43RD ICRO PG Teaching Program

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Management of Complications of Treatment (RT) in Gynaecological Cancers

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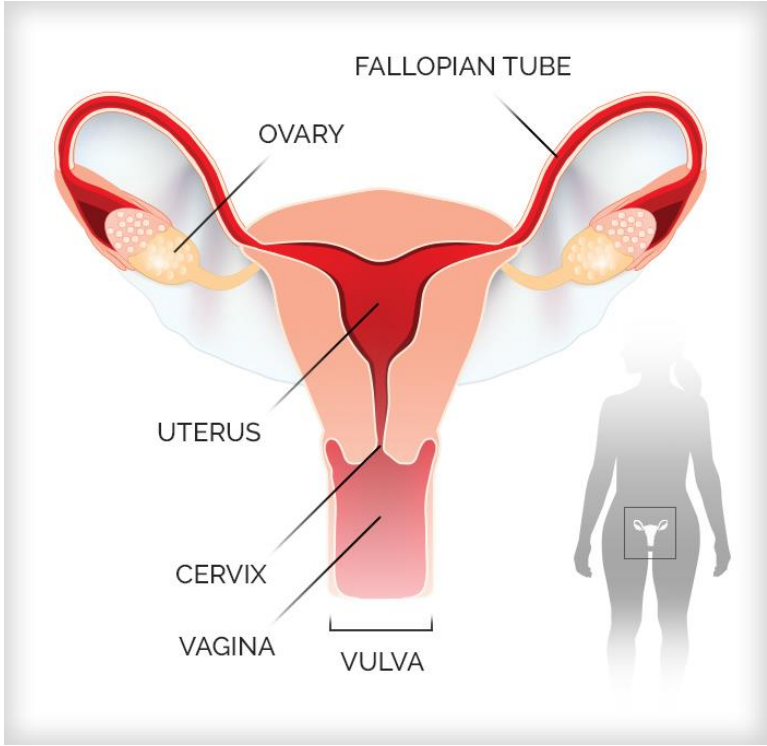
Management of Gynecological Malignancies

- Carcinoma Endometrium:
  - Primary Surgical staging and treatment
  - Adjuvant Radiotherapy/chemotherapy
- Carcinoma Cervix:
  - Surgical: Early stages
  - Radiotherapy: Adjuvant/Definitive
  - Chemotherapy
- Vulvo-vagina: Surgery/RT
- Multi-modality treatment: Improvement in outcome and potential toxicities



Goals of management in gynecological malignancies!!

Loco-regional control and cure

Minimize acute complications

Avoid long term complications

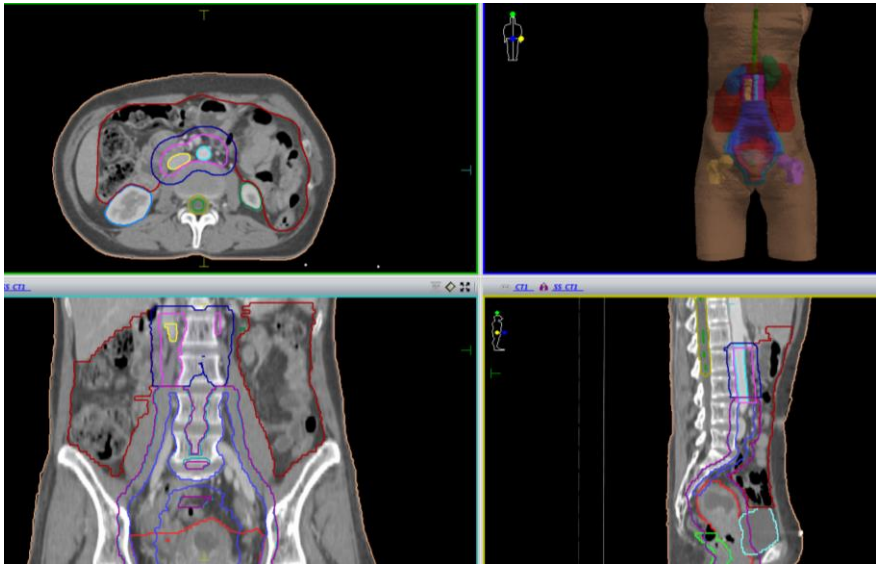
Preserve QOL and Psycho-social function

Preserve fertility and Sexual function

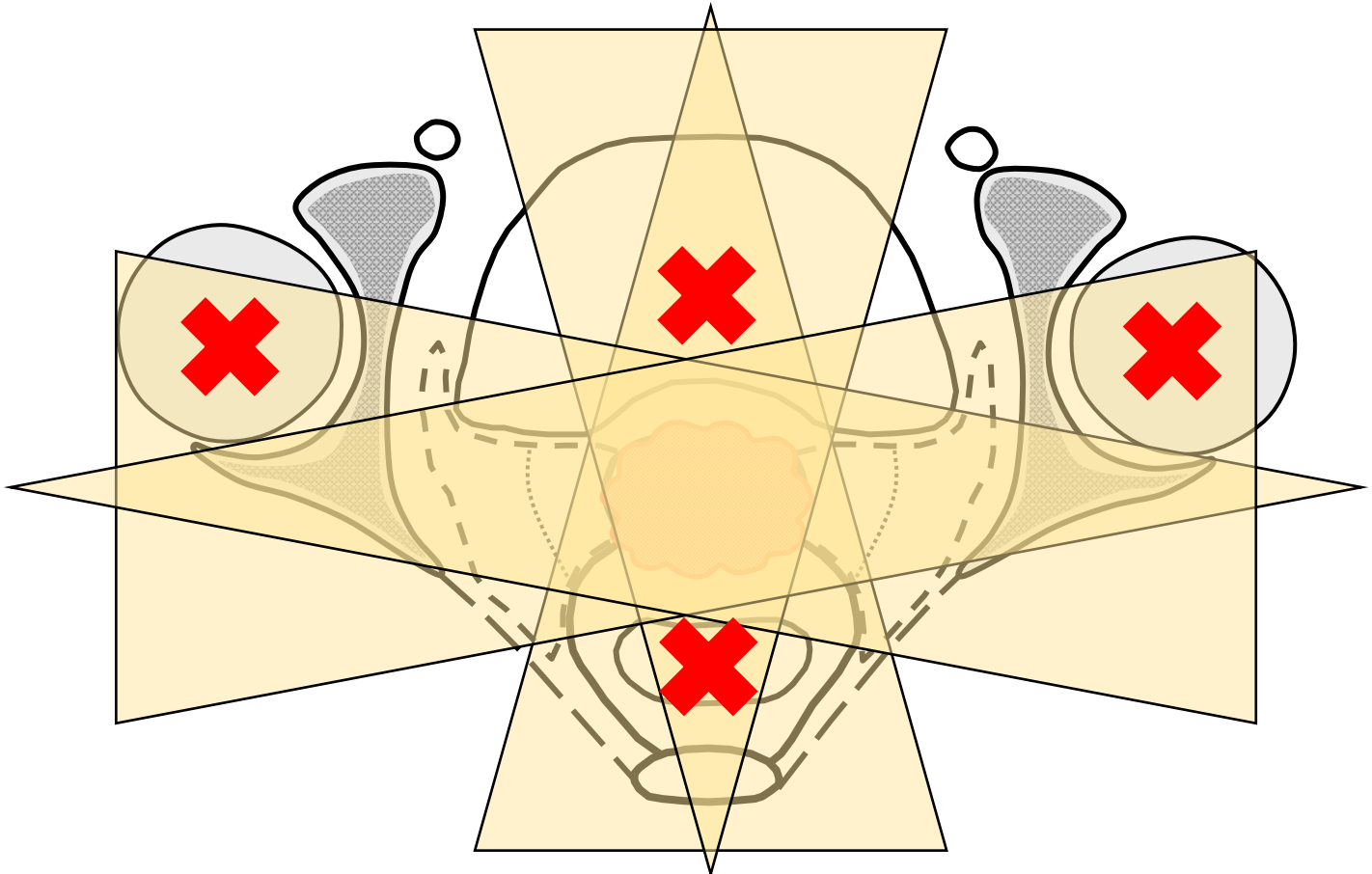
Gynecological Malignancies: Target amidst OARs

- Rectum and anus
- Sigmoid colon
- Bowel
- Bladder
- Urethra
- Ureter
- Vagina

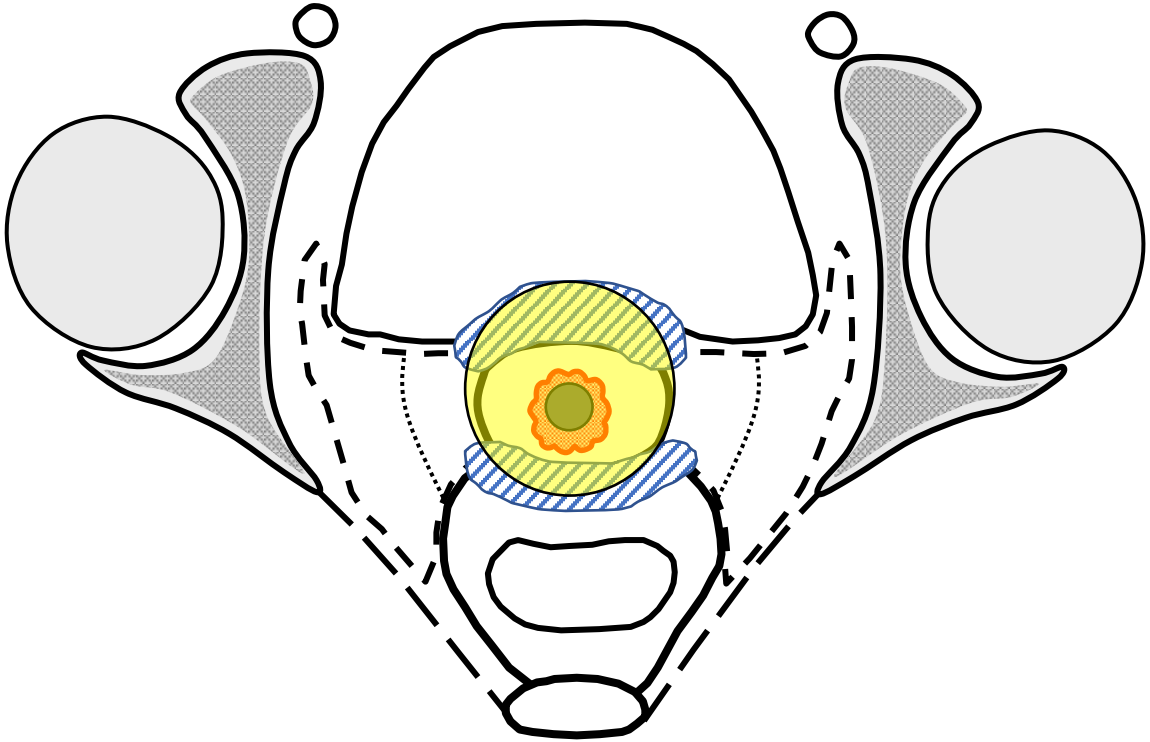
- Ovaries
- Duodenum
- Kidneys
- Spinal Cord
- Pelvic bone Marrow
- Femoral heads
- Lumbosacral plexus



EBRT: Pelvic RT



Brachytherapy



Complications of radiation in GYN malignancies

- Acute
  - Gastrointestinal
  - Genitourinary
  - Hematological
  - Dermatological
- Late
  - Gastrointestinal
  - Genitourinary
  - GYN: Vaginal stenosis, menopause
  - Dermatological
  - Bone related

Prevention of complication is the best management

- Choice of treatment modality:
  - Extent of surgery
  - Avoid dual modalities of treatment: Surgery plus RT
- Refine EBRT techniques:
  - IG-IMRT [Standard for post-operative cases]
  - Treatment volume definitions
- Precise image guided brachytherapy techniques

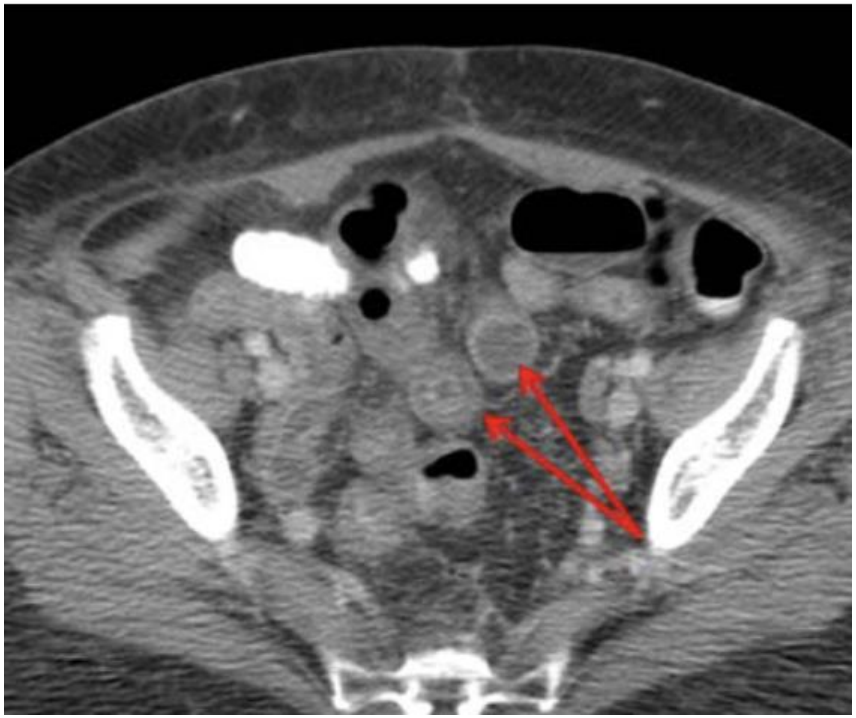
Evaluation of complications!!

- Always keep differentials in mind: not all complications acute/late are related to pelvic RT
- Review treatment and patient related factors
- Thinking in term of LENT-SOMA scale helps:

1. Clinical detection
2. Time course of events
3. Dose/time/volume
4. Chemical/biological modifiers
5. Radiological imaging
6. Laboratory tests
7. Differential diagnosis
8. Pathological diagnosis
9. Management
10. Follow up

Acute Gastrointestinal complications

- Incidence of Grade 3 or higher GI complications: 10-30% [IG-IMRT]
- Time frame: 0-6 months
- Symptoms:
  - Enteritis: Diarrhea, tenesmus, mucus
  - Proctitis: Rectal bleeding
  - Hemorrhoidal symptoms
- Investigations
  - None/Physical examination
  - CT pelvis for severe symptoms
  - Sigmoidoscopy or colonscopy
  - C. diff testing



Management of acute GI complications

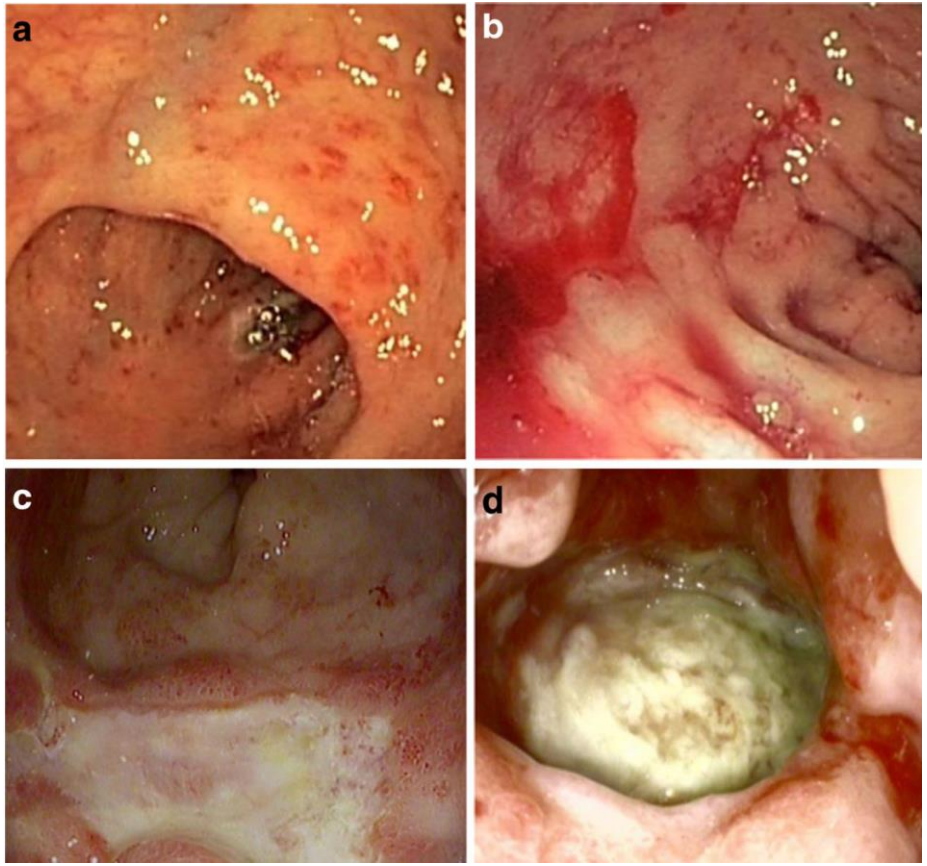
Supportive treatment
Counselling before start of the treatment
Loperamide/diphenoxylate-atropine tablets: May start once a day prior to onset of diarrhea
Maintain hydration and electrolytes
Withhold RT for grade 3 or higher toxicities
Aggressive management required
Short chain fatty acid butyrate enema: Beneficial [Vernia P et al. Lancet 2000;356:1232-5]
Not found useful: Sucralfate, empirical antibiotics, psyllium/husk, probiotics

Chronic Gastrointestinal complications

- Incidence of Grade 3 or higher GI complications: 5-20%
- Time frame >6 months
- Enteritis:
  - Symptoms: Urgency, fecal leakage, diarrhea, malabsorption
  - Investigations: CT with or without UGIE/colonoscopy, Malabsorption; Fecal fat and breath test
  - Management:
    - Diarrhea: psyllium, probiotics, low fiber diet
    - Chronic diarrhea: Loperamide, Meveberine+/- chlordiazepoxide
    - Fecal leakage: pelvic physical therapy
    - Malabsorption: Vitamin B12, Cholestyramine, parenteral nutrition, gastroenterology evaluation

Chronic Radiation Proctitis

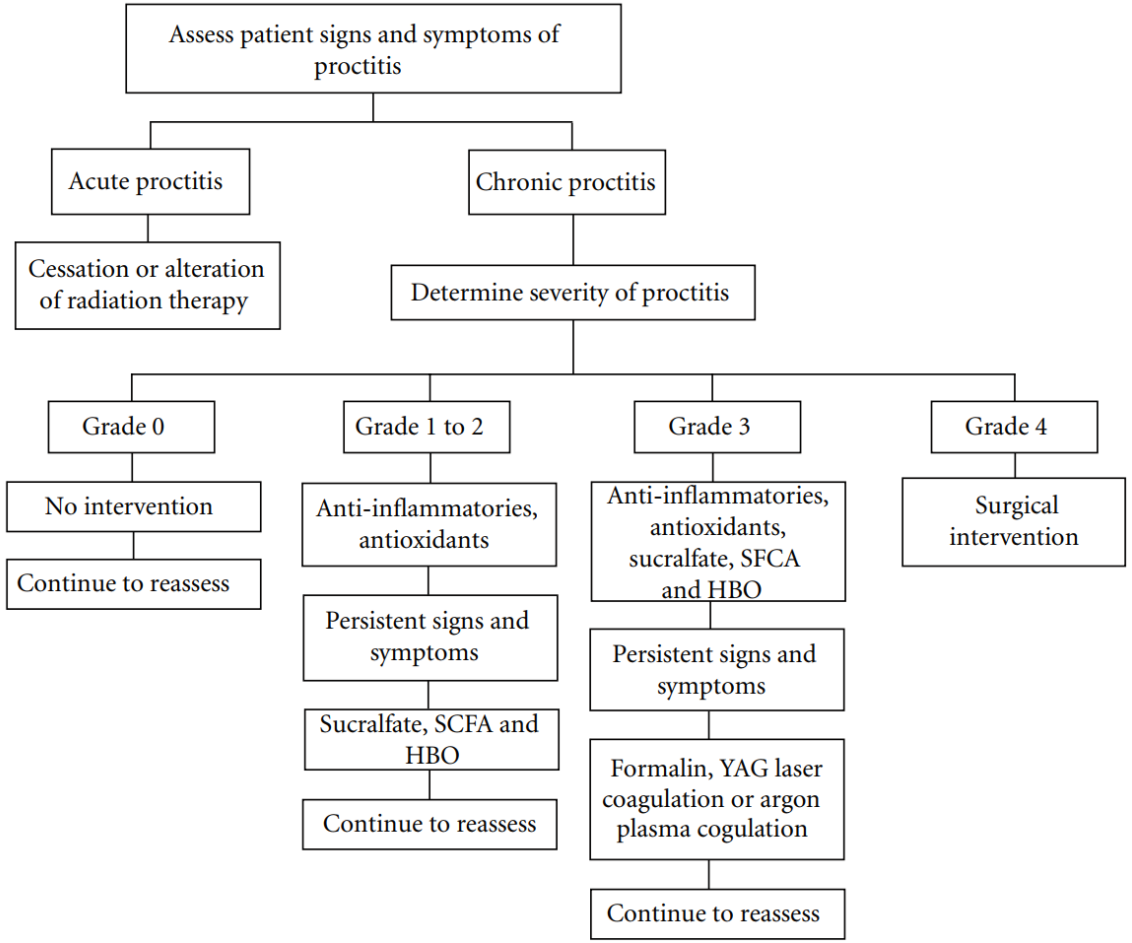
- Symptoms
  - Rectal bleeding only
  - Tenesmus, pain
  - Anemia
- Investigations
  - None
  - Physical examination
  - Sigmoidoscopy
  - Complete blood count



Management: Chronic Radiation Proctitis

- Management:
  - Observation if infrequent and asymptomatic [most cases of Grade ½ will resolve spontaneously]
  - Avoid constipation: stool softeners
  - In patients with severe bleeding: avoid antiplatelets/anti-coagulants
  - 4-week course of metronidazole [Cavcić J, Croat Med J. 2000;41(3):314-8]
  - Sucralfate/steroid enema
  - Argon laser coagulation
  - Hyperbaric oxygen therapy
  - Avoid biopsies (if possible take from posterior/lateral walls)
  - Judiciously use APC (only in refractory cases)

Grade	Symptoms or signs
0	No symptoms
1	Occasional urgency and occasional pain; superficial ulceration <1 cm^2, occult bleeding, and mild stricture
2	Intermittent urgency and intermittent pain; superficial ulceration >1 cm^2, occasional bleeding, and moderate stricture
3	Persistent urgency and persistent pain; deep ulceration, persistent bleeding, severe stricture
4	Refractory urgency and uncontrollable pain; gross hemorrhage, perforation, fistula, complete obstruction
5	Sepsis, multiorgan failure, and death



Chronic Gastrointestinal complications

- Fistula:
  - Symptoms: Malodourous discharge, fecal incontinence
  - Investigations: Endoscopic ultrasound/fistulography X-Ray
  - Management: Surgical evaluation for resection vs. colostomy

- Stricture: Pain, constipation, thin caliber stools; Surgical evaluation for adhesiolysis/resection/colostomy

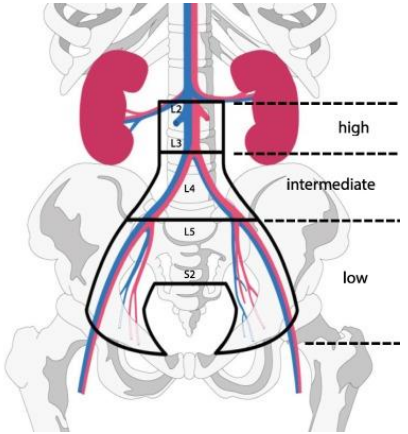
- Obstruction:
  - Triad of symptoms: Abdominal pain, absolute constipation, nausea/vomiting
  - X-ray Erect abdomen/CT abdomen
  - Bowel rest, RT tube insertion, surgical evaluation

Predictive factors for GI complications

- Post-operative patients receiving >45-50 Gray
- Treatment volume:
  - Pelvic vs. Extended field RT
  - Nodal boost
- Concurrent chemotherapy
- Prior pelvic inflammatory disease
- Collagen vascular disease
- Inflammatory bowel disease
- Smoking history
- Vascular disease due to diabetes or atherosclerosis

Minimizing GI complications

- Refine EBRT techniques:
  - Multiple fields [4 field vs 2 field]
  - Dose: 45 vs 50 Gray [1.8 vs 2 Gray/fraction]
  - Prone belly board for post-operative patients
  - IG-IMRT technique
  - Tailor volumes of treatment [Nodal, Primary]
- Refine Brachytherapy technique
  - Judicious use with EBRT in post-operative cases
  - Volumetric imaging with CT/MRI
  - Hybrid/advanced application for sparing OARs
  - Respect cumulative EQD2 D2cc rectum <65 Gray



Genitourinary complications: Pelvic RT

- Acute GU toxicities:
  - Low grade [1-2] are very common during pelvic EBRT: 15-40%
  - Severe [grade 3-4] acute GU complications are rare <5%
  - Mostly in the form of cystitis
- Late GU toxicities:
  - Low grade [1-2] varies from 10-30%
  - Severe [grade 3-4] varies from 0-5%
  - Cystitis, fistula, contracture, stricture etc.

Predictive factors for GU complications

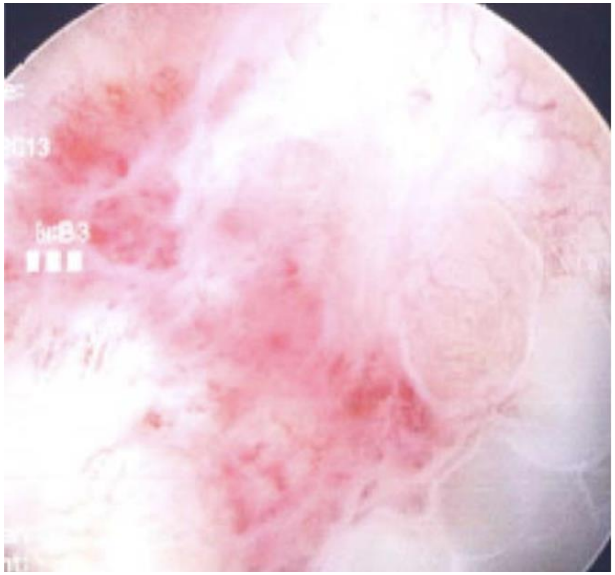
- Prior pelvic surgery [extent of radical surgeries]
- Cumulative radiation dose from EBRT and brachytherapy
  - D2cc EQD2 <80-85 Gray
- Use of anticoagulation
- Smoking history
- Concurrent chemotherapy [?does not affect the late GU]

Acute GU complications

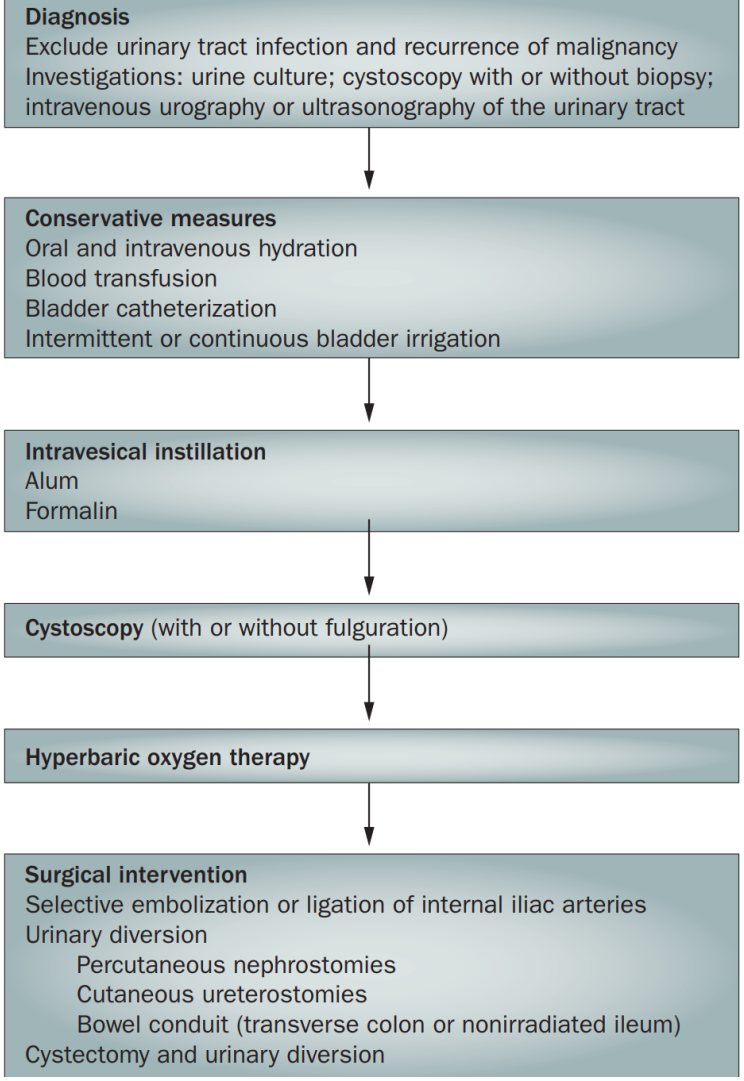
Symptoms	Investigations	Management
• Cystitis: Dysuria, frequency, urgency	• Rule out UTI: Urine routine/microscopic, culture sensitivity	• Antibiotics • Ibuprofen/pyridium • Anti-cholinergics: Tolterodine/trospium • Cystoscopic injection of botulinum A

Chronic GU complications

- Cystitis
  - Hematuria
  - Hematuria with clots leading to acute retention
  - Cystoscopy/ USG KUB/CT
  - Grade 1 (microscopic), Grade 2 (macroscopic), Grade 3 (several generalized telangiectasia, macroscopic), Grade 4 (sever hemorrhagic cystitis)



- Intravesical instillation
  - Alum: 1% aluminum sulphate (heavy bleeding may precipitate clot and retention)
  - Placental extract intravesical: Good outcome
  - Formalin: reflux may lead to pyonephrosis, contracted bladder, used only in cases where urinary diversion has been achieved
- Oral or parenteral agents
  - Hematinic (tranexamic acid)
  - Conjugated estrogens
  - Sodium pentosan polysulfate
  - WF10 (tetrachlorodecaoxide)
  - Pentoxifylline
- Cystoscopic
  - Fulguration/botulinum A/Orgotein injection



Chronic GU complications

- Fistula
  - Patient with stage IVA bladder disease at highest risk
  - Symptoms: Discharge, incontinence, urethral edema
  - Cystoscopy, biopsy to rule out recurrent disease
  - Management:
    - Small fistula with simple fulguration and catheter drainage
    - Surgical repair or ileal conduit
- Contracture
  - Increased urinary frequency, pain
  - Urodynamic studies
  - Cystectomy with ileal conduit or bladder augmentation
- Stricture
  - Pain and hesitancy
  - Retrograde urethrogram
  - Surgical dilatation, urethral stent, urethroplasty or uretroplasty

Chronic GU complications

- Ureteral stricture
  - Denotes recurrence unless proven otherwise
  - CT/MRI pelvis should be done in all cases
  - Dilatation/stent placement
  - Ureteral reimplantation
  - Ileal/ureteral substitution
- Uretro-arterial fistula
  - Carries a high mortality rate
  - Endovascular stent placement/surgical repair

Sexual function after pelvic RT

- Most common GYN complication is ovarian failure in pre-menopausal and vaginal stenosis (VS) in post-menopausal women
- Incidence of vaginal stenosis: 20-90%
- Sexual dysfunction: 50-70%
- Time trends:
  - Menopause: within first 6 months of RT
  - VS: 1 months-5 years [typically within one year of RT]
- Risk factors: Age >50 years, lack of compliance with dilator, concurrent CTRT, RT dose >80 Gray

Management of sexual dysfunction after pelvic RT

- Post-menopausal symptoms: Oral progesterone/estrogen; SSRIs
- Vaginal stenosis:
  - Vaginal dilators: Early use once RT reactions subside
  - Topical estrogen and Benzydamine
  - Hyperbaric oxygen therapy
  - Surgical reconstruction
- Vaginal necrosis
  - May be seen with reirradiation and ISBT to lower vagina
  - H202 douching with 1:10 saline dilution
  - Oral metronidazole and HBOT

Hematological toxicities of pelvic RT

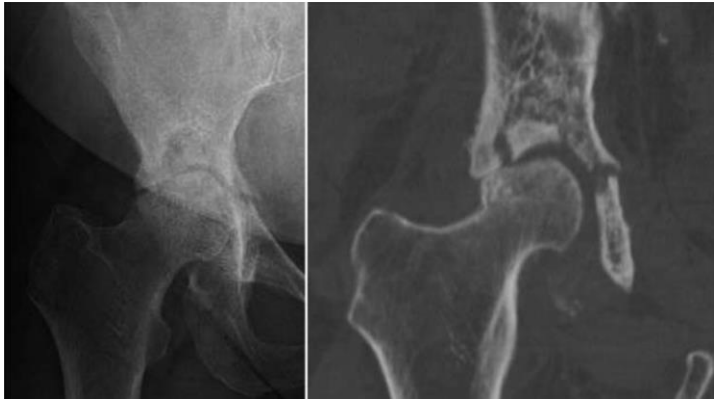
- Grade 3 or higher hematological toxicities with CTRT is 20-25% [higher with extended field RT]
- Risk factors:
  - Pre-existing Anaemia: Iron deficiency, ACD etc
  - Chemotherapy regimen: Higher with higher dose and multiagent (Gem plus Cis; 60-70% Grade ¾)
  - Volume, technique and RT dose (low dose may matter as well)
- Sparing functional BM regions with functional imaging(PET/SPECT) (investigational)

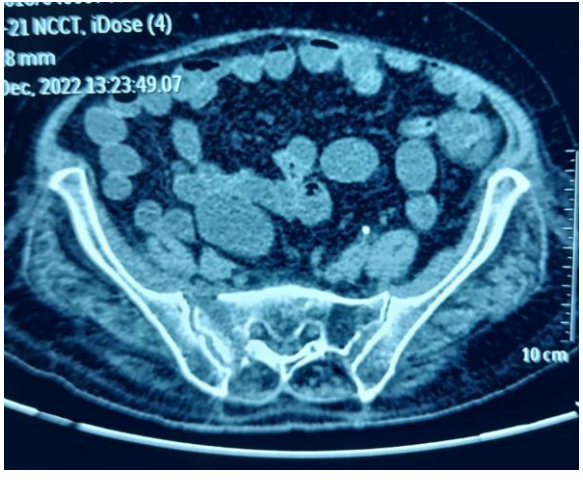
Management of acute hematological toxicity

- Weekly monitoring of counts
  - With hold CT if ANC <1500; Platelets <1 Lakh/microL
  - With hold RT if ANC <500-1000; Platelets <40,000/microL
  - Maintain Hb >10 mg/dL
- Packed red blood cell transfusion: Hb<10 mg/dL; Haematocrit <30 mg/dL
- Neutropenic precautions if ANC <500 and manage as per protocol
- Transfuse platelets if <10-20 thousand/microliter
- Optimize Hb before initiation of treatment: Transfusion, correct iron deficiency etc.

Bone complications from pelvic RT

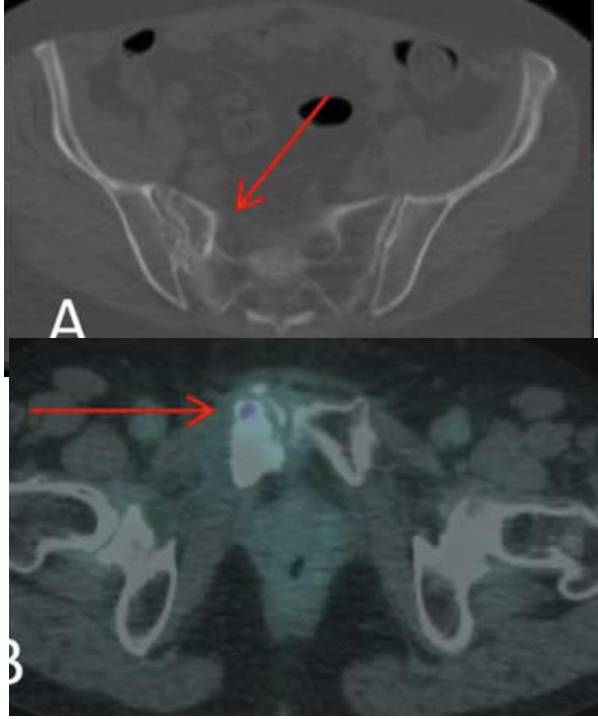
- Uncommon but important sequel:
  - Pathological fractures (insufficiency fractures)
  - Osteoradionecrosis
  - Secondary malignancies
- Risk factors: RT dose >50 Gray, older age, menopausal status, osteoporosis, corticosteroid use, cigarette smoking

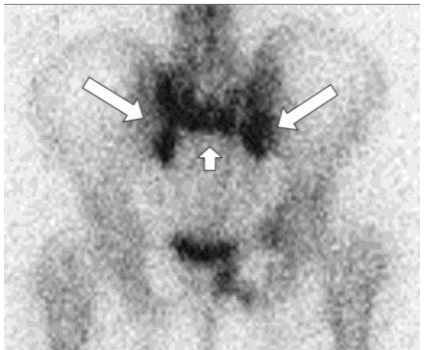




Diagnosis of bone complications

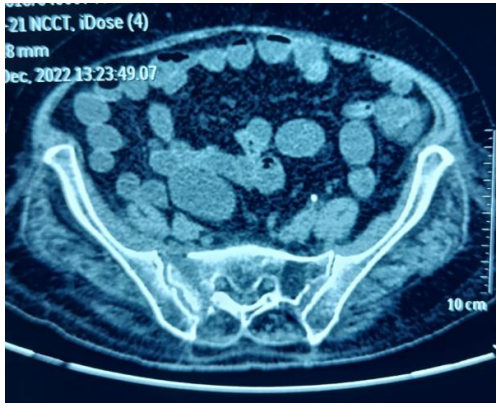
- Nonspecific symptoms: Severe back, hip, leg pain
- Mimics metastatic lesions, hip osteoarthritis, spinal/lumbar stenosis
- X-ray often equivocal
- CT imaging is necessary most times
- MRI: high signal intensity on T2 (bone marrow edema); fracture line on T1
- Bone scan: H shaped pattern common





Management of bone complications

- Non-operative: NSAIDs/ pain medications/physical therapy
- Bisphosphonates, Vitamin D, Calcium
- Operative:
  - Surgical stabilization
  - Sacroplasty
  - Total hip replacement for AVN of femoral head
  - Hemiarthroplasty for AVN discouraged as rates of protrusion acetabuli is high



Dermatological toxicities of pelvic RT

- Grade 1 very common
- Grade 2 (RT dose>40 Gray): 10-50% and 85-100% for vulvar cancer
- Grade 3 (RT dose>50-60 Gray): 1-5%; 20-50% for vulvar cancers
- Typically appear within 1-2 weeks and heals within 3-4 weeks

Dermatological toxicities of pelvic RT

- Vascular disease, smoking, poor nutrition
- Compromised wound healing after surgery
- High BMI, skin and groin folds
- Concurrent fungal/bacterial infections
- Use of IMRT technique: lesser dermatological reactions
- Distal vagina and vulva tolerates radiation poorly and should be kept out of field if possible

Management of dermatological toxicities

- Dermatitis:
  - Moisturizing creams (Aquaphor), sitz bath with sodium bicarbonate, Epsom salt; gentle cleaning with mild unperfumed soap
  - Loose fitting and cotton clothing
  - Antibiotics/antifungals [daily fluconazole for vulvar cancers]
  - 1% hydrocortisone for pruritus
- Desquamation:
  - Non-adherent hydrogel dressing (Strata-XRT)
- Treatment breaks for grade 3 or higher skin reactions
- Pain management: NSAIDs and narcotic analgesics

Management of dermatological toxicities

- Late effects:
  - Pigmentation (hypo/hyper); telangiectasia, textural changes (xerosis/hyperkeratosis), Folliculitis
  - Subcutaneous fibrosis, cellulitis, ulceration, necrosis
- Management:
  - Biopsy to rule out recurrent disease [particularly in vulvar cancers]
  - Hydrogen peroxide douching, metronidazole, hyperbaric oxygen therapy

Take home message!!

- Complications of pelvic RT is multifactorial and affected by patient and treatment related factors
- Differentials exist and not always the complications are due to pelvic RT
- Prevention of complications is the best management
- Acute radiation toxicities are mostly limiting and resolve
- Late radiation toxicities may be disabling at time and should be approached systematically
- Complications are always easier to handle than recurrences and hence therapeutic ratio should always be optimized