EDITORIAL

Pelvic radiation therapy: Between delight and disaster

Kirsten AL Morris, Najib Y Haboubi

Kirsten AL Morris, University of Manchester Medical School, Manchester M13 9PT, United Kingdom

Najib Y Haboubi, Department of Histopathology, University Hospital of South Manchester, Manchester M23 9LT, United Kingdom

Correspondence to: Najib Y Haboubi, MBChB, FRCS, FRCP, FRCPath, DPath, Professor of Health Sciences, Liver and Gastrointestinal Pathology, Consultant Histopathologist, Department of Histopathology, University Hospital of South Manchester, Clinical Sciences Building, Southmoore Rd, Manchester M23 9LT,
United Kingdom. najib.haboubi@uhsm.nhs.uk
Telephone: +44-161-2912143

Abstract

In the last few decades radiotherapy was established as one of the best and most widely used treatment modalities for certain tumours. Unfortunately that came with a price. As more people with cancer survive longer an ever increasing number of patients are living with the complications of radiotherapy and have become, in certain cases, difficult to manage. Pelvic radiation disease (PRD) can result from ionising radiation-induced damage to surrounding non-cancerous tissues resulting in disruption of normal physiological functions and symptoms such as diarrhoea, tenesmus, incontinence and rectal bleeding. The burden of PRD-related symptoms, which impact on a patient's quality of life, has been under appreciated and sub-optimally managed. This article serves to promote awareness of PRD and the vast potential there is to improve current service provision and research activities.

Key words: Pelvic radiotherapy; Radiation; Toxicity

Core tip: Radical cancer treatments have come at a price. Radiotherapy carries the risk of pelvic radiation disease (PRD), a condition that can significantly reduce a patient's quality of life. We argue that PRD is a neglected problem that requires investment in service provision and research studies.

INTRODUCTION

The last four decades have been a golden era for improving cancer survivorship. Three times as many people survive cancer than 30 years ago largely as a result of the increasingly potent, multi-modality treatment regimes[1]. Yet 20%-25% of cancer survivors

report a decline in quality of life secondary to the physical consequences of treatment[2]. A sinister side to cancer research studies is the fixation on survival statistics and prevention of disease recurrence. Patient quality of life has been unacceptably neglected. Toxicity and debilitating short- and long-term complications are inevitable consequences of radical treatments. Patients who receive radiotherapy form a large cohort of patients who report side effects leading to a reduced quality of life[1]. Radiotherapy is a cornerstone treatment for pelvic tumours which includes those of gastrointestinal, gynaecological or urological systems[3].

Radiotherapy to organs of the pelvis renders the bowel at risk of radiation induced injury, a condition recently coined pelvic radiation disease (PRD)[4,5]. This term encapsulates conditions including radiation enteritis, radiation proctitis and radiation cystitis[6] which inaccurately depict the condition as an ongoing inflammatory process. In fact, after the initial three months the inflammation is largely replaced by progressive ischaemia and fibrosis of tissues. This radiation induced damage to healthy tissue around the tumour could be a major limiting factor to curative treatment of localised cancer as treatment regimes may be interrupted.

This editorial outlines the clinical presentation, pathophysiology, histopathological features, prevention and management of PRD and aims to shed light on the future direction of much needed research in this field.

THE MAGNITUDE OF THE PROBLEM

It is truly remarkable how common PRD is. Yet should we be surprised? More people with pelvic tumours are treated with radiotherapy than any other anatomical site and as more people live longer with cancer or indeed survive it the burden of PRD increases. A questionnaire investigating the opinion of clinical oncologists in the United Kingdom reveals that most believe it is a significant problem that is under recognised and inadequately managed[7]. An impasse has been reached: The magnitude of the problem significantly exceeds clinical and research provisions. In fact, the annual incidence of patients adversely affected by PRD with symptoms of gastrointestinal disturbance eclipses the number of patients diagnosed with Crohn's disease[8]. Numerous large studies have documented the rates of complications in patients with pelvic tumours treated with surgery alone or surgery combined with either preoperative or postoperative radiotherapy[9-19]. Yet the funding and service provisions for PRD are a fraction of those for Crohn's disease[8].

A remarkable nine out of ten patients who received pelvic radiotherapy experience chronic change to bowel habit with five out of ten reporting a significant change to their quality of life[20]. Despite this only one fifth of patients with PRD in the United Kingdom are reviewed by a gastroenterologist[2]. This figure is even more remarkable given the fact that the onset of PRD,

unlike inflammatory bowel disease (IBD), is relatively predictable. Acutely PRD occurs simultaneously or within three months of radiotherapy. There should be a low threshold for suspecting chronic PRD in patients previously treated with pelvic radiotherapy. PRD thus represents a model of disease with a predictable onset and a large patient cohort.

Not all patients who receive radiotherapy directed at tumours within the pelvis develop PRD. The reason for this is unclear however evidence suggests it may be a multifactorial process involving patient-related and treatment-related factors. Indeed, there is still uncertainty regarding who are the most susceptible patients, even those that fall into similar cohorts. Consequently, there is major scope for future research to exploit this disease model to shed light on the pathogenesis, preventative measures and management of PRD[21].

THE CLINICAL PRESENTATION

There is a vast spectrum of clinical presentations of PRD owing to numerous influential variables such as timing since radiotherapy, site of the tissue damage, severity of tissue damage, side effects of medications, coexisting medical conditions and psychological issues. The clinical presentations can be crudely classified into three clinical phases: Acute, chronic and delayed (latent)[22]. The timing of gastrointestinal complications of PRD follows a relatively predictable pattern (Table 1). Within these groups the symptoms of PRD may manifest as a result of direct damage to pelvic structures or as secondary phenomena triggered by the radiotherapy. These include small bowel bacterial overgrowth, bile salt malabsorption, malabsorption of lactose and similar fermentable sugars[23].

The acute phase
Acute PRD is defined as an acute inflammatory reaction to radiation treatment that can occur during, immediately after or within the first three months of radiotherapy. It occurs in 60%-80% of patients treated with abdominal or pelvic radiotherapy and is a major risk factor for modification of the planned treatment regime. Such changes could have ramifications on local tumour control[3]. Common symptoms include nausea, diarrhoea, tenesmus, abdominal cramps, urgency, mucus discharge, faecal urgency, loss of appetite and bleeding. Such non-specific symptoms can overlap with differential diagnoses such as infection, which needs to be excluded. Bleeding occurs in 50% of patients who receive pelvic radiotherapy as a consequence of radiation induced telangectasia which usually form on the anterior rectal wall[5]. Symptoms of acute PRD most commonly manifest in the second week post-radiotherapy and peak in week four or five and resolve within two to six months[23]. Importantly, the occurrence of acute PRD does not increase the risk of developing chronic PRD later on and patients can be reassured that resolution of symptoms generally occurs with cessation

Table 1 The timing of gastrointestinal complications of pelvic radiation disease in relation to tissue type damage

Complication	Primary tissue type damage	Timing
Acute proctitis	Epithelial	0-4 wk
Acute enteritis	Epithelial	0-4 wk
Rectal bleeding	Vascular	4-12 mo
Anal/perianal pain	Stromal	6-9 mo
Chronic abscess	Stromal	9-15 mo
Fistula	Stromal	18-24 mo
Stricture/malabsorption	Stromal	2-20 yr
Rectal malignancy	Epithelial	5-30 yr

of radiotherapy[24].

The chronic phase

Chronic PRD is a progressive condition and major source of morbidity for cancer survivors. Symptoms of chronic PRD begin to develop after a period of 6 mo to 3 years but can occur up to three decades following treatment. Occasionally the onset of symptoms crosses over with the acute phase of PRD. Clinically the signs of chronic PRD are symptoms of bowel dysmotility such as urgency. Altered transit of faeces and malabsorption are other prominent features[3]. In fact, when treating rectal cancer with radiation, it has been estimated that the majority will suffer from faecal incontinence[25]. Vascular telangectasia often lead to bleeding in the chronic phase. The bowel has a limited range of symptoms and therefore PRD manifests similarly to other bowel conditions including celiac disease, IBD, infection, malignancy, diverticular disease. The timing of radiotherapy in relationship to symptom manifestation is key to raising clinical suspicion and providing tailored support for PRD.

Patients that experience long standing chronic PRD can also experience sudden complications. Radiotherapy increases the risk of bowel wall stricture formation, adhesions, fissures, severe bleeding and bowel wall perforation. Surgeons should be alert to the fact that PRD may be the cause of acute or sub-acute small bowel obstruction.

The latent phase

A third stage of the clinical pathological presentation of PRD is well recognised. Latent clinical symptoms first arise years or decades after the initial radiotherapy treatment. Latent phase symptoms are in fact those of secondary malignancies, which can arise within or outside of the irradiation field. Radiotherapy used to treat the first malignancy can induce minor alterations to the nuclear DNA that predispose the cellular DNA to novel mutations, carcinogenesis and teratogenesis[22]. Studies have shown patients treated with radiotherapy for cervical or ovarian cancer developed endometrial cancer between approximately 15 years later[26,27]. Importantly there was a preponderance for high-risk histological sub-types in endometrial cancers that develop after pelvic radiotherapy[27]. Prostate cacner not

treated with RT is not associated with an increased risk of other malignancies. Bostrom and Soloway[28] (2007) showed that there is a slight increase in radiation-induced secondary malignancies after prostate radiotherapy. Approximately one in seventy of such patients who survive longer than ten years will develop a secondary malignancy. There is a predilection for secondary rectal or bladder tumours[28]. Despite the association between radiotherapy and secondary malignancies there is a lack of definitive evidence for a direct relationship.

Clinicians should be suspicious of a primary tumour in any patient who has received pelvic radiotherapy and has new onset red flag symptoms of cancer, such as *per rectum* bleeding. Furthermore, although the risk of secondary malignancies after pelvic radiotherapy is modestly above the overall population patients should be informed about the risk.

THE PATHOPHYSIOLOGY OF PRD

Cells exposed to ionising radiation experience oxidative stress injuries. The damage is widespread however the principle sub-cellular target is the nuclear DNA[29]. Both direct and indirect mechanisms inhibit DNA from fulfilling its function as a template for DNA transcription. The nuclear chromatin is directly targeted, causing DNA damage through the generation of inter- and intra-strand cross-linkages, breaks and mutations. The plasma membrane is directly affected as radiotherapy disrupts the rigidity of the phospholipid bilayer and electric gradient; injuries which challenge integrity of the cell. Indirect damage occurs secondary to the formation of free radicals from the ionisation of water molecules[22].

Intricate and coordinated DNA repair mechanisms have evolved to fix damage induced by ionising radiation, including strand breaks and replication errors. At low levels of radiation repair mechanisms in the cell can resolve injuries such as double strand breaks. With increasing amounts of radiation the damage inflicted overwhelms these systems and the cell either enters programmed cell death (apoptosis) or mitosis is inhibited. The amount of ionising radiation required to inflict cell inactivation and cell death varies between each tumour and its surrounding tissues[30]. A further variable that influences a cell's response to radiotherapy is whether adjuvant chemotherapy features in the treatment regime. Concomitant chemotherapy often leads to delay or prevention of the reparative process thus aggravating the disease. Chemotherapeutic agents may help to accumulate cells in the more radiosensitive stages of the cell cycle. Timing of radiotherapy in relation to chemotherapy is an essential consideration[31].

The damaging affect of radiotherapy is most potent against tissues with a high turnover, making it an ideal modality to treat typically rapidly proliferating tumour cells. This is because the potential cell injury is dependent not only upon the cellular repair processes but also the stage of the cell cycle that the cell is in. Certain stages within the cell cycle optimise the

opportunity to repair damage. For example, ionising radiation damage results in cell cycle arrest and initiation of a temporary cell cycle check point. This aims to provide time to conduct repairs. A crucial protein in the checkpoint machinery is the tumour suppressor gene *p53*. Highly proliferative cells, such as those residing in the crypt epithelium of the bowel, are frequently in the more radiosensitive G_2-M phase[31]. Crypt cell death results in insufficient renewal of the villous epithelium. The mucosa and lamina propria become inflamed and the mucosal barrier breaks down[3]. In comparison slowly dividing tissues, such as those in vascular or fibrous tissue, spend more time in the less radiosensitive G_1 and S phases and damage to these tissues are usually not responsible for acute clinical presentations[22].

Impaired anorectal functionality

Maintenance of faecal continence is regulated by the tonic contractions of the internal and external anal sphincters. The former is a smooth muscle and is supplied by intrinsic myenteric innervation and has the chief role of maintaining a tonic contraction and thus continence whilst at rest. Comparatively the external sphincter is composed of striated muscle and is innervated by an extrinsic supply. In health these work together to provide an effective seal to solids, liquids and flatus. The anorectum has a rich nervous supply, which includes pain, temperature and touch sensory components, each of which aid the maintenance of continence through the ability to differentiate between solids and flatus. Impaired anal functioning can result from damage to the nerves of the pelvis including the pudendal nerve, the lumbo-sacral plexus and the myenteric plexus. The external anal sphincter is relatively radioresistant and it is postulated that faecal incontinence is strongly influenced by nerve damage. Case reports demonstrate that damage to the pudendal nerve may lead to morphological changes in the muscle. Some case reports have proposed that injury to the lumbo-sacral plexus can indirectly affect the external anal sphincter by causing perianal anaesthesia[32].

MICROSCOPIC CHANGES TO THE BOWEL MUCOSA

An appreciation of the radiation induced microscopic changes observed in patients with PRD is a window to understanding the clinical symptoms, stages of the disease and how best to manage the condition. The epithelial cells within the bowel wall, particularly those in the small bowel, have a high turnover rate which renders them vulnerable to ionising radiation. A fine balance lies between the dose tolerated by the epithelium and the dose that destroys the neoplasm. Histologically the damage inflicted upon surrounding healthy tissues has characteristic appearances depending upon the time interval since the radiotherapy. There are three main histological phases depending upon

the tissue type that is predominantly affected. The epithelial phase generally correlates with acute phase clinical symptoms with vascular and stromal changes commence several weeks later (Table 1)[33].

In the epithelial phase damage to the epithelium, seen as sloughing of epithelial cells into crypt lumina, can be observed within eight hours of exposure to ionising radiation. Other characteristic acute phase histological changes include patchy fibroblastic changes to the submucosa, epithelial meganucleosis and significant eosinophilic infiltrate with formation of eosinophilic microabscesses. Caution and experience is required to interpret these morphological changes as they can resemble dysplasia. Nuclear and cytoplasmic early phase changes are usually reversible[33]. Mitosis is inhibited preventing epithelial re-growth and causing denudation of the underlying structures. Importantly, during the acute phase the vasculature appears normal[33,34].

Severe fibrovascular changes, depletion of goblet cells and atrophy are core features of chronic PRD and the vascular phase. Extensive fibrosis can be seen in submucosal arterioles and the lamina propria, which contributes to deformed architecture such as crypt distortion. Characteristic changes during the vascular are telangectasia of capillaries and post-capillary venules, fibrin deposition, subendothelial odema and platelet thrombi formation that can cause *per rectum* bleeding[33]. Ultimately there is significant narrowing of the vascular lumina that leads to ischaemia and further fibrosis. Macroscopically these microscopic changes correlate with a pale, non-compliant bowel wall with telangectasia[24]. The reversibility of the vascular phase morphological changes is unclear however the stromal phase which includes mesenchymal and stomal fibrosis is irreversible[33].

Despite these distinctions the bowel has a limited array of modifications in response to damage. In fact under a microscope a canny mimic of chronic PRD is the quiescent phase of IBD. Since chronic PRD can take months, if not years to develop, is quite possible that PRD is overlooked as a differential diagnosis and the histopathologist could remain oblivious to the patient's history of irradiation. Relevant clinical information is therefore essential for the histopathologist. As they trawl through mounds of rectal biopsies labelled with minimal clinical information the biopsy from the patient with chronic PRD could be mistaken for chronic IBD[35].

Importantly, a study profiling the time patterns of histological mucosal changes in relation to the clinical manifestation of PRD indicated that they do not always coincide. Microscopic evidence of inflammation in rectal biopsies precedes the onset of symptoms. Thus pathological changes do not always cause the symptoms but it is the disruption to normal physiological processes that results in the symptoms such as diarrhoea. These findings suggest that pre-emptive, prophylactic treatment that tries to prevent PRD may be a prudent way to tackle the condition[36].

HOW TO PREVENT PRD

Preventing the adverse impact of radiotherapy and development of PRD is a multi-disciplinary responsibility. Prior to receiving radiotherapy the patient should be optimised for treatment by attempting to control and treat pre-existing co-morbidities, such as hypertension and diabetes, and making lifestyle modifications like smoking cessation. Clinical oncologists have, over the decades, honed the radiotherapy regimes to try to reduce damage from too high doses or too large field sizes. Medical oncologists should liase closely with surgeons and clinical oncologists to attempt to minimise the increased toxic effects of concurrent chemotherapy.

Factors related to the host

Hypertension, arterial disease, IBD and diabetes mellitus are co-morbidities that predispose a patient to PRD. Previous abdominal surgery also increases the likehood of PRD owing to the tethering effect of adhesions that reduce bowel motility out of the radiation field[22]. Tobacco smoking is an independent risk factor for predicting the development of complications to radiotherapy. A body mass index greater than 30 is found to be protective against pelvic and abdominal radiotherapy whereas low body mass increase the risk of toxicity. Genetic predisposition is thought to explain the varying level of complications observed between patients who receive the same radiotherapy regime[3].

Factors related to therapy

When radiotherapy was initially used against tumours within the pelvis the development of resistance to the radiation was a common set back. This was especially problematic in patients with rectal cancer. Higher doses were discovered to overcome the resistance but are associated with higher collateral damage to surrounding healthy tissue in the radiotherapy beam[24].

High doses and large field sizes are associated with increased radiotherapy toxicity. Large doses per fraction facilitate a quicker completion of the radiotherapy regime and progression to surgery. Larger doses are believed to increase the chronic complications of radiotherapy as increase the safety problems of concurrent chemotherapy. These observations were particularly pertinent in the 1970s when patients with carcinoma of the uterine cervix were treated with > 1000 cGy/min over 2-3 min resulting in irreparable tissue damage. Modifications to radiotherapy doses have since resolved this risk[22]. Dose-volume histograms are routinely used by clinical oncologists to plot cumulative dose-volume frequency to help safeguard against toxicity and PRD[37].

Radiation therapy can be administered to a patient in two main ways: *Via* external beam radiation or brachytherapy (radioactive implants). The field size used in external beam radiotherapy is crucial to the level of exposure that surrounding healthy tissues receives. Large field sizes increase the acute side effects, in particular diarrhoea. Radiotherapy is delivered using an external photon generator that exposes the patient to X-rays, electron beams and gamma rays in a four beam approach which results in significant exposure to surrounding tissues[24]. Development of three dimensional conformal radiation therapy and intensity-modulated radiation therapy attempts to minimise the field size thus sparing non-cancerous tissue. Large field exposure can be avoided by limiting the field to 2-3 cm beyond the tumour margin on computed tomography (CT) or magnetic resonance imaging scans. This strategy accounts for natural bowel motility and infiltration of metastatic cells beyond tumour margins. Alternatively, surgical clips at sites of residual disease can be used as landmarks for post-operative radiotherapy although they are less reliable indicators than scans. Consequently, post-operative radiotherapy often utilises larger field sizes in comparison to pre-operative fields[22].

Post-operative radiotherapy is more toxic than preoperative radiotherapy due to disturbance to the natural reflections of the perineum and allowing it to enter the pelvis. Following surgery adhesions form around the bowel limiting its movement and tethering it in potential radiation fields. The Swedish rectal cancer trial involving 1168 patients randomly assigned to surgery alone or surgery with neoadjuvant radiotherapy showed five year survival rates as 48% and 58% ($P = 0.004$), respectively[38]. Studies comparing surgery with either pre-operative or post-operative radiotherapy for rectal cancer showed significant differences between the incidence of bowel habit disturbance (minimal *vs* 90% respectively)[11,39].

A retrospective study explored the use of non-absorbable mesh implanted during surgery which would act to protect the small bowel from radiation injury and suggests a reduction in chronic PRD from 90% to 3%[40]. Prophylactic surgical techniques such as pelvic reconstruction, omentoplasty and transposition of the large bowel can reduce the volume of bowel at risk of radiation exposure by 60%. Additionally clinical oncologists have developed a range of techniques to reduce PRD. Image guidance techniques such as megavoltage and kilovoltage cone beam CT performed immediately before radiotherapy can accurately assess location and mobility of the bowel. Manoeuvring the patient into the supine position during the radiotherapy has significantly reduced the incidence of PRD in patients treated for prostate, rectal, small bowel and bladder cancer[37].

MANAGEMENT

How to manage patients with PRD is a contentious subject. It was largely believed to be untreatable until a better understanding of the aetiology and pathogenesis paved the way for a paradigm shift in treatment. Medicines, dietary modifications and supportive measures are some of the components of current guidelines. In the

majority of cases the cornerstone of management after prevention is symptom control. Symptoms can originate from a variety of affected sites therefore a crucial step in PRD management is the understanding that urological, gastrointestinal, gynaecological, dermatological, lymphatic, nervous, vascular structures and sexual organs can be involved. The severity of damage and whether the patient is in the acute or chronic phase of PRD are additional variables that make each patients case unique. A degree of flexibility is essential when approaching PRD to cater for this wide spectrum of clinical presentations. Several scoring systems have been developed or adopted from elsewhere to quantify and categorise a patient's symptoms and quality of life. The inflammatory bowel disease questionnaire-bowel subset score[2] and the Franco-Italian glossary which classifies symptom severity 0 to 4[41] are two such examples.

Additionally, the psychological impact of PRD should never be underestimated. Evidence shows that 24 mo after radiotherapy for cervical cancer disease-free patients have a reduced quality of life and experience psychological reactions such as inability to perform daily household tasks and making plans for the future[42]. Sexual functioning in both males and females, ejaculation disorders and erectile dysfunction are significantly more common in patients who have received pelvic radiation when compared to surgery alone[17]. Although the bowel is the most affected site radiotherapy to the pelvis can cause complications such as vaginal stenosis. The pathogenesis of this condition is akin to that in the bowel; inflammation within the connective tissues and blood vessels leads to fibrosis and a reduced blood supply. Consequently, the hypoxic conditions encourage loss of elastin, atrophy and collagen deposition[43]. A holistic approach addressing the physical, psychological, social and emotional hurdles of PRD is thus gold standard management.

Management during the acute phase

Treatment of acute PRD can take the form of supportive and/or dietary modifications. To tackle the problem of diarrhoea bulking agents and anti-kinetic drugs, such as fybogel, codeine and loperamide, are commonly prescribed to increase excess fluid absorption in the bowel and to reduce the peristaltic activity, respectively. Anti-cholinergic anti-spasmodics, anti-emetics and analgesia are other agents offering effective symptom control. Most patients respond to this regime however patients with profuse diarrhoea leading to malabsorption and dehydration require more intensive supportive measures with fluids and electrolyte balance support. The use of these measures is generally based on anecdotal evidence and experience of the attending healthcare professionals. A salient point about acute PRD is that symptoms often recede once the radiotherapy regime has ceased[23]. Transparency about the potential for chronic manifestations of PRD through education and counselling can encourage patients to seek medical attention if needed.

Management during the chronic phase

Making the diagnosis of chronic PRD can be a convoluted process. Irritable bowel syndrome is a common misdisgnosis. Once the diagnosis is made many patients symptoms improve with modification of their diet. Ionising radiation can cause damaged intestinal villi and insufficient enzyme production leading to malabsorption of nutrients. Low fat, low roughage and low residue diets are encouraged and adequate calorific and fluid intake is essential. Dietetic input can provided structured and targeted advice[23]. Should symptoms persist, medical management can be added to this conservative approach through the addition of anti-inflammatory agents. Steroid enemas or suppositories and oral 5 acetyl salicylic acid preparations may offer symptomatic relief of *per rectum* bleeding, tenesmus or urgency[22].

In 2010, the United Kingdom national cancer survivorship initiative vision was launched. Its aims were to stimulate development of new models of care to manage patients with chronic cancer related symptoms. The initiative came into being after the recognition that surviving cancer does not equate to a good quality of life. The consequences of cancer treatment can result in debilitating chronic symptoms[2]. In total 23 different gastrointestinal symptoms have been associated with chronic PRD. The cluster of symptoms, severity, frequency of symptoms all vary between individual patients making chronic PRD a highly heterogenous condition. Andreyev *et al*[1] (2013) devised an investigative and management algorithm to help improve the gastrointestinal symptoms of chronic PRD. Results of the randomised control trial showed that use of the algorithm-based care improved symptoms in patients with PRD. Additionally, the study indicated that nurse-led care is sufficient for the majority of patients with PRD[2].

Malabsorption of bile acids is believed to be the cause diarrheal symptoms in between 35%-72% of patients with chronic PRD[23]. Ninety-five percent of all bile acid salts are absorbed in the terminal ileum which means that damage to this area or decreased transit time leads to bile acid malabsorption[44]. The terminal ileum is the most commonly affected portion of small bowel affected by PRD. An important factor which determines the risk of radiation induced damage to the bowel is its mobility. An area that is not tethered and therefore mobile has a chance of migrating into areas outside the radiation field in the weeks between radiation fractions. The entire duodenum, the jejunum at the ligament of trietz and the terminal ileum are tethered in place making them vulnerable for repeated radiation exposure[34]. Cholestyramine, colestipol and colesevelam bind bile salts and have been administered to patients with PRD[23]. There is evidence that patients with PRD respond well to the former agent but palatability is an issue[45].

LATEST DEVELOPMENTS AND FUTURE RESEARCH PRIORITIES

Rather disturbingly, although there have been a plethora of expensive multi-centre studies into the treatment of cancer, there is scant evidence of how to optimally manage the debilitating consequences of treatment. Several strategies of PRD management are being researched and are potential avenues for future PRD management.

Antibiotics vs probiotics

As outlined above, ionising radiation modifies the intestinal muscosa, inducing changes to the vascular permeability of the mucosa and overall motility. These changes directly impact on the natural bacteria that colonise the bowel[46]. Specifically, dysmotility and stasis encourages bacterial overgrowth in the small bowel. In comparison to the colon the small bowel usually harbours few microorganisms. Jejunal cultures from one in three people detect no bacteria. Ionising radiation disturbs the homeostasis of indigenous intestinal microflora which directly influences bowel functions. For example, they have a role in processing unabsorbed dietary carbohydrates and converting them into fatty acids: An energy source for the colonic mucosa. Enteric bacteria contribute to their host's health by synthesising essential molecules such as vitamin K and folate. Commensal bacteria also interact with the host immune response inducing a state of controlled inflammation which maintains a fine homeostasis between protection against disease and chronic inflammation[47].

There is contradictory evidence of how to combat this radiotherapy - induced pathophysiological change. Broad spectrum antibiotics including co-amoxiclav, ciprofloxacin, tetracycline and rifaximim are frequently used but some patients require repeated courses or low dose, long-term maintenance therapy[48]. Understanding the pathophysiology led to studies into the use of probiotics which aim to restore the balance of the commensal microbiota. Trials have yielded mixed results with some heralding lactobacilli probiotics as a cheap, safe and feasible method of reducing diarrhoea in the acute phase[46,49] with others finding no significant reduction in diarrhoeal symptoms[50]. There is currently no evidence supporting their use in the prevention of chronic PRD. This remains an area for future research studies[51].

Medications

Patients who take angiotensin I-converting enzyme inhibitors (ACEi) and the cholesterol lowering statins have been observed to have fewer gastrointestinal complications from radiotherapy to the pelvis. *In vitro* studies have supported this by showing the anti-inflammatory, anti-thrombotic and anti-fibrotic properties of statins when administered to human cells treated with ionising radiation[52]. The mechanism of action of statins is to inhibit 3-hydroxymethylglutaryl co-enzyme A reductase whilst ACEi block the conversion of angiotensin I to angiotensin II, which influences blood pressure homeostasis. These drug-induced physiological changes have recently been shown to have a protective effect on the bowel when it is exposed to ionising radiation. Wedlake *et al*[53] (2012) showed that in a study of 308 patients the use of a statin or stain with an ACEi significantly reduced the incidence of gastrointestinal symptoms following radiotherapy. Further prospective, randomised, blinded, adequately powered and stratified by disease stage trials with adequate follow up are required to support the use of statins and ACEi in PRD management.

Hyperbaric oxygen

Hyperbaric oxygen (HBO) therapy has been utilised to treat chronic PRD for several decades[54] but with insufficient evidence of its exact mechanism of action or to support its use in clinical practice. More recently HBO has been found to decrease tissue hypoxia by inducing angiogenesis in bowel affected by the ischaemic and fibrotic changes associated with chronic PRD changes[55]. Clarke *et al*[56] (2008) conducted the first randomised control trial and provided support for its use in refractory PRD. Specifically, HBO induced healing responses and was associated with an absolute risk reduction of 32%. Furthermore, bowel specific quality of life was improved. HBO treatment does require a significant time commitment, logistical hurdles and is expensive to fund. A complete regime consists of eight weeks of daily treatment in a specialist unit that typically have vast catchment areas[5].

Argon plasma coagulation

Three main strategies for managing PRD exist: Medical, surgical and endoscopic. New techniques are emerging in the endoscopy arena, such as argon plasma coagulation (APC) therapy, which followed the limited success of treating vascular telangiectasia with locally applied formaline solution. APC therapy is a noncontact thermal coagulation technique on a probe that can be passed through the scope during endoscopy. The probe delivers argon gas to bowel mucosa targeted by the endoscopist. A high voltage filament then ionises the gas which heats the mucosa and results in coagulation of tissues damaged by PRD and aims to prevent them from bleeding. So far, several case series have shown that APC reduces rectal bleeding in 80%-90% of treated patients[57]. APC should be used with caution as serious complications have been documented in as high as 26% of patients[58]. A case series of 16 patients states that it is a safe, well tolerated treatment for rectal bleeding in PRD and should be considered as first line treatment[59]. However, currently the evidence for its use in clinical practice is insufficient. There is a need for large, prospective, blinded, randomised control trials to explore the use of APC in PRD management and to explore its safety and outcomes in the short- and long-term[12].

Key research priorities

An area that requires serious consideration is clarification of the most effective - by considering both survival and quality of life parameters - radiotherapy regime for mid and lower rectal carcinomas. There is wide variation between treatment centres across the world. Short course with immediate surgery, short course with delayed surgery, long course with neoadjuvant chemotherapy then surgery and chemoradiotherapy without surgery are some of the approaches utilised to treat patients with the same stage of disease. It is concerning that without a unified approach that some centres or clinicians may be basing their clinical decisions on anecdotal evidence. A consensus meeting to address the application and modality of radiotherapy to low and mid rectal cancers could be a key step in reducing the incidence of future PRD cases.

Key research priorities revolve around the need for randomised trials of best supportive care *vs* hyperbaric oxygen or argon plasma coagulation or intrarectal formalin for bleeding associated with PRD. A large multi-centre phase three study in the United Kingdom, the Hyperbaric Oxygen Therapy (HOT-Ⅱ) study is completed, the results of which are eagerly awaited.

Further research into service provision would shed light on how best to use the resources that are currently in place. Simple amendments and interventions have the potential to improve patient care. The findings of a trial conducted by Andreyev *et al*[1] (2013) provided evidence that the use of an investigative and management algorithm for practitioners to follow improves patient symptoms when compared to current care.

CONCLUSION

A crucial step in management planning for patients with cancer is consideration of the risk-benefit ratio. Clinicians are faced with the task of weighing up the benefit of prolonged survival following surgery and radiotherapy *vs* the risks of treatment related complications such as PRD. As the number of cancer survivors continues to increase the long-term outcomes related to health and well-being, exemplified by those patients who develop PRD, becomes an ever more significant health issue. However, striving to improve cancer survivorship has meant that the recognition and management of treatment associated complications has not been prioritised. Thousands of patients with PRD are poorly managed and denied a service that is tailored to meet their needs. Although it is an uncomfortable notion we must not shy away from iatrogenic causes of patient debility[4]. Effective methods to prevent PRD and an optimal, unified strategy to manage affected patients remain elusive making PRD a well-placed focus for future research[3].

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