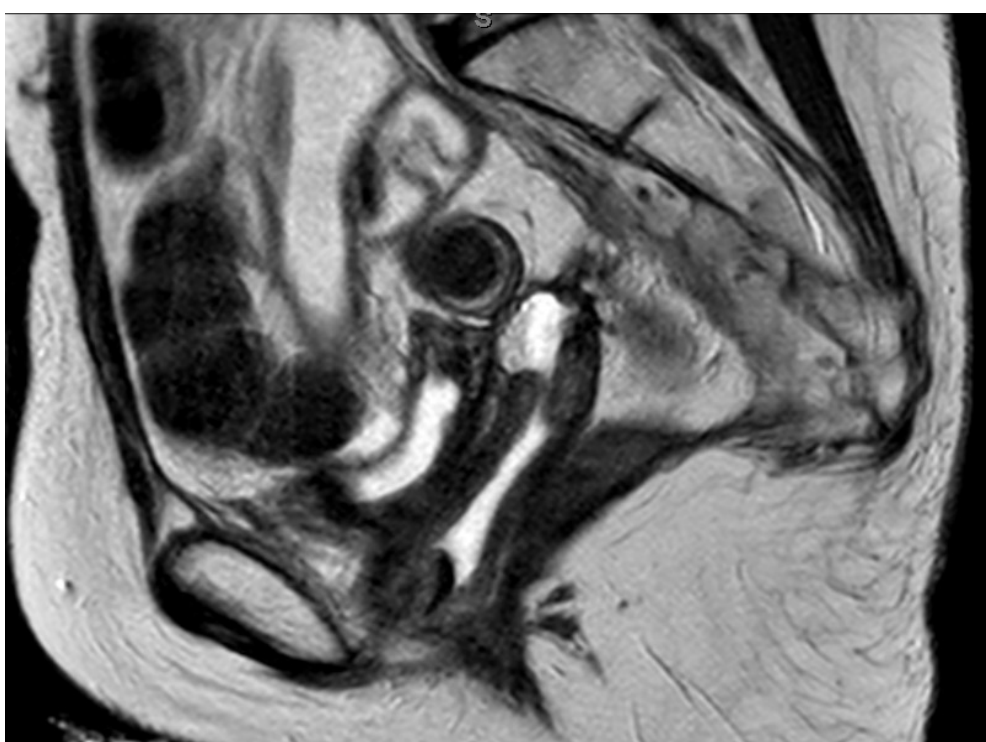


Radiotherapy for Gynaecological Malignancy; Complexity of Post Treatment Individualised Management'

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Pelvic Radiation Disease (PRD)

- ‘One or more symptoms of variable complexity as a consequence of pelvic radiotherapy’⁽³⁾
- Affects over **6000 patients annually** in the UK, over 24% report bowel symptoms at a year^(1,2).
- Organ systems affected include: **genitourinary**, nerves, vessels and lymphatics, **gastrointestinal**
- **Gastrointestinal symptoms due to PRD outnumber new Crohn’s diagnoses per year⁽¹⁾**
- Symptoms range from dyschezia and bowel disturbances to bowel obstructions and fistulas



Preventative considerations:

- **Intensity modulated radiotherapy** showed reduction in PRD up to 1 year after treatment in endometrial and cervical cancer patients however no difference at 3 or 10 years in incidence^(4,8).
- **Improvements in linear accelerators** - three-dimensional conformal radiotherapy demonstrates reduced late gastrointestinal toxicity⁽¹⁰⁾
- **Amifostine** is a thiophosphate cytoprotective radioprotective agent and free radical scavenger drug. Can be given IV, subcutaneously or per rectum during radiation treatment⁽⁹⁾.
 - IV hard to tolerate >20% discontinuation due to side effects (nausea, vomiting, asthenia, hypotension, local erythema and pruritis).
- Overall evidence demonstrates good effect in prevention of early PRD (intrarectally). Effect in late PRD limited research, conflicting results⁽⁹⁾.

Pathogenesis:

- Complex and multi-faceted.
- Ionising radiation **direct effects** include breaks in double stranded DNA, inability for RNA to be transcribed, or sugar and base damage can lead to cell death due to an inability to undergo cell repair^(5,6,7).
- The result is altered gene expression, protein modification, and apoptosis.
- Radiolysis of water molecules creates **reactive oxygen species** causing oxidative stress to cells resulting in injury^(5,6,7).
- Adjacent cells outside the radiation boundary via cell signalling pathways can undergo change known as **bystander effect**^(5,6,7).

Sequalae of pelvic radiation disease

- Acute Phase is the inflammatory phase in response to oxidative stress on tissues. Occurs within the 1st 3 months after treatment^(4,7).
- Late (Chronic) phase is a combination of obliterative vasculitis, fibrosis, atrophy resulting in overall change in tissue make up. Occurs from 3 months post treatment cessation^(4,7).
- **Pre-operative optimisation** of clinic condition for example optimal Hb levels.
- Place sigmoid colon at vault intraoperatively to prevent small bowel descent reducing risk of enteritis and subsequent complications of this

Conclusion

- PRD is common and has a significant impact on patients quality of life after cancer treatment⁽¹⁻³⁾.
- PRD is a complex multifaceted disease that is challenging to treat. An individualised patient-centred multidisciplinary approach is essential for optimal care.
- Surgical management is highly complex with procedures being technically difficult and high complication rates⁽¹⁴⁻¹⁶⁾
- Alternatives to surgery are available. Research is limited, often small trials with contradicting evidence⁽⁸⁻¹³⁾.
- Research into both surgical and alternative interventions lack focus on late complications of radiation therapy.
- Further research and funding into the management of pelvic radiation disease and its prevention is required

Sucralfate (Enema/Oral)^(4,9,11)

- Stimulates prostaglandin production, and epithelial growth factor production providing barrier protection and mucosal tissue repair
- Given with metronidazole to increase effect
- Targets: symptomatic relief
- Advantages: non invasive, minimal complications
- Disadvantages: minimal effect on late or severe complications
- Small randomised control trials have suggested symptomatic relief in acute phase PRD up to 1 year. No significant difference, limited evidence base for late phase disease.

Other Alternatives^(9,11)

- Endoscopic argon plasma coagulation has limited depth of coagulation up to 3mm. Advantages: uniform and predictable. High complication rates reported with severe complications at 10%, therefore not recommended.
- **Mesenchymal stromal cells** have a role in extracellular matrix remodelling, are proangiogenesis and inflammatory modulators. Animal studies suggest improvement in fibrosis. Expensive and not used in NHS practice at present.
- Laser therapy e.g. NdYAG is used, complications rates between 5-15% including severe complications such as stricture/fistula.

Hyperbaric Oxygen Therapy^(12,13)

- Targets: induce neovascularisation to reverse some hypoxic tissue damage
- Currently considered in severe refractory proctitis with significant impact on quality of life (main benefits are on PR bleeding, pain and diarrhoea) and chronic radiation enteritis. Complex conditions such as strictures and fistulas excluded from many trials.
- Advantages: non-invasive, targets non-continuous small bowel
- Disadvantages: expensive, time consuming with travel and daily treatment for many weeks for the patient.
- Multiple small studies with contradictory results regarding efficacy in late phase complications.

Surgical Therapies (2-17% post radiotherapy patients) according to the literature⁽¹⁴⁻¹⁶⁾

- Indications for surgery
 - Complications refractory to or unsuitable for medical therapy
 - Fistula
 - Bowel stenosis or Perforation
 - Abscess
 - Refractory Proctitis
- Surgical Aims
 - Symptom control (with realistic expectations – 14% have ongoing symptoms)
- Operative procedures
 - Resection preferable to bypass
 - Colostomy with excision of radiated tissue +/- Anastomosis
 - Terminal enterostomy with mucous fistula if no further options
- Operative techniques
 - Aim for resection to non-irradiated tissue
 - Balance with risk of short-bowel syndrome
 - Early MDT and colorectal involvement
- Surgical risks
 - Suture line breakdown – anastomotic leak
 - Visceral injury (altered anatomical boundaries)
 - High post-operative infection rates
 - Return to theatre (13%)
 - Death (up to 10.5%)

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22,000 patients
per year receive
radiotherapy for
pelvic cancer in
the UK⁽⁴³⁾

Up to 50% patients
undergoing surgery for
chronic radiation
enteritis complications
require further
surgeries⁽¹⁸⁾

Case 2 – 58yo

Uterine carcinosarcoma stage 3B grade 3 2011
Total abdominal hysterectomy, bilateral salpingo-oophorectomy in 2011 with adjuvant external beam radiotherapy & 2 fractions of brachytherapy
Disease recurrence 2013 in vaginal vault – pelvic exenteration, ileal conduit and colostomy, appendectomy and removal of abnormal tissue

Radiotherapy related complications:

- Multiple gastrointestinal symptoms including dyschezia, diarrhoea, skin changes.
- Small bowel obstruction resulting in small bowel resection
 - Enterovaginal fistula
- Ischaemic colon requiring colectomy
- Ureteric stents, nephrostomies

Patient is still alive and free of cancer

Case 1 – 25yo

Stage 2B-1 Cervical cancer 2011
Chemotherapy, Radiotherapy & Brachytherapy 2011 followed by radical hysterectomy 2012

Radiotherapy related complications:

- Ureteric narrowing requiring multiple stents and eventually a left nephrectomy
 - Urge incontinence requiring clam ileocystoplasty & right ureteric reimplantation
- Gastrointestinal: multiple symptoms including PR bleed, tenesmus, dyschezia. Intermittent incomplete small bowel obstruction and narrowing of areas of colon
 - Enterovaginal fistula
 - Chronic pain
- 2022 bowel resection, removal of fistula, colostomy and ileostomy.

Patient is still alive and free of cancer

Case 3 45yo

Stage 4a cervical cancer 2013, lynch syndrome diagnosis 2014
Chemoradiotherapy and brachytherapy preceded anterior pelvic exenteration and ileal conduit (urinary diversion)

Radiotherapy related complications:

- Radiation enteritis
 - Subacute then chronic small bowel obstruction requiring bypass surgery with ileostomy 2014 resulting in short gut syndrome
- Chronic inflammatory gluteal muscle changes causing severe pain
 - Portal vein thrombosis
 - Bilateral ureteric stents
- Common iliac artery – left ureteric fistula requiring common iliac stent

Patient is still alive and free of cancer

50% of patients with
Gastrointestinal PRD
report a reduced quality
of life⁽¹⁷⁾