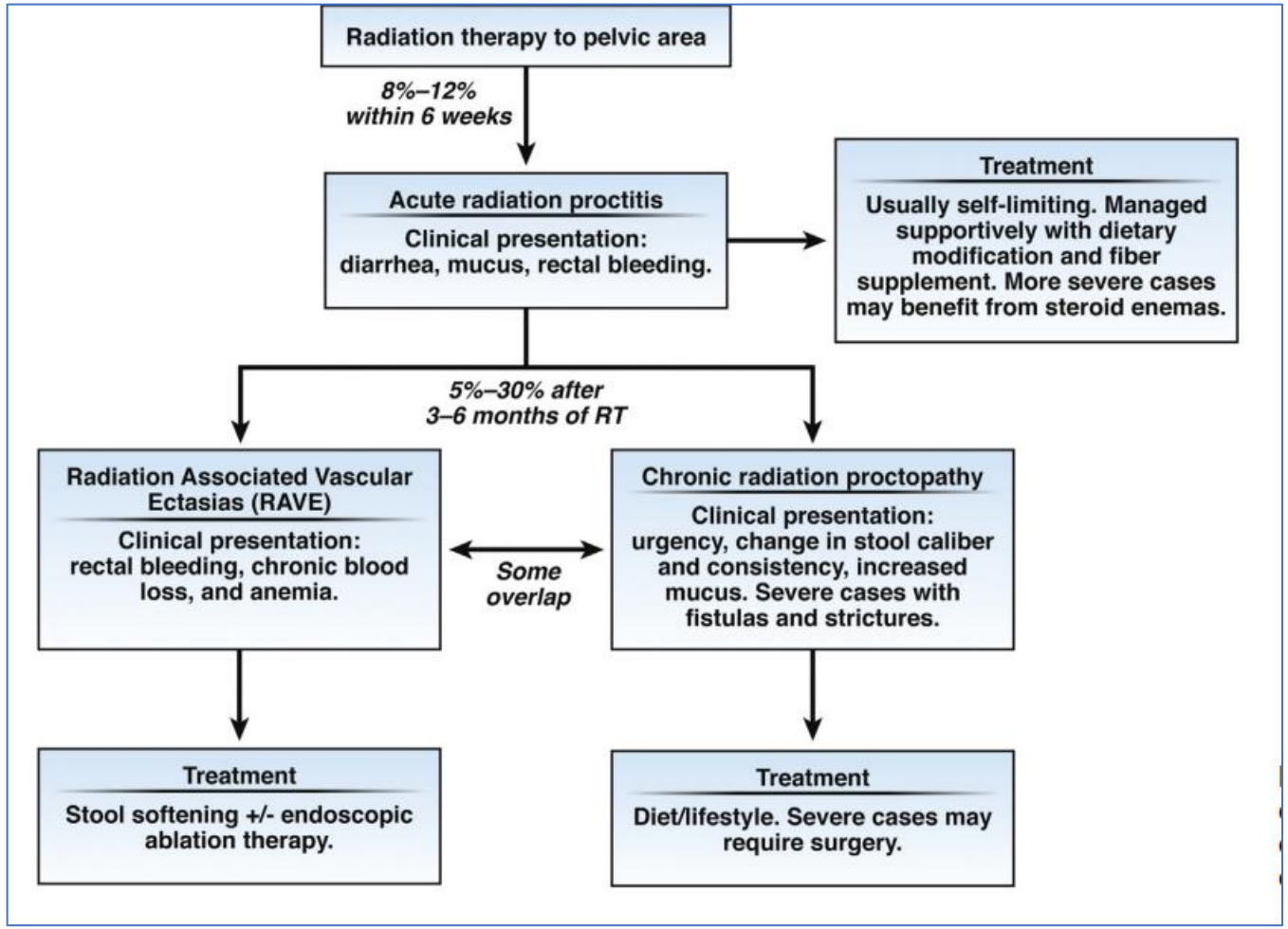
Role of Surgery – Fistula

- Preventive and nonsurgical management techniques -preferred, pts refractory to these interventions require operative management
- HBOT
- Small fistula –diversion colostomy, fistula heals on its own
- Repair - excision of the fistula tract, closure of the defect in layers without tension, and possible incorporation of well-vascularized tissue into the repair.

Late Toxicities- GI

TOXICITY	SYMPTOMS	DIAGNOSIS	TREATMENT
Enteritis	Urgency, fecal leakage, Diarrhea, malabsorption	CT with or without EGD/colonoscopy; malabsorption: fecal fat, breath test	Diarrhea: psyllium, probiotics fecal leakage: physical therapy for perineal strengthening malabsorption: vitamin B12, cholestyramine, parenteral nutrition, gastroenterology evaluation
Stricture	Pain, constipation, thin-caliber stools		resection and primary anastomosis, lysis of adhesions, colostomy
Obstruction	Nausea, pain, persistent ileus, adhesions	Must know how to examine and read the x ray abdomen Auscultation for BS	Hospitalization, Bowel rest; I.V fluids refractory: surgical evaluation for resection vs. colostomy Dietary modifications – low fibre diet

Schema describing different clinical presentations treatment of radiation induced damage to the rectum.



Genito urinary Toxicity

GU toxicity

- Acute grade 1-2 - 17% to 40% in the definitive treatment of cervical cancer with concurrent chemoradiotherapy
- Severe urinary tract toxicity during treatment - 2%- 5%
- The PORTEC-2 trial -urinary frequency was more common after VBT than EBRT for endometrial cancer (6% vs.1% over baseline).

Acute toxicity - GU

TOXICITY	SYMPTOMS	DIAGNOSIS	TREATMENT
Cystitis	Dysuria, frequency, urgency	Assess for UTI	• if infectious source –Antibiotics • if non-infectious, dysuria- pyridium, ibuprofen • Anticholinergic agents – frequency, urgency • Do not chase pus cells in urine if pt is asymptomatic and culture is sterile

Cystitis

- Haemorrhagic cystitis – morbid and potentially life threatening
- Presentation - heamutria
- If infectious - antibiotics
- Cystoscopy

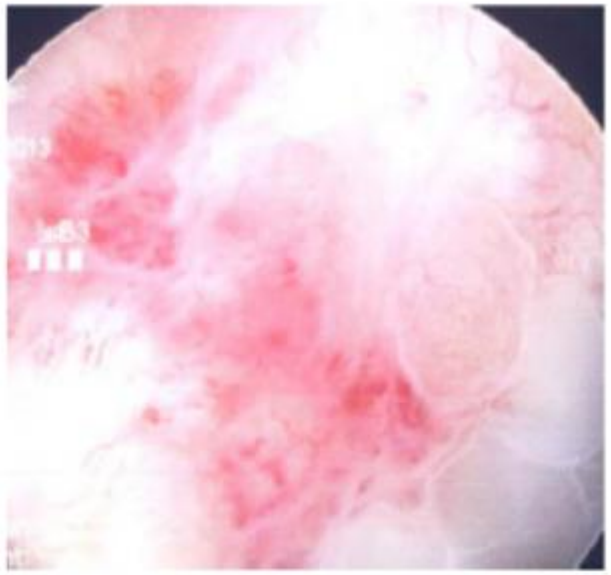


Figure 5. This image shows cystitis as observed during cystoscopy (courtesy of Dr. Graeme Steele).

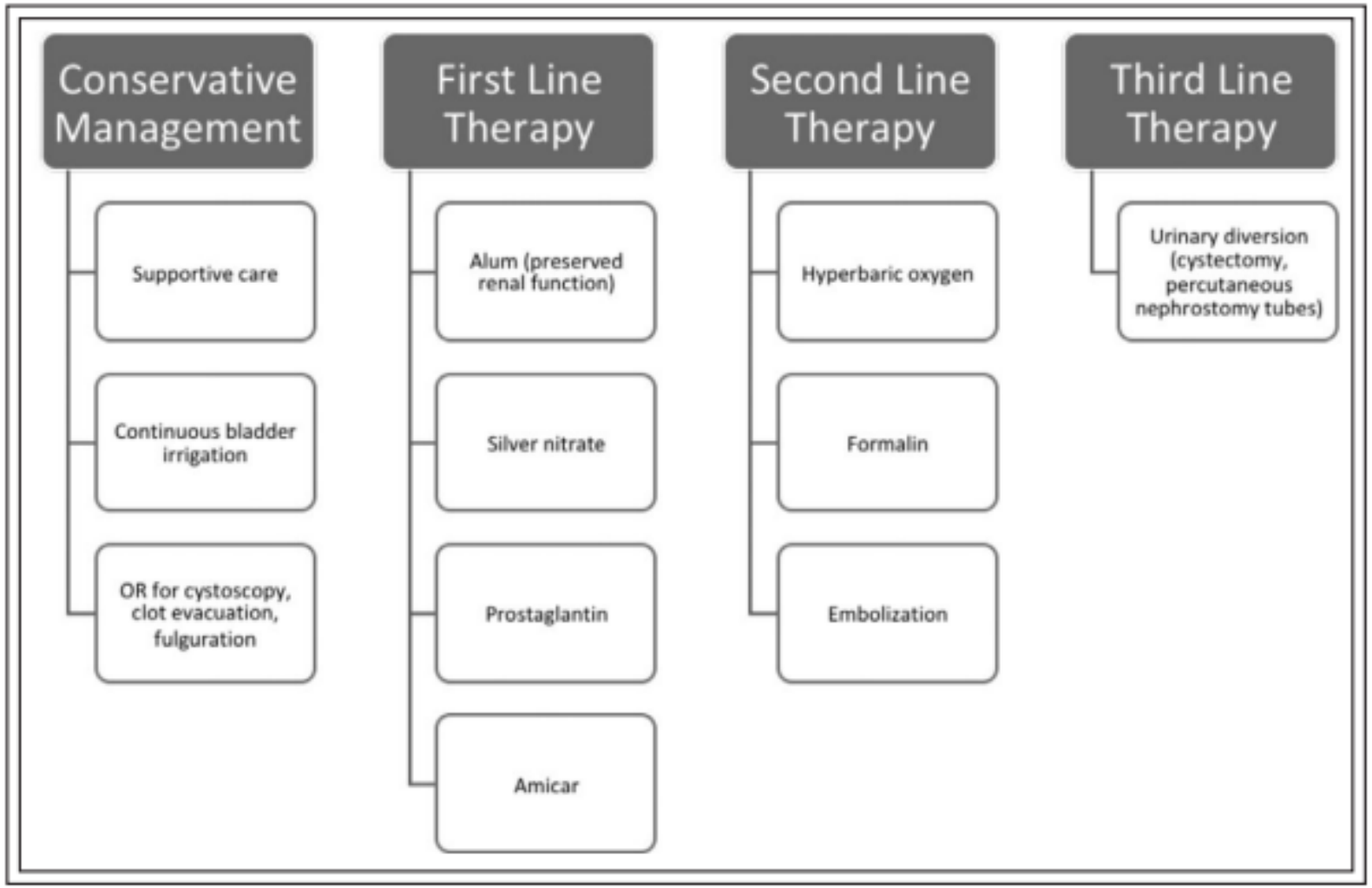


Figure 1. Algorithm for managing hemorrhagic cystitis.

TABLE 3. **Treatment regimens for hemorrhagic cystitis beyond irrigation and fulguration**

Treatment	Dosage/Regimen*	Notes
Alum (aluminum potassium sulfate)	50g/5L sterile water 1% solution instillation @ 250-300mL/hr	Irrigation for 2-3 days; check serum aluminum with prolonged irrigation or renal insufficiency; can be given without anesthesia.
Silver nitrate	0.5%-1% solution	Instilled for 20-30 minutes
Aminocaproic acid (Amicar)	200mg aminocaproic acid/L NS acid/L NSS	
Prostaglandins (PGE-2, others)	8-10 mg/L at 100 mL/h Or 0.4 to 1% solution with CBI for 2 hours QID with NS CBI between	Up to 10 hours at a time with NS CBI between
Formalin	1-2% solution, up to 10% 10-300mL	Instill under gravity <15cm above pubic bone for 10-15 minutes max; r/o ureteral reflux before; requires anesthesia
Hyperbaric oxygen	100% oxygen at 1.5-3 atm for 60-120 minutes	Up to 20-40 sessions

*solutions by indwelling bladder catheter; NS = normal saline; CBI = continuous bladder irrigation

Ureteral stricture

- Ureteral strictures - 2.5%
- Presentation – pain, hesitancy
- Managed
  - by endoscopic procedures - dilation or stent placement,
  - urethroplasty or ureteroplasty
  - ureteral reimplantation or ileal ureteral substitution
- The classical teaching is that a ureteral stricture represents recurrent cancer until proven otherwise; imaging with CT or MRI is recommended.

Fistula (vesicovaginal) – 0.3%

- Pts. who have bladder involvement at diagnosis are at risk
- Fistulae first undergo biopsy to rule out recurrence of malignancy.
- Small fistulae - managed with simple fulguration and catheter drainage, may require open surgical repair and, occasionally, urinary diversion.
- Surgical repair - challenging due to the poor vascularity and wound healing following radiation.

Gynecologic

Toxicities

- Ovarian failure – typically within 6 mths of Rx
- VS - 20% to 88% of pts
- Sexual dysfunction – 50% of women who receive RT. Treatment – dialogue, Vaginal dilators and lubricants.
- Uterine distension is limited because of fibrosis after pelvic radiation. Consequently, the delivery of a full-term infant is not feasible after pelvic radiation

Late toxicity – Gyne.

TOXICITY	SYMPTOMS	DIAGNOSIS	TREATMENT
Vaginal stenosis	Bleeding with dilator use, and/or pain with intercourse	Physical examination with assessment of narrowing/ length	Vaginal dilator; evaluation by sexual function clinic
Menopause	Hot flashes Vaginal dryness		serotonin reuptake inhibitors, natural products, Vaginal estrogen (caution in using for patients with ER-positive adenocarcinoma)

Vaginal necrosis

- Pts. treated with interstitial brachytherapy to the distal vagina, may be at greater risk
- Re irradiated cases
- Rx - Hydrogen peroxide douching with a dilution of at least 1:10 with saline, oral metronidazole, and hyperbaric oxygen may be considered.

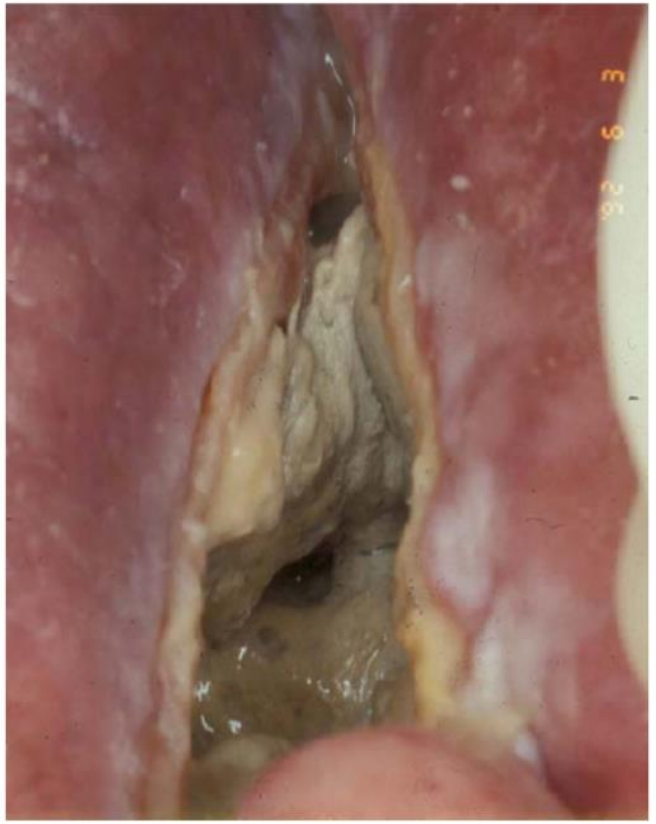


Figure 6. Lower vaginal necrosis is shown (courtesy of Dr. Beth Erickson).

Preserving fertility

- Sperm or ova banking
- Orchiopexy
- Ovarian transposition
- Shield testis – when feasible

Dermatologic

Factors associated with skin toxicity

- Immunocompromised patients
- collagen vascular disease, specifically scleroderma
- Obesity - due to increased apposition of skin in the groin and pannus
- Vascular compromise
- Tobacco use
- diabetes

Prevent – draw skin, control doses, weekly review

Acute toxicity - dermatologic

TOXICITY	SYMPTOMS	DIAGNOSIS	TREATMENT
Dermatitis, Dry desquamation	Pruritis, tenderness		Moisturizing creams, antibiotics, antifungal agents
Desquamation	Pain, wound drainage		- Silicone dressings – Mepilex - Paraffin gauze - Bactigras, Jelonet - Oral antibiotics - Oral Analgesics - warrants assessment for a treatment break before proceeding with further RT.

Late toxicity - dermatologic

TOXICITY	SYMPTOMS	DIAGNOSIS	TREATMENT
Necrosis	Severe pain, infection, odorous	Biopsy to exclude recurrent disease	Hydrogen peroxide douching, metronidazole, hyperbaric oxygen
Fibrosis			Physiotherapy, massage, Pentoxifylline and vitamin E, Hyperbaric oxygen
Telangiectasia	Not bothersome		Laser intervention – cosmesis
Ulceration	Pain	biopsy to rule out radiation-induced skin cancer	wound care, debridement as needed

Bone

Bone toxicity

- ACUTE – none

Chronic toxicity – (7-15%)

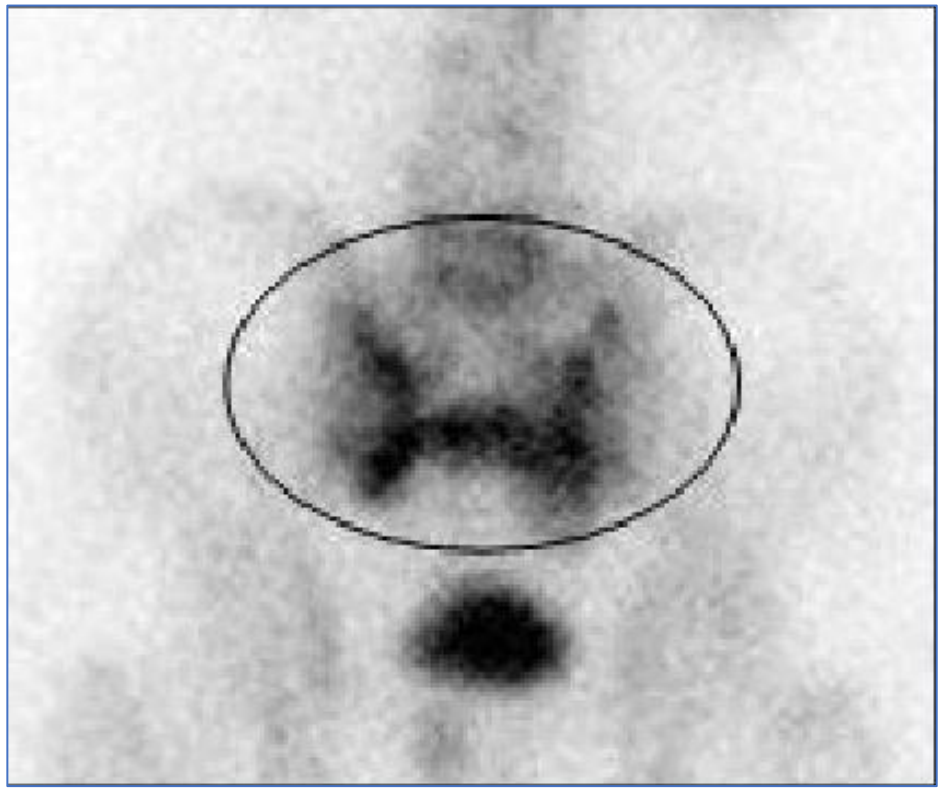
TOXICITY	SYMPTOMS	DIAGNOSIS	TREATMENT
Osteopenia		DEXA	Bisphosphonates; vitamin D and calcium, wt bearing exercises,
Avascular necrosis, Femoral neck #	Pain, disability	X-ray, bone scan, CT, MRI	Surgical repair (total hip replacement)
Insufficiency fracture	Pain, inability to ambulate	X-ray, CT, PET, MRI, bone scan	

PIF

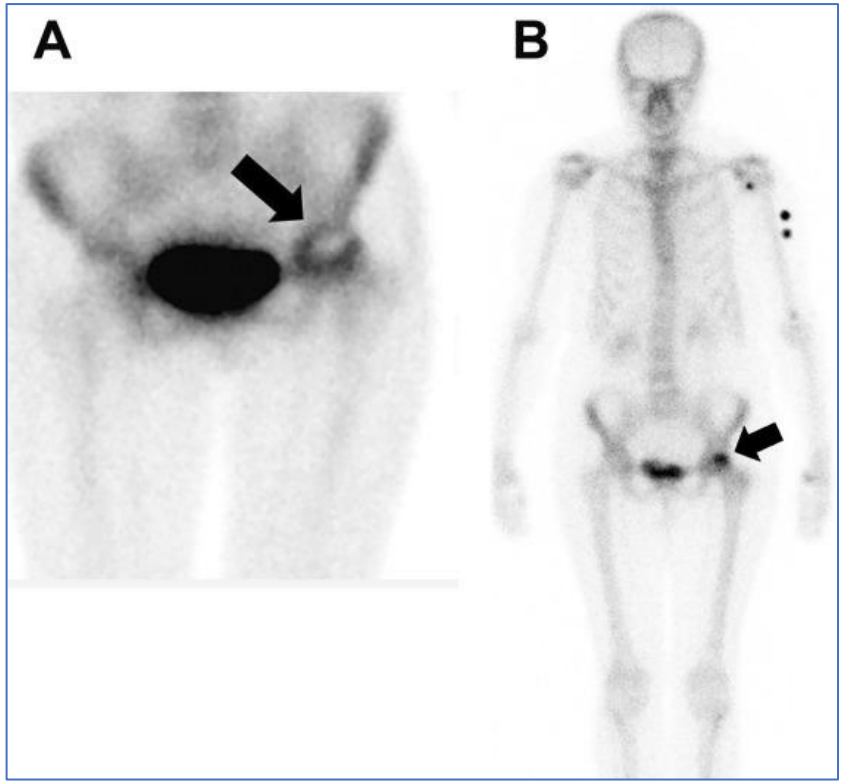
- Sites - the pubic symphysis, pubic rami and sacrum
- A 4-level instability classification system has been proposed to guide the management.
- The classification recommends
  - nonoperative Rx -for type I fractures
  - nonoperative or minimally invasive surgical fixation - type 2 fractures
  - surgical stabilization for type 3 and 4 fracture patterns.
- Nonoperative Rx - Pain meds, physiotherapy (6 to 12 mths)
- For incomplete and isolated sacral ala fractures, sacroplasty may be considered.

Bone scan

Sacral insufficiency # - H sign



AVN



Hematologic

- Pelvis contains approximately 50% of the human hematopoietic BM
- Many studies show a decrease in bone marrow dose and hematologic toxicity with IMRT instead of 3D radiation
- Study by Mell et al –reported a decrease in grade 3 neutropenia in pts with cervical cancer treated with bone marrow – sparing IMRT, from 27.1% - 8.6%.
- Contour bone marrow and give constraints

Acute toxicity - Hematologic

TOXICITY	SYMPTOMS	DIAGNOSIS	TREATMENT
Anemia		Hb <10 mg/dl	Consider transfusion of packed erythrocytes
Neutropenia		ANC <500/lL	Infection risk precautions
Thrombocytopenia		Platelets <40 mg/lL	Consider holding radiation; transfuse platelets if count <10 $x10^3$ / lL

- Advancements in imaging techniques may provide avenues to avoid active bone marrow and decrease hematologic toxicity.
- Both[18F] fluorothymidine positron emission tomography imaging and 18FDG-positron emission identifies active bone marrow and can limit dose to the bone marrow region
- Still investigational

Practical Tips and Tricks

- History taking – ask for symptoms, duration. Spend atleast 10 mins on taking a good history
- Simulation – bladder protocol, rectal dilatation
- Contour the OARs correctly - Contouring guidelines
- IMRT is a double edged sword – dose dumping
- Plan evaluation – slice by slice distribution, respect tolerances
- Excel sheets for dose recording
-
-

Prevention is better than cure

Physicist

Oncologist

Biological Documentation of Gynaecological HDR

Patient [redacted] ID S-0154-24 Application Type ICRT

Prescription		No of Fractions	Dose/Fraction (Gy)	Total Dose (Gy)	BED (Gy) [α/β=10]	EQD_2 [α/β=10]
α/β=10	EBRT	25	1.8	45	53.10	44.25
	1st ICRT/ OVOID	1	8	8	14.40	12.00
	2nd ICRT/ OVOID	1	8	8	14.40	12.00
	3rd ICRT	1	8	8	14.40	12.00
	MUPIT/SORBO	0		0	0.00	0.00
	Total				96.30	80.25
	MUPIT/SORBO	1				
	Total					

GTV		No of Fractions	Dose/Fraction (Gy)	Total Dose (Gy)	BED (Gy) [α/β=10]	EQD_2 [α/β=10]
α/β=10	EBRT	25	1.824	45.6	53.92	44.93
	1st ICRT/ OVOID	1	8.5	8.5	15.73	13.10
	2nd ICRT/ OVOID	1	8.3	8.3	15.19	12.66
	3rd ICRT	1	8.6	8.6	16.00	13.33
	MUPIT/SORBO	0		0	0.00	0.00
	Total				100.83	84.02

HR CTV		No of Fractions	Dose/Fraction (Gy)	Total Dose (Gy)	BED (Gy) [α/β=10]	EQD_2 [α/β=10]
α/β=10	EBRT	25	1.8	45	53.10	44.25
	1st ICRT/ OVOID	1	8.1	8.1	14.66	12.22
	2nd ICRT/ OVOID	1	8	8	14.40	12.00
	3rd ICRT	1	7.9	7.9	14.14	11.78
	MUPIT/SORBO	0		0	0.00	0.00
	Total				96.30	80.25

IR CTV		No of Fractions	Dose/Fraction (Gy)	Total Dose (Gy)	BED (Gy) [α/β=10]	EQD_2 [α/β=10]
α/β=10	EBRT	25	1.8	45	53.10	44.25
	1st ICRT/ OVOID	1		0	0.00	0.00
	2nd ICRT/ OVOID	1		0	0.00	0.00
	3rd ICRT	1		0	0.00	0.00
	MUPIT/SORBO	0		0	0.00	0.00
	Total				53.10	44.25

Physicist

Oncologist

Biological Documentation of Gynaecological HDR

Patient [redacted] ID S-0154-24 Application Type ICRT

OAR

Bladder

		No of Fractions	V_{2cc}/Fraction (Gy)	V_{2cc} Total (Gy)	BED (Gy) [α/β=3]	EQD_2 [α/β=3]
α/β=3	EBRT	25	1.8624	46.56	75.46	45.28
	1st ICRT/ OVOID	1	4.8	4.8	12.48	7.49
	2nd ICRT/ OVOID	1	7.8	7.8	28.08	16.85
	3rd ICRT	1	7	7	23.33	14.00
	MUPIT/SORBO	0		0	0.00	0.00
	Total				139.36	83.61
	MUPIT/SORBO	0				
	Total				139.36	83.61

Sigmoid

		No of Fractions	V_{2cc}/Fraction (Gy)	V_{2cc} Total (Gy)	BED (Gy) [α/β=3]	EQD_2 [α/β=3]
α/β=3	EBRT	25	1.8	45	72.00	43.20
	1st ICRT/ OVOID	1	6.4	6.4	20.05	12.03
	2nd ICRT/ OVOID	1	5	5	13.33	8.00
	3rd ICRT	1	5.1	5.1	13.77	8.26
	MUPIT/SORBO	0		0	0.00	0.00
	Total				119.16	71.49

Rectum

		No of Fractions	V_{2cc}/Fraction (Gy)	V_{2cc} Total (Gy)	BED (Gy) [α/β=3]	EQD_2 [α/β=3]
α/β=3	EBRT	25	1.7804	44.51	70.93	42.56
	1st ICRT/ OVOID	1	5	5	13.33	8.00
	2nd ICRT/ OVOID	1	5	5	13.33	8.00
	3rd ICRT	1	6.5	6.5	20.58	12.35
	MUPIT/SORBO	0		0	0.00	0.00
	Total				118.18	70.91
	MUPIT/SORBO	0				0.00
	Total				118.18	70.91

Intestine

		No of Fractions	V_{2cc}/Fraction (Gy)	V_{2cc} Total (Gy)	BED (Gy) [α/β=3]	EQD_2 [α/β=3]
α/β=3	EBRT	25	1.8	45	72.00	43.20
	1st ICRT/ OVOID	1	6.2	6.2	19.01	11.41
	2nd ICRT/ OVOID	1	5.4	5.4	15.12	9.07
	3rd ICRT	1	5	5	13.33	8.00
	MUPIT/SORBO	0		0	0.00	0.00
	Total				119.47	71.68


THANK
YOU!

Management of Hemorrhagic Cystitis