RADIATION INDUCED SMALL BOWEL DISEASE

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INTRODUCTION

- Radiation therapy is not regularly indicated in the treatment of small bowel disease.
- Reasons are complex and related to the relative sensitivity of the small bowel to radiation, its mobility and the difficulty in defining the treated area.
- The small bowel is very susceptible to radiotherapy as doses that cause injury are very close to therapeutic doses.
- We discuss Radiation Induced Small Bowel Disease- pathophysiology, clinical presentation, prevention strategies and treatment.

INTRODUCTION

- Small bowel: consists of duodenum, jejunum, ileum
  - Extends from pylorus of stomach to ileocecal junction
  - Joins cecum(first part of large intestine) at ileocecal junction
  - Duodenum is the first and shortest (25cm) part. Most fixed part
  - Together ileum and jejunum 6-7 meters long in cadavers, shorter in living humans due to tonic contractions. Not fixed.
  - Terminal ileum usually lies in the pelvis
  - Small bowel is closely related to colon and rectum
- Radiotherapy indications include GI, Urological, Gynae cancers
- Pts subsequently develop GI side effects/injuries
- NB: injuries may overlap

RT INDUCED SMALL BOWEL DISEASE

- Injury to small bowel resulting from RT, excludes colon & rectum
- Radiation enteropathy / mucositis - describes disease process
- Pelvic radiation disease – describes the phenomenon of GI injury secondary to RT
- RT induced small bowel disease- is the most accurate description
- Two types of injuries exist: acute and chronic

ACUTE FORM

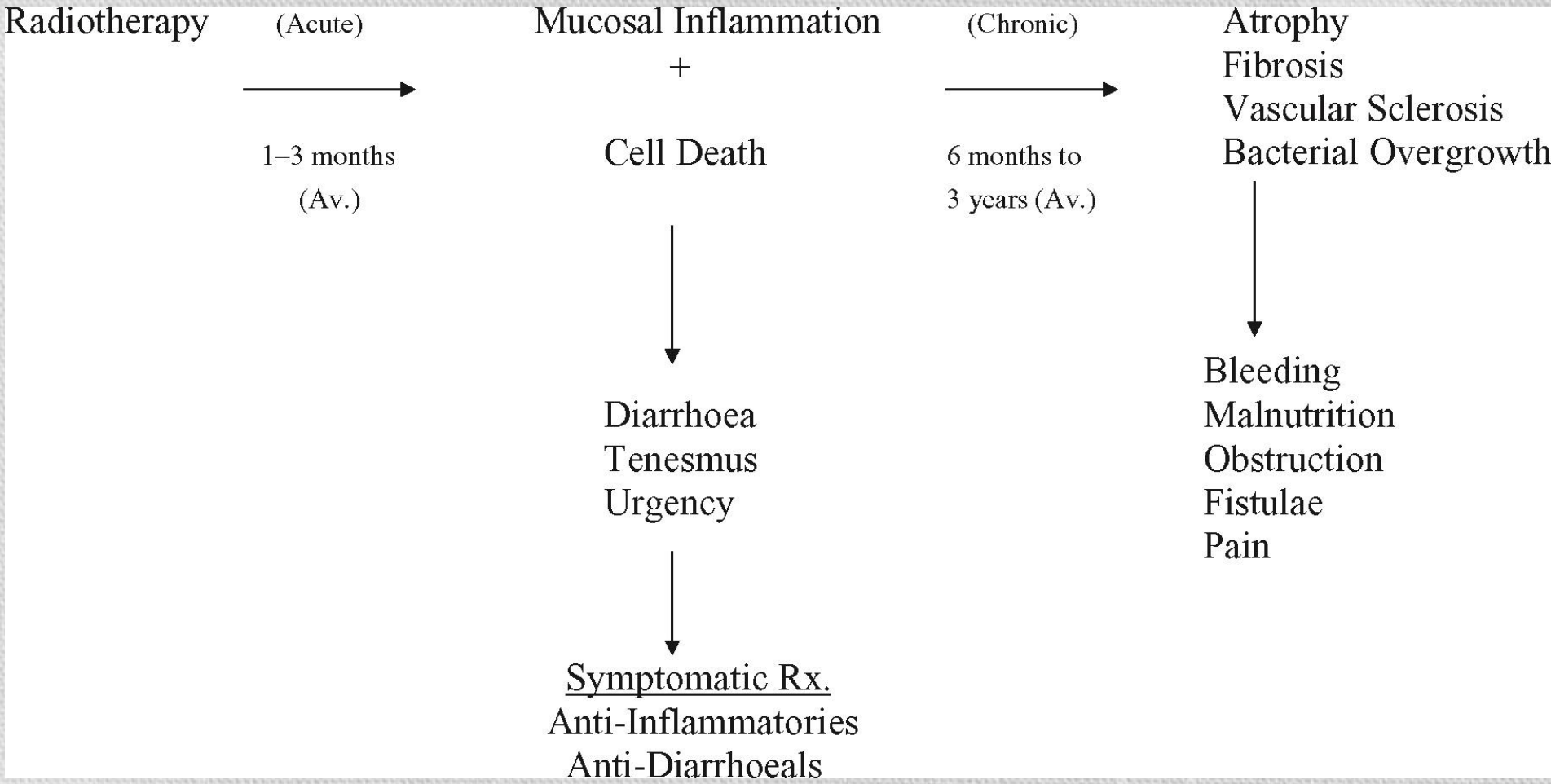
- Presents during or shortly after a course of radiotherapy
- Acute injury is due to damage to mitotically active intestinal crypt cells.
- Patients notice symptoms during the second week of treatment- when tissue damage and inflammation is probably at a maximum
- Symptoms peak by 4^{th}-5^{th} week – when histological changes are stable/improving
- Symptoms: colicky abdominal pain, bloating, loss of appetite, nausea, diarrhea and fecal urgency

CHRONIC FORM

- Develops between 18months and 6years after completed course of radiotherapy
- chronic injury affects less mitotically active vascular endothelial and connective tissue cells.
- Chronic enteropathy presents in many different ways including post-prandial pain, acute or intermittent small bowel obstruction, nausea, anorexia, weight loss, bloating, diarrhea, steatorrhea and malabsorption of nutrients

PATHOGENESIS

- Complex injury type- repetitive injury, different healing
- Changes in small bowel
  - inflammation/cell death
  - persistent cytokine activation in submucosa
  - fibrosis of connective tissue with arteriolar endarteritis
  - tissue ischemia, mucosal friability, neovascularization, progressive fibrosis
  - multiple areas of dysfunction, stricturing disease
- Clinical presentation depends on
  - degree/extent of tissue damage
  - site of injury


Radiotherapy
(Acute)
1–3 months
(Av.)
Mucosal Inflammation
+
Cell Death
Diarrhoea
Tenesmus
Urgency
Symptomatic Rx.
Anti-Inflammatories
Anti-Diarrhoeals
(Chronic)
6 months to
3 years (Av.)
Atrophy
Fibrosis
Vascular Sclerosis
Bacterial Overgrowth
Bleeding
Malnutrition
Obstruction
Fistulae
Pain

PATHOGENESIS

- Intestinal damage is related to
  - radiation regime
  - size of treatment field
  - site of treatment field
  - area of normal bowel that is exposed
  - use of concurrent chemo
  - presence of radiation implants
- Decreased blood flow to bowel wall increases the risk of radiation injury.

PATHOGENESIS

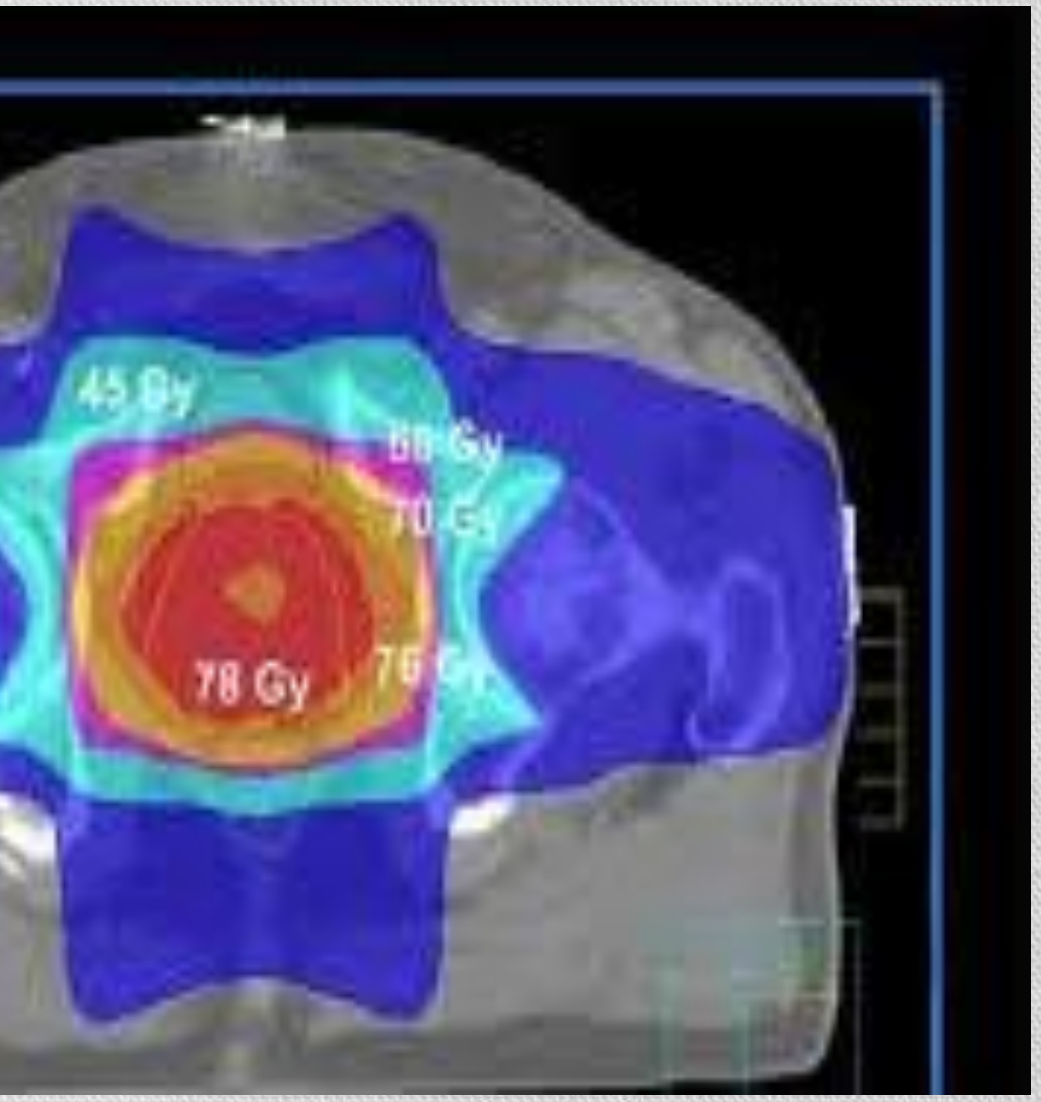
- Patients at increased risk
  - Hypertension, DM, generalised atherosclerosis
  - Previous surgery
  - chemotherapy (Doxorubicin, Methotrexate, 5Fu, Bleomycin- all increase sensitivity to RT)
  - ? Irritable bowel disorder (limited data)
  - Thin elderly females (more intestines in the pelvic area)

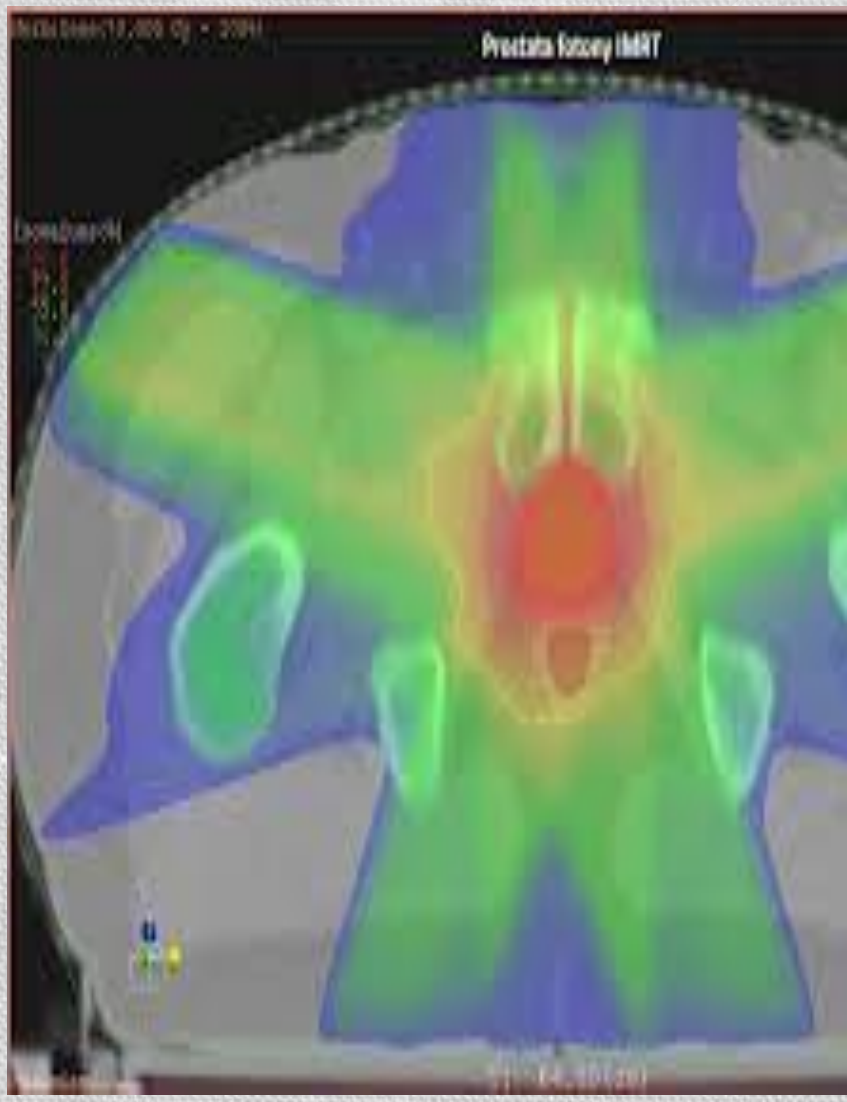
CLINICAL PRESENTATION

- Gastrointestinal symptoms
  - commonest for oncology patients
  - impact quality of life
  - under-reported
- NB – educate patients on S/E and self reporting
- Symptoms under recognized by doctors
- Alarm features – rectal bleeding, weight loss ➔ prompt gastro referral
- Surgeons need to be aware
  - prior radiotherapy is a risk factor for strictures and adhesions
  - Patients can present with sub-acute or intermittent bowel obstruction

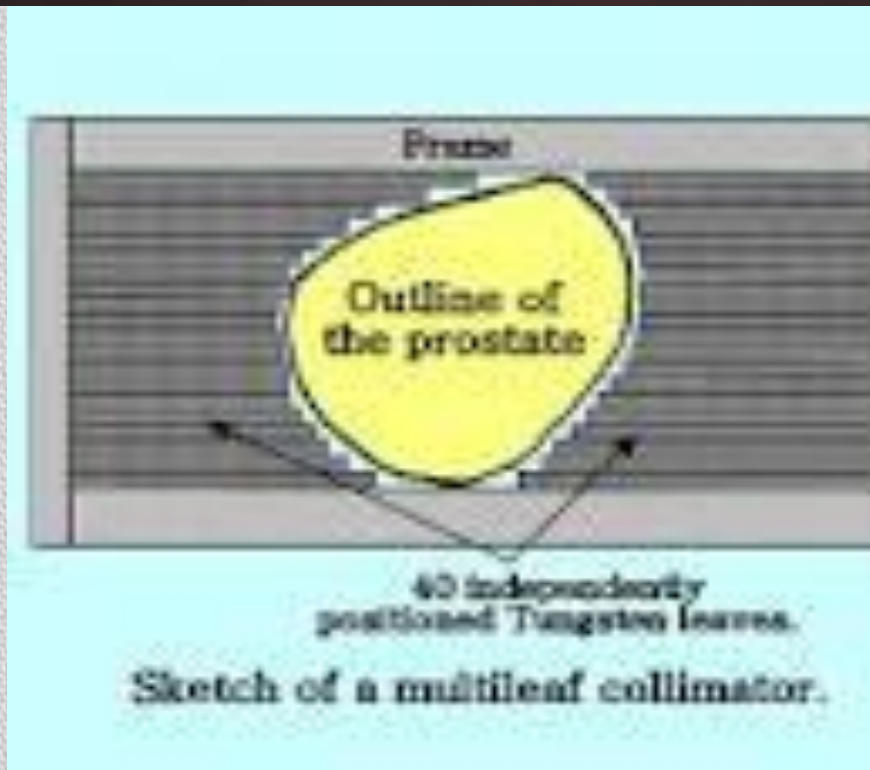
PREVENTION STRATEGIES

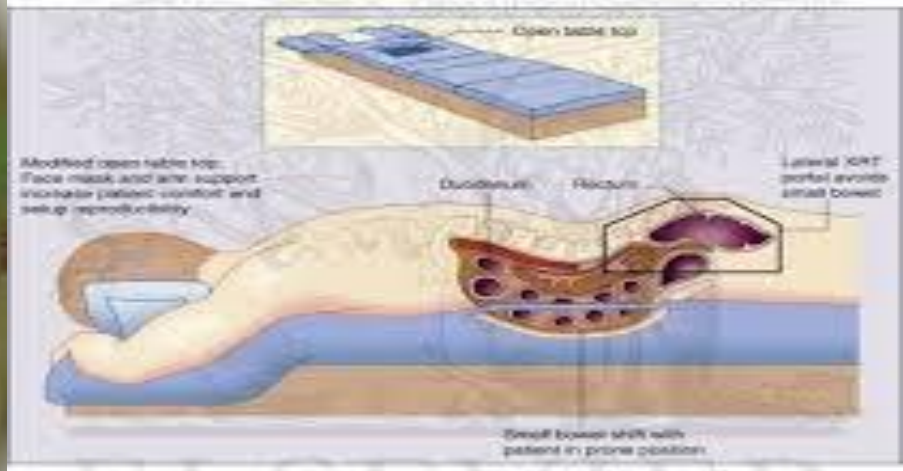
- Use of modern imaging and radiotherapy techniques to minimize radiation exposure to normal tissues
  - IMRT(multiple beams, nonuniform dose across field)
  - image guided techniques (cone beam CT prior to Rx)
  - patient position (prone/decubitus) and positioning devices (belly board)
  - Full bladder
- Consider circadian rhythm effects
  - patients treated in the morning have more GI side effects, similar oncological therapeutic response
  - logistical problem – limited capacity for evening treatments
- Use of Statins and ACE inhibitors
  - In vitro studies show anti-inflammatory/fibrotic/thrombotic potential of statins in irradiated human cells
  - ACE inhibitors play a role in blood pressure homeostasis


45 Gy
78 Gy


Prostate Fatcey IMRT


motors
leaves
motors
leaves


Outline of
the prostate
40 independently
positioned Tungsten leaves.
Sketch of a multileaf collimator.



PREVENTION STRATEGIES

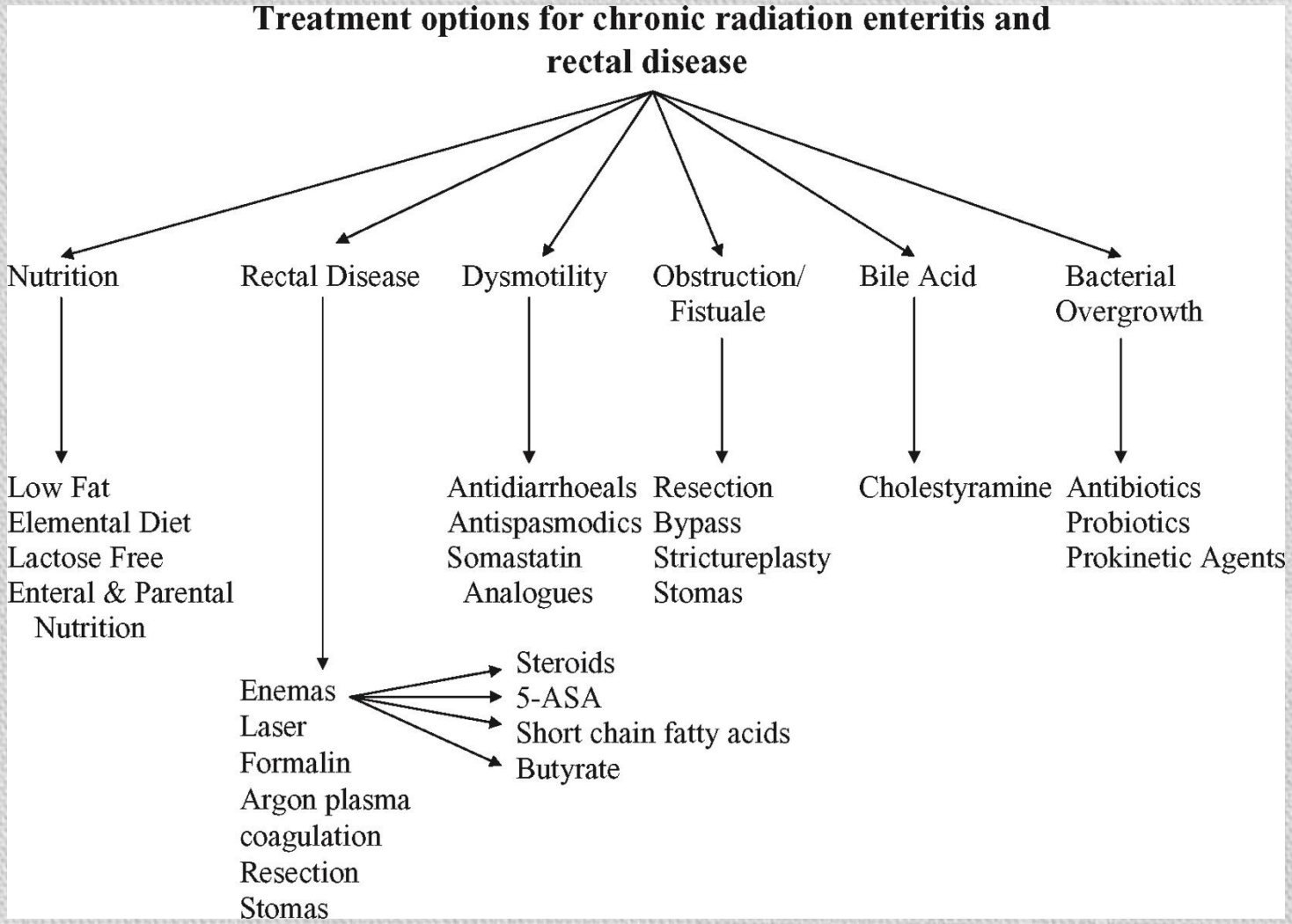
- Use of pro-biotics
  - help restore indigenous gut flora – NB for normal mucosa function
  - emerging evidence they may have radio-protective effect
- Surgical techniques
  - absorbable mesh slings- in early postop period these prevent the small bowel becoming adhered into the pelvis
  - space-occupying silicone prosthesis have been used to exclude the small bowel from pelvis
  - repeat surgery post radiotherapy – to remove implants, alternatively inflatable implants may be used

QUANTEC

- V15< 120cc – individual bowel loops
- Normal tissue constraint guidelines in clinical practice

TREATMENT

- Acute setting
  - Supportive- eg. loperamide, octreotide
  - Dietary – lactose free diet, low fat
- Chronic setting
  - Supportive Rx- symptom based eg. antimotility, analgesics, anti-emetics
  - antibiotics for small bowel bacterial overgrowth
  - Cholestyramine for bile salt malabsorption
  - Dietician consult- patients need sufficient caloric intake, vitamin & mineral supplements
  - In some patients parenteral support is necessary
  - Hyperbaric oxygen- decreases tissue hypoxia, encourage angiogenesis
  - Endoscopic therapies- argon plasma coagulation, enteroscopy


Treatment options for chronic radiation enteritis and rectal disease
Nutrition
Rectal Disease
Dysmotility
Obstruction/ Fistuale
Bile Acid
Bacterial Overgrowth
Low Fat
Elemental Diet
Lactose Free
Enteral & Parental Nutrition
Antidiarrhoeals
Antispasmodics
Somastatin Analogues
Resection
Bypass
Strictureplasty
Stomas
Cholestyramine
Antibiotics
Probiotics
Prokinetic Agents
Enemas
Laser
Formalin
Argon plasma coagulation
Resection
Stomas
Steroids
5-ASA
Short chain fatty acids
Butyrate

TREATMENT

- Surgery in post radiotherapy setting
  - Contoversy : resection vs bypass
  - Resection with primary anastamosis- ?bowel ends viability and fistula formation
  - Bypassing- leave behind diseased bowel, prone to perforation+ sepsis+fistula formation+ blind loop syndrome
  - Challenging surgery due to adhesions & fibrosis
  - Difficult wound healing
  - Patients with strictures & bowel obstruction need surgery
  - Patients with extensive bowel involvement are at increased risk for high output stoma
  - Surgical candidates need thorough evaluation pre-op
  - Need dedicated/ interested surgeons as part of the team

CONCLUSION

- New radiotherapy techniques decrease inadvertent exposure to adjacent normal tissue
- Preventative agents including ACE inhibitors and statins are an area of new research
- Treatment in acute phase is mostly supportive
- In the chronic phase – the key is to recognize and refer patients for specialist advice, eg gastroenterologist with interest in the field
- Patients need a targeted workup for the symptoms they have
- The small subset who require surgery should be directed to surgeons with experience in dealing with this challenging situation