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Overview

Prevention and Management of Radiation-induced Late Gastrointestinal Toxicity

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Abstract

In the UK, about 90 000 cancer survivors will suffer from pelvic radiation disease (PRD) due to their curative treatment including radiotherapy. The National Cancer Survivorship Initiative aims to improve the understanding and management of PRD by the oncology community. This overview covers the prevention, investigation and treatment for late radiation-induced gastrointestinal symptoms in PRD. Multiple pharmacological and nutritional interventions have been studied, as prophylaxis for acute gastrointestinal toxicity (aiming to prevent late consequential effects), although predominantly only small randomised controlled trials have been conducted. These have produced mixed results, although promising signals for some agents have been observed. Evidence for the pharmacological prevention of late gastrointestinal toxicity is scarce. Even fewer randomised controlled trials have investigated the late gastrointestinal toxicity profile of advanced radiotherapy technologies. There are nationally agreed algorithms for the investigation and management of PRD, but a lack of awareness means patients still do not get referred appropriately. This overview outlines the management of radiation proctopathy and diarrhoea, and signposts other accessible resources. Finally, we provide recommendations for the management of late gastrointestinal symptoms in PRD and research in this field, especially the need for high-quality clinical trials.

Key words: Bowel toxicity; cancer; management; pelvic radiation disease; prevention; radiotherapy; review

Statement of Search Strategies Used and Sources of Information

A systematic search of the PubMed, EMBASE, MEDLINE and the Cochrane Library databases was carried out. Keywords included: 'radiotherapy', 'chemoradiotherapy', 'cancer', 'neoplasm', 'pelvic radiation disease', 'radiation enteropathy', 'radiation injuries', 'toxicity', 'morbidity', 'enteritis', 'prevention', 'radiomodulation' and 'disease management'. Specific therapeutic names were also searched, such as 'intensity-modulated radiotherapy', 'amifostine', 'aminosalicylates' and 'hyperbaric oxygen'.

Introduction

In the UK, two million people live with or have survived cancer, of whom at least half had abdominal or pelvic cancer [1–3]. About 90 000 cancer survivors will suffer from pelvic radiation disease (PRD) as a consequence of receiving either definitive or adjuvant radiotherapy [4,5]. Half of them are estimated to suffer from chronic gastrointestinal symptoms sufficient to inhibit daily living [5–8]. These estimates, based on patient-reported outcomes (PRO), contrast with more conservative clinician estimates (up to 24%) [9]. This discrepancy is due to the lack of recognition and under-reporting of patient symptoms by clinicians [10,11].

The effect of advanced radiotherapy technology, such as intensity-modulated radiotherapy (IMRT), on the prevalence of PRD is uncertain. Although these technologies reduce the normal tissue volume exposed to high radiation doses, a larger volume receives a low radiation dose and the

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consequences of this are unclear [12]. PRD incidence may also increase with the use of this technology for dose escalation with the intention of improving oncological outcomes [13–15] or with current interest in radiotherapy for organ preservation strategies in early rectal cancer [16–18].

The National Cancer Survivorship Initiative [1] aims to improve the understanding and treatment of PRD. This overview focuses on the prevention and management of late radiation-induced gastrointestinal symptoms in PRD. Finally, we provide recommendations to aid the oncologist in managing this disease.

Pelvic Radiation Disease and Gastrointestinal Symptoms

PRD is defined as the 'transient or longer term problems, ranging from mild to very severe, arising in non-cancerous tissues resulting from radiotherapy treatment to a tumour located in the pelvis' [12]. PRD can present with up to 22 simultaneous gastrointestinal symptoms (Table 1) [19–22]. Multiple diagnoses are frequently involved, with patients commonly having at least two diagnoses contributing to their symptoms, of which one-third are not radiotherapy related [20]. Although potentially treatable, there is low recognition of PRD symptoms by clinical oncologists and lack of uptake of standardised screening questionnaires, resulting in low referral rates with a minority of symptomatic patients having further investigations or management [9].

Clinician Toxicity Grading Versus Patient-reported Outcomes

Clinician reporting of symptom severity is based on the Common Terminology Criteria for Adverse Events (CTCAE) due to its familiarity and being the preferred reporting tool in clinical trials [23]. However, clinicians predominantly focus on more serious toxicities (CTCAE grade $\geq$3), grouping symptoms around a presumed affected organ unit. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) recommendations used to guide radiotherapy dose-volume constraints for rectal and small bowel toxicity are based on the risk of grade $\geq$2 and grade $\geq$3 toxicity, respectively [24,25].

Yet, 'milder' toxicity, such as grade 1 and 2 diarrhoea or faecal urgency, can have a very significant effect on daily life. Clinician CTCAE grading is poorly concordant with PRO for 'degree of distress', 'problems' and quality of life [26,27]. PRO validated questionnaires, such as the Late Effects of Normal Tissues - Subjective, Objective, Management and Analytic Measure (LENT-SOMA) and the cancer-specific CTCAE/LENT-SOMA questionnaires, are significantly associated with patient symptoms, toxicity and quality of life [21,27–29]. The increasing inclusion in clinical trials of PROs will hopefully increase its clinical familiarity and routine clinical use.

Prevention of Late Radiation Gastrointestinal Toxicity

There is a very limited evidence base for the prevention of radiation gastrointestinal toxicity. This review will focus on key examples and their effect on late toxicity.

Lifestyle Modification

In a retrospective survey of prostate cancer patients treated with radiotherapy, Thomas *et al.* [30] showed increased gastrointestinal symptoms in smokers, overweight and physically inactive men. Prospective studies evaluating the role of lifestyle intervention in preventing PRD are awaited.

Pharmacological Prevention

Only a few pharmacological agents have been studied in the prevention of late radiation gastrointestinal toxicity, based on free radical scavengers or modulation of the transforming growth factor beta, Smad and Rho GTPase/Rho-associated protein kinase (ROCK) signalling pathways involved in radiation-induced fibrosis.

Amifostine is thought to confer radioprotection by acting as a free radical scavenger. In head and neck cancers, it significantly reduced xerostomia, mucositis and dysphagia with radiotherapy, but not with chemoradiotherapy [31,32]. Conflicting results for the prevention of radiation pneumonitis have been reported [33,34]. In pelvic cancers, seven small, randomised controlled trials (RCTs) have investigated amifostine (n = 596) [35–41]. All seven trials reported significant reductions in acute gastrointestinal toxicity, but conflicting results in late toxicity: three trials no benefit [36–38], two trials reduced toxicity [35,39]. No compromises in oncological outcomes have been reported [42]. The lack of standardised toxicity end points [43] and adequately powered trials with amifostine are significant limitations in forming firm conclusions of its role in preventing PRD.

Statins may down-regulate the Rho/ROCK pathway by inhibiting HMG-CoA reductase [44], whereas ACE-inhibitors may reduce transforming growth factor beta expression [45]. A single-centre prospective cohort treated with pelvic radiotherapy reported better PRO scores for 1 year gastrointestinal symptoms in statin and/or ACE-inhibitor users [46]. No RCTs have tested these agents and further research is warranted.

More studies have attempted to modulate acute gastrointestinal toxicity, which could indirectly reduce consequential late effects. However, studies were predominantly negative, with late gastrointestinal toxicity frequently unreported.

5-aminosalicylate anti-inflammatories have been evaluated in five small, RCTs (n = 196) – three trials closed early due to increased gastrointestinal toxicity