

Complications and Management of Gynecological Malignancies

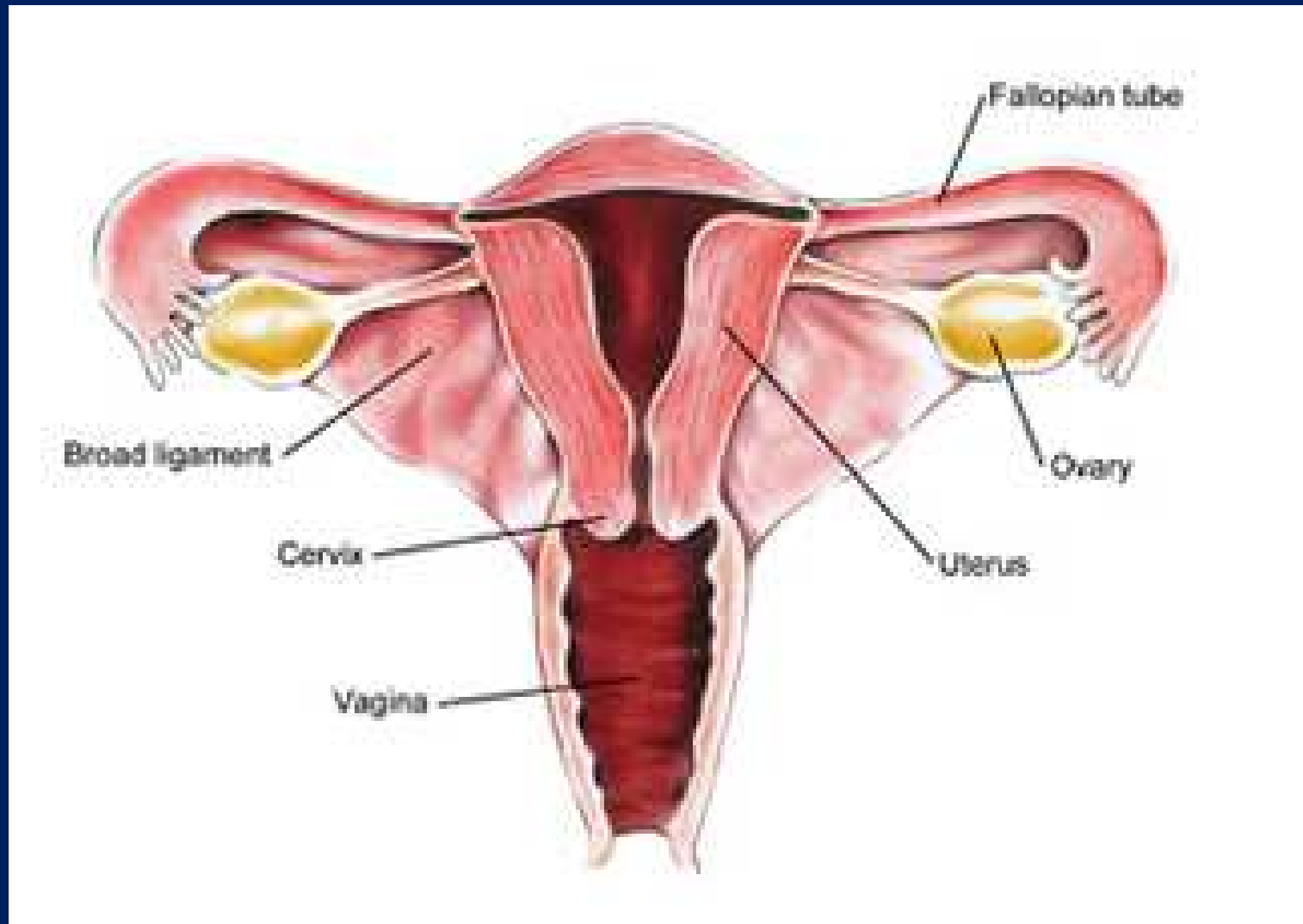
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Gynecological cancers



Primary Mangement

- Surgery
- Radiotherapy
- Chemotherapy

Pelvic Radiation Related Complications

- GI toxicity (acute or late)
- GU toxicity (acute or late)
- Sexual Dysfunction
- Hematologic toxicity
- Bone complications
- Dermatologic toxicity

Gastrointestinal Complications of
Pelvic Radiation

Gastrointestinal Complications

- Acute (0-6 months)
 - Enteritis
 - Proctitis
 - Hemorrhoids
- Late (>6 months)
 - Enteritis
 - Proctitis
 - Fistula
 - Stricture
 - Obstruction

Incidence of GI complications

- 30% of patients with endometrial cancer treated with postoperative RT experienced acute diarrhea.
- Late toxicities
 - 3% to 8% of patients who receive postoperative treatment to the pelvis.
 - Up to 20% of patients with locally advanced and unresectable tumors who require EBRT with both dose escalation and brachytherapy.
 - Significantly reduced overall long-term complication rates from 22.7% to 2.6% with the use of image-guided and HDR brachytherapy.

Diagnosis of GI complications

- No radiologic or invasive tests for common symptoms like acute diarrhea, mucus, tenesmus, pain, or hemorrhoids controlled with medication.
- CT scan for progressive symptoms
 - Acute radiation enteritis manifests as diffuse thickening, hyperemia, and hyper-enhancement of the small bowel wall in the pelvis.



- Flexible sigmoidoscopy or colonoscopy for persistent, symptomatic rectal bleeding
 - to rule out disease recurrence or an occult primary tumor.
 - Rectal pallor, telangiectasias, strictures, fistulae, or regions of ulceration



Pale Mucosa +
Telangiectasia



Ulceration,
Bleeding, Fibrosis

Factors related with GI toxocity

- Patient related
 - Prior abdominal or pelvic surgery
 - Coexisting comorbidities, including prior PID, diabetes, arteriosclerosis, collagen vascular disease, inflammatory bowel disease
 - Smoking history

- Treatment related
 - Radiation dose (>50Gy)
 - Daily fraction size
 - Treatment duration
 - Volume of small bowel, large bowel & rectum within RT field
 - Delivery method (intracavity > EBRT)
 - Radiosensitizers, chemotherapy

Improvement in Radiation techniques

- Multiple RT fields
 - to avoid significant dose inhomogeneity
- Belly board with the patient in the prone position and treatment with the patient's bladder full
 - to optimize physical displacement of the small bowel

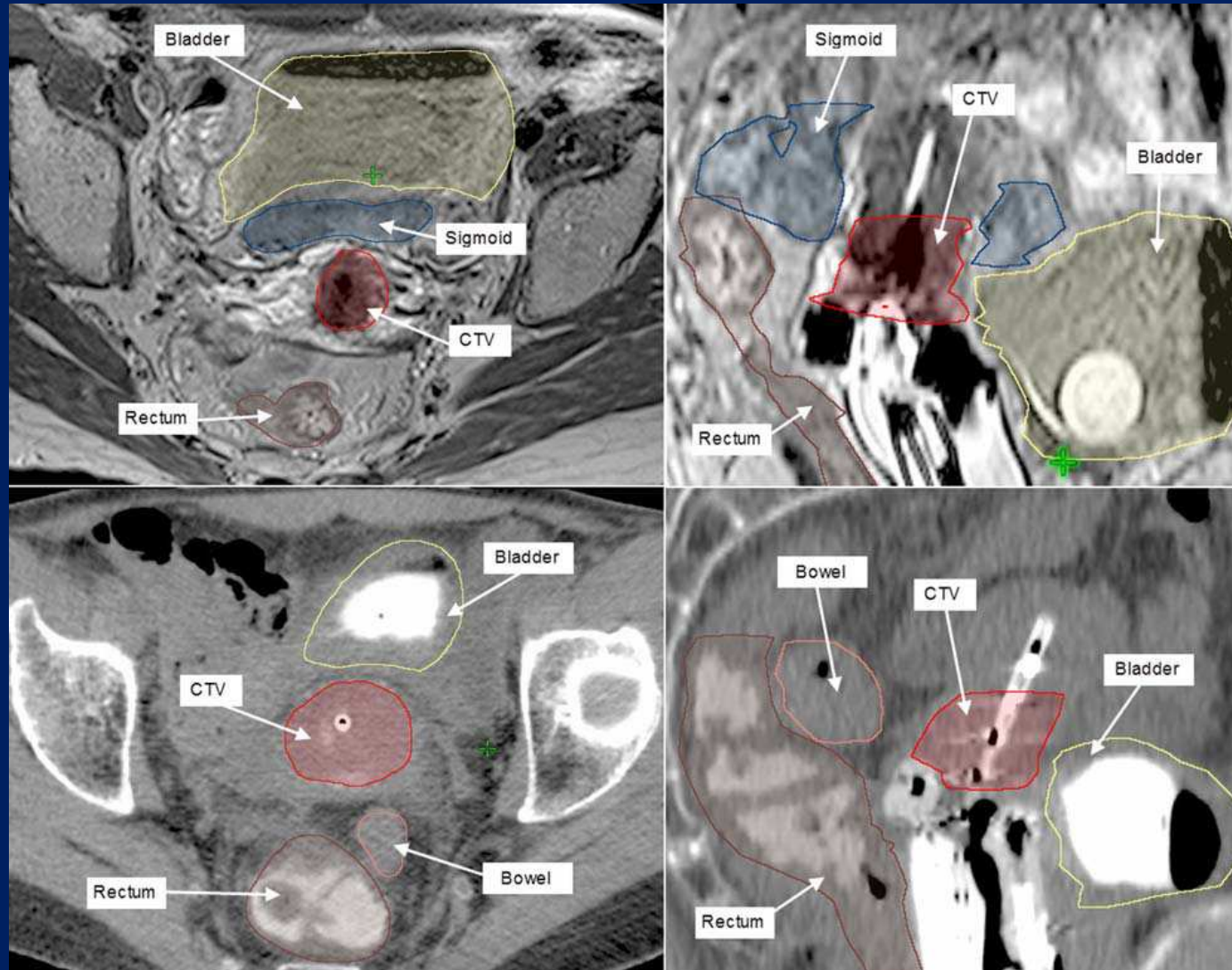
- IMRT optimization
 - uses multiple beams to conform to the tumor and minimize surrounding normal-tissue dose



3-dimensional conformal plans compared with IMRT plan for postoperative endometrial cancer. These images demonstrate bowel sparing with the intensity-modulated radiotherapy plan.

- Adaptive IMRT (image-guided radiation, IGRT)
 - adjustments during treatment with further dose reduction to normal tissues.

- CT or MRI guided HDR brachytherapy



MR axial and sagittal (top) and CT (bottom) brachytherapy images for cervical cancer showing the optimized maximal dose to the tumor while minimizing the dose to the bladder, rectum, and sigmoid.

Published Randomised Study

- A study evaluated the toxicity and clinical outcomes of 44 patients with locally advanced cervical cancer who received either whole-pelvis RT or IMRT at a dose of 50.4 Gy in 28 # administered with concurrent cisplatin 40 mg/m² followed by HDR intracavitary RT.
 - Significantly fewer grade 2 acute GI toxicities with IMRT (63.6% vs 31.8%; p=0.034) and grade 3 acute GI toxicities (27.3% vs 4.5%; p=0.47).
 - Less chronic GI toxicity with IMRT (50% vs 13.6%; p=0.011).
 - Significantly less dose to the rectum and small bowel.

Treatment of common GI toxicities

- Acute Radiation Enteritis
- Chronic Radiation Enteritis
- Acute Radiation Proctitis
- Chronic Radiation Proctitis

Acute Radiation Enteritis

- Mainly supportive
- Encourage oral fluids, IV fluids may be required if patients unable to adequately maintain fluid intake
- Psyllium, probiotics
- Antidiarrheal agents, such as loperamide or diphenoxylate
- Careful monitoring of fluid status & electrolytes
- Aggressive management during treatment is important to reduce the risk of chronic enteropathy.

Chronic Radiation Enteritis

- For Diarrhea - Psyllium, probiotics, low fiber diet
- For Fecal leakage - Physical therapy for perineal strengthening
- For Malabsorption - Vit B12, Cholestyramine
- Parenteral nutrition
- Gastroenterology evaluation
- Surgical intervention for:
 - Persistent ileus
 - Intestinal fistulization
 - Adhesions

Acute Radiation Proctitis (ARP)

- Mainly supportive
- Antidiarrheals
- IV hydration
- Short chain fatty acid butyrate enemas

Late Radiation Proctitis

Medical Management

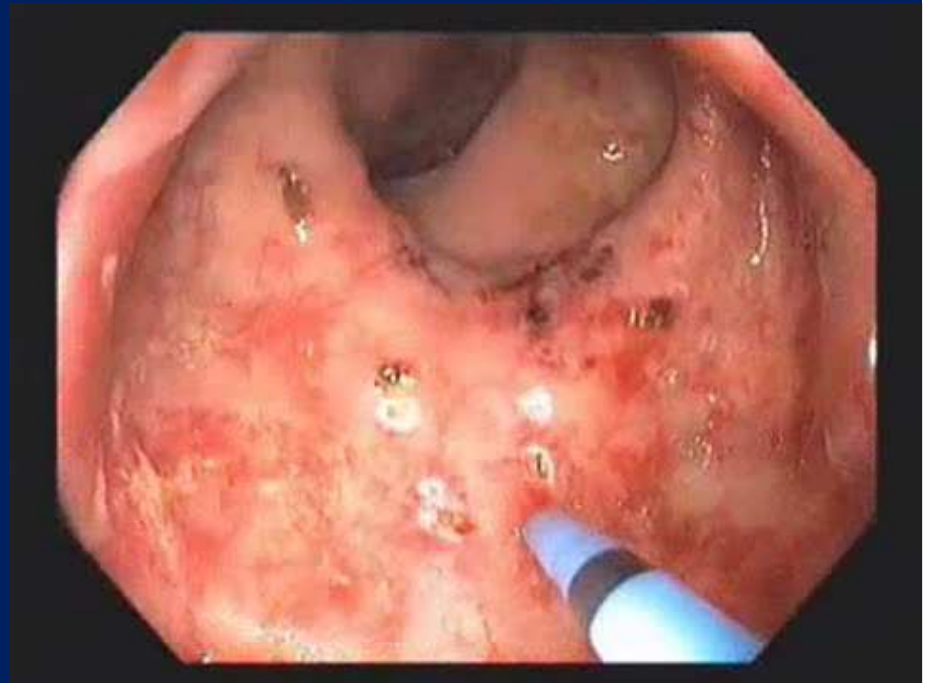
- Enemas (no proven efficacy)
 - Steroids
 - Sucralfate
 - 5-aminosalicylates
 - Butyrate
- Metronidazole 4-week course
- Hyperbaric O₂
 - For chronic rectal bleeding refractory to all other therapy
 - Limited data
 - Expensive
 - Time-consuming (20 - 40 treatments required)

Late Radiation Proctitis – Endoscopic Management

- Topical Formalin
 - Adapted from use in radiation cystitis
 - 4% formalin solution applied
 - Contact time 2-3 min
 - 59 – 100% short term response
 - Minimal relapse
 - Protection of perianal skin important
 - GA often required
 - Fissures, ulcers, strictures reported

Late Radiation Proctitis – Endoscopic Management

- Diathermy
 - Electrode “sticks” to mucosa
 - Unpredictable depth of coagulation
 - Ineffective in excessive bleeding

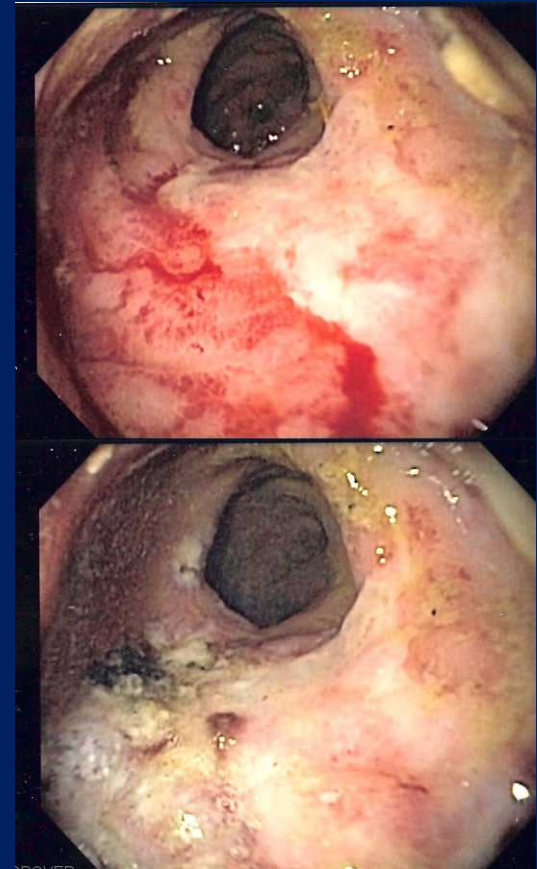


Late Radiation Proctitis – Endoscopic Management

- Laser (Nd:YAG, Argon)
 - 87% short term response
 - 2 - 3 treatments required
 - 70% relapse after cessation of bleeding
 - Maintenance treatments required at 7 month intervals
 - Disadvantages
 - Expensive
 - Inaccessible
 - Risk of perforation
 - Protective precautions required

Late Radiation Proctitis – Endoscopic Management

- Argon Plasma Coagulation
 - Bipolar diathermy current via ionized Argon gas stream
 - Effective in short term
 - 2 - 4 treatments required
 - Minimal relapse
 - Advantages
 - Reduced perforation risk
 - Easier painting of large areas
 - More affordable/accessible than laser
 - Disadvantages
 - Rectal strictures reported
 - Ineffective with excessive bleeding
 - Overdistension with Argon gas



Late Radiation Proctitis – Surgical Management

- Complicated disease
 - Strictures
 - Fistulae
 - Refractory bleeding
- High complication rate (15 - 79%)
 - Postop fistulae (up to 25%)
 - Anastomotic leaks
 - Wound dehiscence
 - Pelvic sepsis

Late Radiation Proctitis – Surgical Management

- Excision - preferred approach
 - Anterior resection + reconstruction
 - APR – perineal wound breakdown in 45%
- Diversion
 - Prior to definitive surgery for strictures or fistulae
 - Not indicated for bleeding

Treatment of other GI toxicities (less common)

- Hemorrhoids
 - Aquaphor/ lidocaine (mixed 1:1) topically
 - Oral pain regimen if severe
- Fistula
 - Surgical evaluation for resection vs. colostomy

- Stricture
 - Surgical evaluation for resection, lysis of adhesions vs. colostomy
- Obstruction:
 - Bowel rest
 - In refractory cases: surgical evaluation for resection vs. colostomy

Genito-urinary Complications of
Pelvic Radiation

Genitourinary Complications

- Occurs in 5-21% patients treated with pelvic RT
- After definitive treatment of cervical cancer with chemoRT
 - 17-40% incidence of low grade acute GU toxicity
 - 28% to 45% grade 1 and 2 late bladder reactions
 - Major urologic complications range from 1.3% to 14.5% at 3 years

- After postoperative RT for endometrial cancer
 - GU complications less common.
 - Low grade toxicity reported in 11-16% of patients.
 - Grade 3 and 4 toxicity is rare.
- For cervical cancer treatment, ureteral strictures incidence
 - 5% after preoperative RT
 - 2.5% after definitive RT

Factors related with GU toxicity

- Patient related
 - Tobacco use
- Treatment related
 - Cumulative RT dose
 - Treatment volume
 - Radiation modality (EBRT, brachytherapy, or both)
 - Prior pelvic surgery

Common GU toxicities

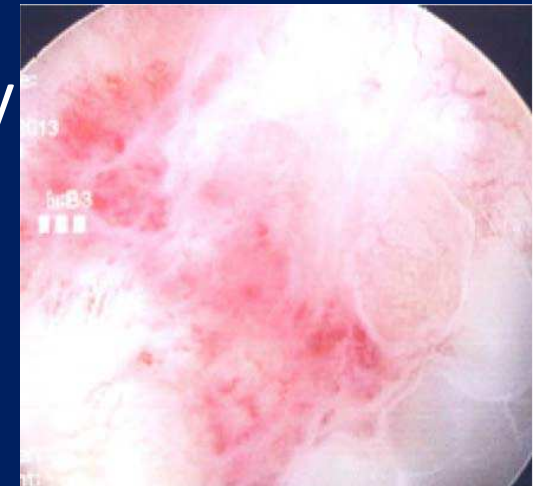
- Acute (0-6 months)
 - Cystitis
- Late (>6 months)
 - Fistula
 - Contracture
 - Cystitis
 - Strictures

Acute Cystitis

- Irritative symptoms (dysuria, frequency, urgency)
- Usually self limiting.
- Urinalysis & urine culture to rule out infection
- Antibiotics if infectious source
- Pyridium/ibuprofen for dysuria
- Anticholinergics like oxybutinin, tolterodine, trospium for urgency.
- If oral agents fail, cystoscopic injection of botulinum toxin
 - 6 to 9 months relief; may be repeated.

Late Radiation Cystitis

- Nonspecific symptoms:
 - Hematuria mild to life threatening
 - Urinary retention due to clot formation
 - Lower urinary tract symptoms like pain, frequency, urgency, incontinence
- Investigations
 - Cystoscopy \pm bladder biopsy if necessary
 - USG or excretory urography



Late Radiation Cystitis - Management

- Resuscitation if hemorrhagic shock is present
 - Aggressive IV fluid replacement ,&
 - Blood transfusion if low hematocrit.
- Bladder catheterisation
- Intermittent or continuous bladder irrigation
 - Continued till urine becomes clear.

Late Radiation Cystitis – Endoscopic Therapy

- TUR / Coagulation for persistent hematuria or unexplained hematuria

Late Radiation Cystitis – Intravesical Therapy

- Aluminium salts, like alum
 - first-line intravesical instillation agent to halt severe hematuria that does not respond to continuous bladder irrigation
 - Used in 1% solution for irrigation with 100-600 ml/hr.
 - Acts by precipitating proteins on cell surface & in interstitial spaces.
 - Aluminium toxicity is possible with underlying renal impairment

Late Radiation Cystitis – Intravesical Therapy

- Formalin
 - Used in patients with severe radiation cystitis refractory to other treatment options
 - 1% solution; instillation under anaesthesia for 10 min.
 - After exclusion of Vesicoureteral reflux
 - Causes denaturation of superficial urothelial layers (creates hemostasis and causes severe pain)
 - S/E common – ureteric stricture, bladder perforation, fistula, contracted bladder, ATN, anuria

Late Radiation Cystitis – Intravesical Therapy

- Other agents:
 - Placental extract
 - Prostaglandins
 - Silver nitrate
 - Cystistat (Sodium hyaluronate)

Late Radiation Cystitis – Other Interventions

- Cystoscopy with fulguration
 - By electrocoagulation, diathermy, argon laser or Nd-Yag laser
- Cystoscopic injection of Botulinum toxin A
- Surgical interventions:
 - Selective embolization or ligation of iliac arteries
 - Urinary diversion \pm cystectomy
- Hyperbaric oxygen therapy

Uncommon Late GU Toxicities

- Ureteral strictures
- Fistulae
- Contractures

Ureteral strictures

- Symptoms:
 - Pain, hesitancy
- Investigation:
 - Retrograde urethrogram
 - CT or MRI to rule out recurrent disease
- Management:
 - Surgical dilatation (urethral)
 - Stent placement (ureteral)
 - Urethroplasty
 - Ureteroplasty

Fistulae

- Vesicovaginal fistula
 - Patients with bladder involvement at diagnosis are at increased risk of VVF after definitive RT.
 - Biopsy to rule out recurrence
 - Management:
 - Simple fulguration & catheter drainage
 - Open surgical repair
 - Ileal conduit

Fistulae

- Ureteroarterial fistula
 - Rare
 - Treatment
 - Endovascular stent placement
 - Open surgical repair

Contractures

- May present with frequency & pain
- Treatment:
 - Cystectomy with ileal conduit
 - Bladder augmentation in severe cases

*Sexual Dysfunction after Pelvic
Radiation*

Sexual Function after Pelvic Radiation

- Sexual dysfunction in upto ~50% women receiving pelvic RT for gynecological malignancies.
- Ovarian failure in premenopausal patients
 - Typically within 6 months of treatment.
- Vaginal stenosis (20-88%)
 - Most likely to occur within first year of treatment.

Factors related with sexual dysfunction

- Patient related
 - Age >50 yrs
 - Lack of compliance with dilator use
- Treatment related
 - Higher RT dose
 - Concomitant chemoRT

Treatment of Sexual Dysfunction

Vaginal stenosis

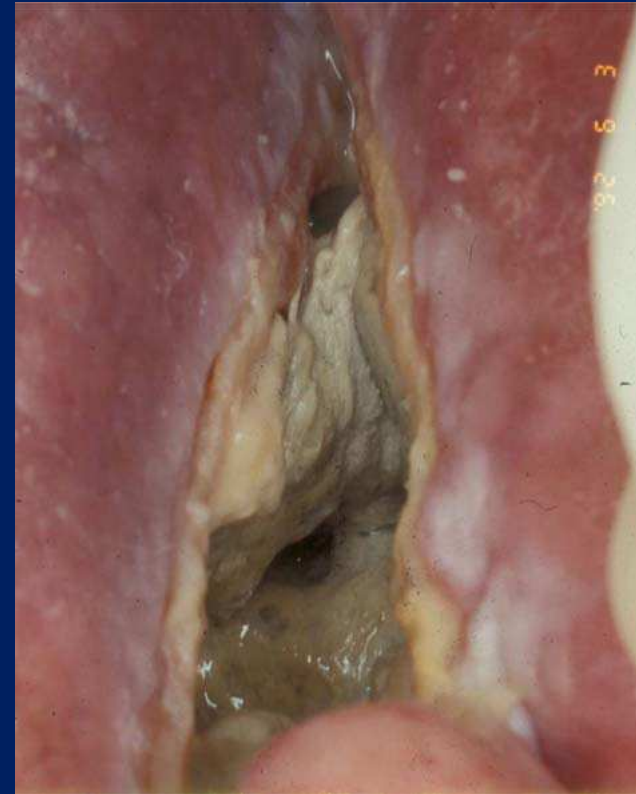
- Prevention
 - Vaginal dilators
- Treatment
 - Topical estrogen
 - Benzylamine
 - Hyperbaric O₂
 - Surgical reconstruction

Ovarian failure

- Hot flashes, mood changes
 - Supplemental oral progesterone &/or estrogen or SSRI
- Vaginal dryness
 - Vaginal estrogen

Rare Toxicity - Vaginal Necrosis

- May result from high doses of RT, especially in patients who underwent reirradiation
- ↑ risk with HDR interstitial BT
- Treatment
 - Hydrogen peroxide douching with a dilution of at least 1:10 with saline
 - Oral metronidazole
 - Hyperbaric oxygen



*Hematological Toxicity of Pelvic
Radiation*

Factors related with hematological toxicity

- Higher RT dose
- Extended field RT
- Radiation technique (conventional vs. IMRT)
- Concurrent chemotherapy

Hematologic toxicity

- Damage to bone marrow microenvironment.
- Predisposes to infection, hospitalization
- Requirements of transfusions & growth factors.
- May lead to delayed or missed CT cycles & treatment breaks –↓disease control.
- 20-25% grade ≥ 3 hematologic toxicity with cisplatin-based pelvic chemoRT

Limiting hematological toxicity

- IMRT – less BM irradiation
- Sparing functional BM subregions
 - May be identified using PET, SPECT or specialised MRI sequences
 - Irradiation of BM subregions with higher F¹⁸-FDG PET activity was associated with hematologic toxicity, whereas irradiation of subregions with lower FDG activity was not.

Acute Hematological Toxicity- Management

- Routine weekly blood counts.
- CT typically held when
 - Neutrophil count $< 1500 /\mu\text{L}$
 - Platelet count $< 100,000/\mu\text{L}$
- RT held when
 - Neutrophil count approaches $500/\mu\text{L}$ to $1000/\mu\text{L}$.
 - Platelet count $< 40,000/\mu\text{L}$

Acute Hematological Toxicity- Anemia

- Standard recommendation for patients with cervical cancer is to transfuse to maintain a hemoglobin level above 10 mg/dL for patient's QOL, treatment tolerance & potential impact on outcomes.

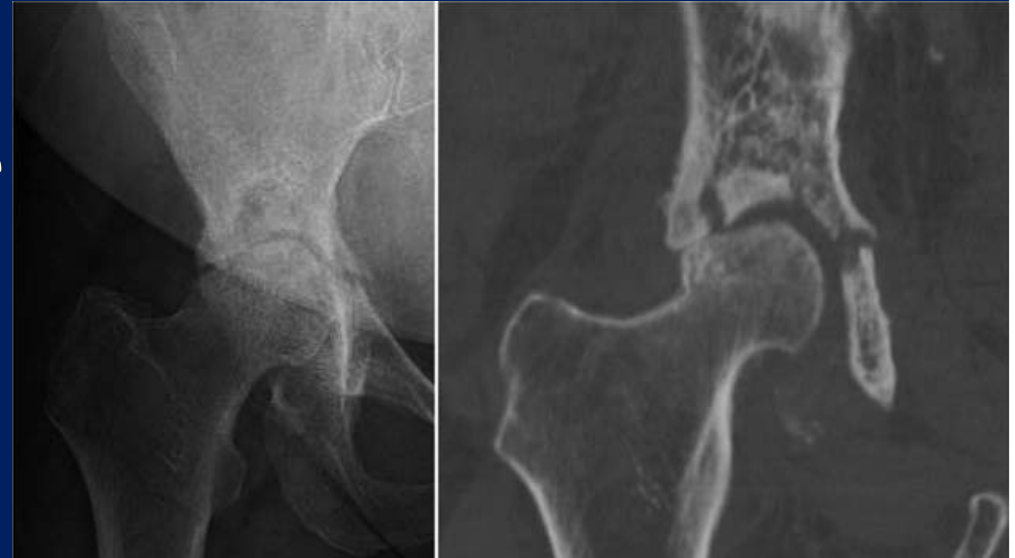
Acute Hematological Toxicity- Anemia

- Erythropoietin.
 - Risks:
 - ↑ Thrombotic events
 - Possible ↓ survival
 - Time to tumor progression ↓
 - Benefits: transfusion avoidance & gradual improvement in anemia related symptoms

*Bone Complications of Pelvic
Radiation*

Bone complications

- Osteopenia
- Pelvic insufficiency fracture (PIF)
 - 10-29% reported incidence
 - >60% multiple fractures involving sacrum, acetabulum, or pubic bone
 - Upto 50% bilateral
- Avascular necrosis
- Second malignancies



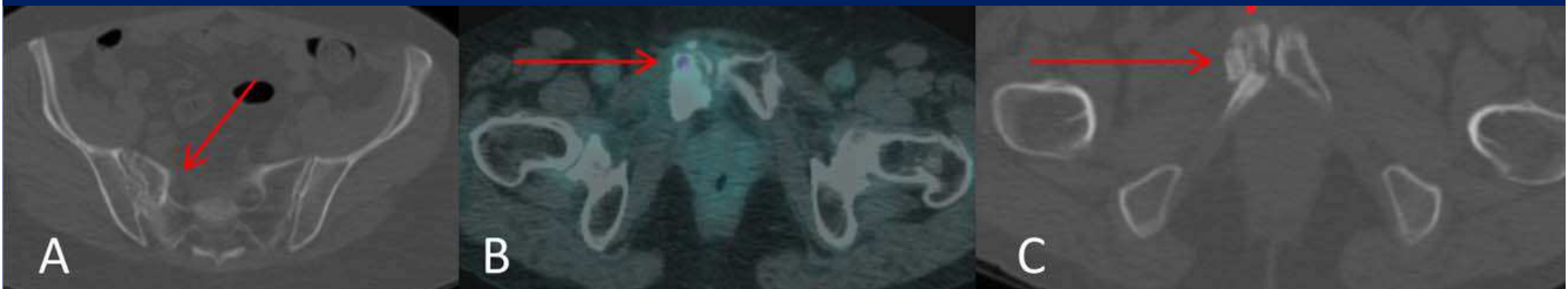
Avascular necrosis of the femoral head in a 50-year-old 13 years after chemoradiation for cervical cancer. Right femoral head/acetabulum pathologic fracture identified on (Left) x-ray and (Right) computed tomography.

Factors related with bone complications

- Radiation dose (>50 Gy)
- Age
- Menopausal status
- Underlying bone weakness (osteopenia or osteoporosis)
- Corticosteroid use
- Cigarette smoking
- Vascular integrity
- Low BMI
- Prior fractures
- Reirradiation
- Prior hormone replacement therapy

Bone complications - Diagnosis

- Often delayed because clinical presentation & radiographic findings may mimic metastatic lesions, hip osteoarthritis & spinal stenosis.
- Nonspecific clinical features
 - Back, hip & leg pain
- X ray, CT scan \pm MRI
- Bone scintigraphy sensitive to detect PIF
- DEXA scan for osteopenia



(A) Sacral insufficiency fracture (B) A pubic symphyseal fracture
(C) Fracture lucency with adjacent sclerosis

Bone complications - Treatment

- Fractures classified into 4 types to guide management of PIF
 - based on the ability of the bony and ligamentous pelvic structures to withstand physiologic loads without displacement.
- Stable type I fractures: nonoperative treatment
- Type 2 fractures: nonoperative or minimally invasive surgical fixation
- Type 3 & 4: surgical stabilization.

Bone complications - Treatment

- Nonoperative treatment measures
 - NSAIDs & pain medication
 - Slow progression from bed rest to full mobilization with full weight-bearing on affected side
- Prolonged course of physical therapy
 - For 6 to 12 months
- Incomplete & isolated sacral ala fractures
 - Sacroplasty
- Femoral neck fractures
 - Surgical intervention within 24 to 48 hrs
 - Total hip replacement
 - Hemiarthroplasty

*Dermatological Toxicity of Pelvic
Radiation*

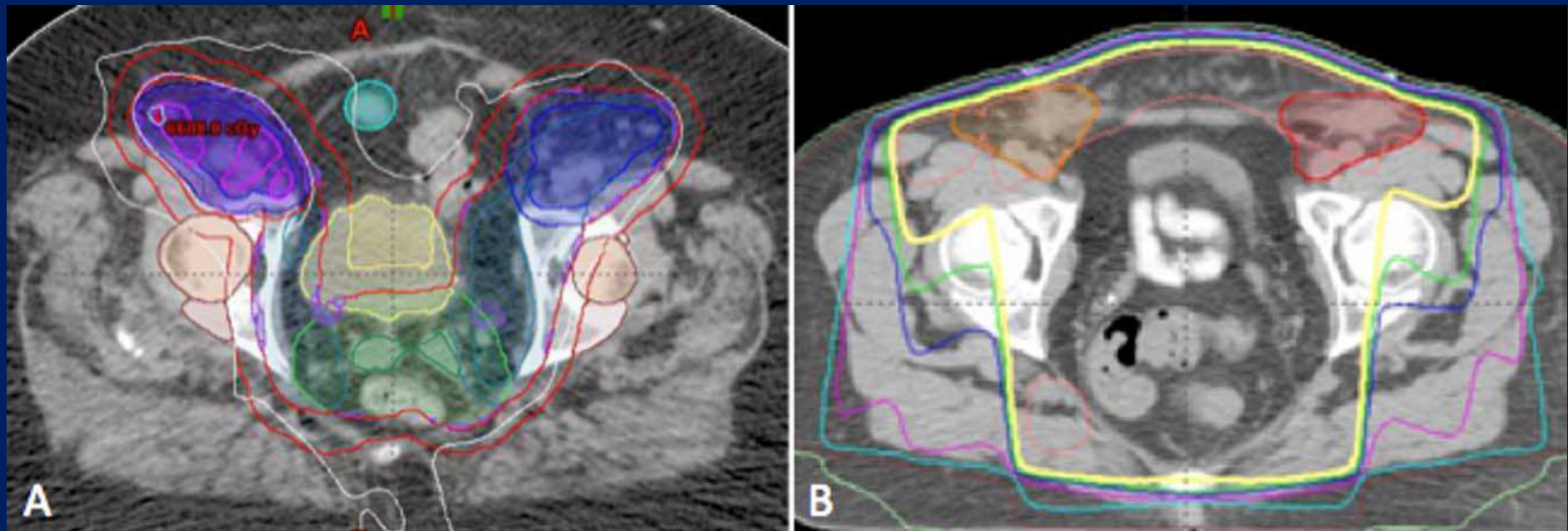
Dermatologic toxicity

- Acute
 - Dermatitis
 - Desquamation
- Late
 - Hyperpigmentation or hypopigmentation
 - Telangiectasia
 - Textural changes (xerosis & hyperkeratosis)
 - Fibrosis
 - Ulceration
 - Necrosis

Factors related with dermatologic complications

- Patient related
 - Vascular disease
 - Smoking
 - Poor nutrition
 - High BMI due to skin folds
 - Concurrent fungal or bacterial infection
- Treatment related
 - Radiation technique

- IMRT may decrease risk of vulvar toxicity
 - Lower radiation dose within skin & subcutaneous tissue, particularly within groin.



(A) intensity-modulated radiotherapy (IMRT) versus (B) 3-dimensional conformal radiotherapy treatment plans for a patient with vulvar carcinoma. The IMRT plan depicts femoral head sparing.

Acute Dermatologic toxicity

- Grade 1 and 2 skin reactions are common in gynecologic RT
 - 10% - 50% in cervical and endometrial cancer
 - 85% to 100% in the treatment of vulvar cancer.
- Severe skin reactions are rare (1%-5%) in the treatment of endometrial and cervical cancer, whereas patients with vulvar cancer are at significantly higher risk (24%-53%) of moist desquamation and wound complication.

Acute Dermatologic toxicity - Treatment

- Mild skin reactions
 - Topical moisturisers without added perfumes or metals
 - Moisturising creams may prevent onset.
 - Daily sitz bath with addition of sodium bicarbonate, epsom salts, or Domeboro soaks
 - Gentle cleaning with mild, unperfumed soap
- Candida infection
 - Daily treatment with fluconazole
- Loose-fitting & cotton clothing
- Pruritis:
 - 1% hydrocortisone cream

Acute Dermatologic toxicity - Treatment

- Desquamation
 - Application of silver clear nylon, nonadherent or hydrogel dressings
 - Vaseline gel impregnated with antibiotics
 - Treatment break should be considered
 - Pain medications like NSAIDs

Late Dermatological Toxicity

- Incidence
 - 0% for cervical cancer (grade 3)
 - Upto 20% in vulvar cancer (grade ≥ 2)
- Recurrent episodes of cellulitis reported in 1 - 16% vulvar cancer patients.
- Twice daily use of a 1:10 diluted hydrogen peroxide douche can prevent the formation of necrotic tissue.

Chemotherapy Related Complications

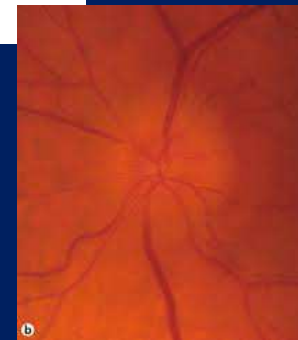
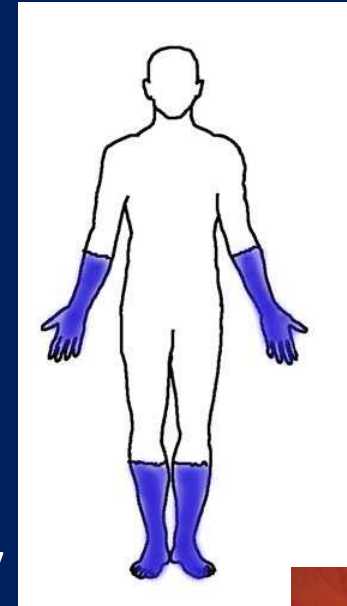
Concurrent Cisplatin

Most commonly used agent for concurrent chemotherapy

Common side effects are:

- Nephrotoxicity
 - 35-40% patients
 - Dose related, reversible
- Ototoxicity
 - high frequency hearing loss & tinnitus
- Myelosuppression
 - 25-30% patients
- Gastrointestinal
 - Nausea & vomiting: acute or delayed
 - Diarrhea
- Metallic taste of food & loss of appetite

- Electrolyte imbalances
 - ↓ Mg^{2+} , ↓ Ca^{2+} , ↓ K^{+}
- Hyperuricemia
- Neurotoxicity:
 - peripheral sensory neuropathy
- Ocular toxicity:
 - optic neuritis, papilledema, cerebral blindness
- Hypersensitivity reactions
 - Facial edema, wheezing, hypotension & bronchospasm.



Other less common side effects are:

- Vascular toxicities like myocardial infarction, cerebrovascular accident, etc
- Hepatotoxicity
- SIADH
- Alopecia

Other Chemotherapy Drugs

Used as

- Neoadjuvant
- Adjuvant
- Palliative in case of recurrence

Paclitaxel - Carboplatin

- Myelosuppression
- Infusion reactions
- Neurotoxicity
- Alopecia
- Mucositis
- Diarrhea



Cyclophosphamide/ Adriamycin/ Cisplatin regime

- Myelosuppression
- Nausea & vomiting, diarrhea
- Alopecia
- Cardiotoxicity
- Amenorrhea, sterility
- Strong vesicant



Liposomal Doxorubicin Based Regimes

- Myelosuppression
- Hand-foot syndrome
- Stomatitis
- Cardiac toxicity
- Infusion related reactions

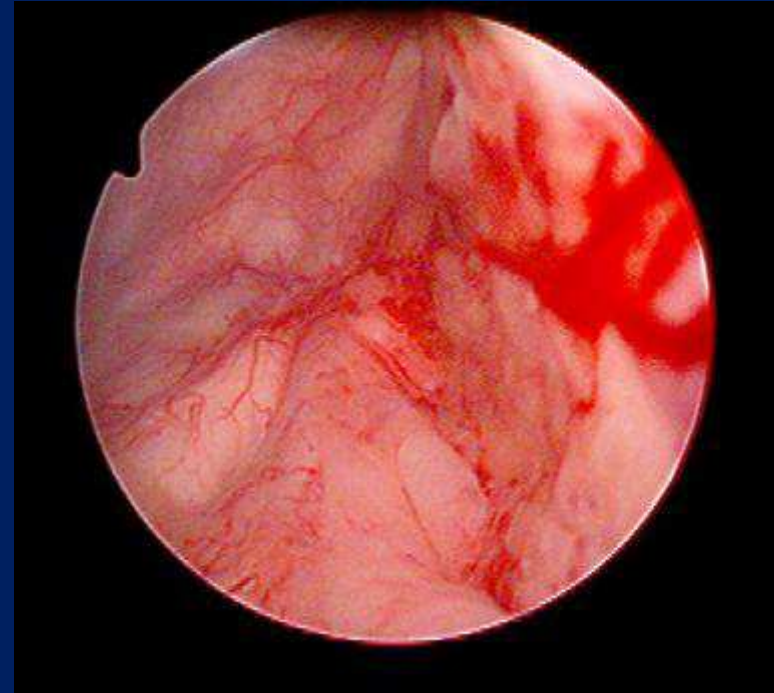


Gemcitabine Based Regimes

- Schedule dependent toxicity
 - Infusion >60 mins
 - Hypotension, Flu-like syndrome, myelosuppression & asthenia
- Myelosuppression
- Pulmonary toxicity & respiratory failure
- Hemolytic uremic syndrome
- Hepatic toxicity
- Capillary leak syndrome
- Posterior reversible encephalopathy syndrome

Ifosfamide Based Regimes

- Hemorrhagic cystitis
- Myelosuppression
- Neurotoxicity
- Alopecia



Other Newer Drugs

- Topotecan
 - Myelosuppression
 - Diarrhea
 - Interstitial lung disease
- Bevacizumab
 - GI perforation
 - Hemorrhage: GI bleed, hemoptysis, epistaxis, CNS hemorrhage, vaginal bleeding
 - Wound healing complications

Chemotherapy Induced Neutropenia

- Febrile Neutropenia: Single temperature ≥ 38.3 °C orally or ≥ 38.0 °C over 1 hr; neutropenia < 500 neutrophils/ μL or < 1000 neutrophils/ μL & a predicted decline to < 500 neutrophils/ μL over next 48 hrs.

Chemotherapy Induced Neutropenia

- Risk assessment for infection based on
 - Underlying malignancy
 - Duration of neutropenia
 - Prior Chemotherapy

Risk	Antimicrobial prophylaxis
Low	None
Intermediate to High	Bacterial- Consider fluoroquinolone Fungal- Consider fluconazole during neutropenia Viral- during neutropenia & longer depending on risk

Prophylactic G-CSF

- For high risk (>20%) of febrile neutropenia.
- Risk assessment for febrile neutropenia based on
 - Disease
 - Chemotherapy regimen
 - (High-dose or Dose-dense or standard-dose therapy)
 - Patient risk factors
 - (MASCC risk index: ≥ 21 =low)
 - Treatment intent
 - (curative vs. palliative)

MASCC risk index.	
Characteristic	Score
Burden of illness	
No or mild symptoms	5
Moderate symptoms	3
No hypotension	5
No chronic obstructive pulmonary disease	4
Solid tumour/lymphoma or no previous fungal infection	4
No dehydration	3
Outpatient status at onset of fever	3
Age < 60 years	2

MASCC, Multinational Association for Supportive Care in Cancer.

Therapeutic G-CSF

- Possible indications:
 - Sepsis syndrome
 - Age >65 yrs
 - Severe neutropenia (ANC <100/ μ L)
 - Neutropenia expected to be > 10 days duration
 - Pneumonia
 - Invasive fungal infection
 - Clinically documented infections
 - Hospitalization at time of fever
 - Prior episode of febrile neutropenia
- Filgrastim or filgrastim-sndz 5 μ g/kg daily or sargramostim 250 μ g/m²/day continue through post-nadir recovery.

Thank you