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Overview

External Beam Re-irradiation in Rectal Cancer

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Abstract

Locally recurrent rectal cancer results in significant symptoms and is associated with prognosis of less than 1 year unless radical resection can be offered. Unfortunately, radical resection rates are low and therefore strategies to palliate symptoms and to maximise downstaging are of significant interest. As the majority of those presenting with locally recurrent rectal cancer will have received previous irradiation for their primary tumour, re-irradiation may offer benefit in this setting. The literature to date is considered in both palliative patients and those with potentially operable disease. Palliative patients gain significant symptomatic relief from standard dose fractionations of up to 30 Gy. In potentially operable patients, the evidence is discussed in the context of key questions; including indications for treatment, dose and fractionation, radiotherapy technique, margins and constraints. Finally, we highlight some additional areas of interest for consideration in future research and development.

Key words: Radiotherapy; re-irradiation; rectum; resection status; retreat; symptoms

Statement of Search Strategies Used and Sources of Information

The aim of this article is to provide an overview of external beam re-irradiation in rectal cancer; it is not a formal systematic review or meta-analysis. A Pubmed search was carried out in August 2017 using the terms: rectal OR rectum AND re-irradiation OR re-irradiation OR retreat OR re-treat. Papers were limited to full papers published in the English language and excluded if they did not include details of radiotherapy or solely described the delivery of brachytherapy or intraoperative radiotherapy. Additional studies were identified from the reference lists of full-text articles and reviewed for potential inclusion.

Introduction

Over the last few decades, local recurrence in rectal cancer has reduced significantly after the introduction of neoadjuvant (chemo) radiotherapy and the development of the total mesorectal excision as standard of care [1,2]. Despite these advances, the local recurrence rate remains about 10%. Of those who recur, around 80% will have received neoadjuvant (chemo) radiotherapy as initial multimodality treatment [3,4]. In addition, the number of survivors from all pelvic malignancies has increased over a similar timeframe [5], resulting in more patients with a history of pelvic irradiation for other pelvic malignancies, presenting with locally advanced rectal cancer. Although numbers are relatively small, the consequences of uncontrolled pelvic disease, either primary or recurrent, are significant. The median survival of this group is 10 months and over 80% of patients with locally recurrent rectal cancer (LRRC) suffer symptoms [6]. These include symptoms of pelvic pain, faecal discharge, incontinence, fistulas and bleeding, resulting in a significant reduction in quality of life [6,7]. As such, in this cohort of patients, re-irradiation should be considered.

Traditionally, with historic radiotherapy techniques there has been a hesitance towards re-irradiation due to concerns regarding the potential toxicities. However, more advanced radiotherapy techniques, including intensity-modulated radiotherapy (IMRT), image-guided radiotherapy and stereotactic body radiotherapy (SABR), are now in routine use. These facilitate the sparing of organs at risk (OARs) by

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improving conformality and reducing margins, among other advances. We currently find ourselves in an exciting era where the toxicity of re-irradiation may be more acceptable; as such there is a renewed interest in radiation in this setting.

There are three main clinical scenarios where re-irradiation in rectal cancer warrants consideration.

(1) For symptom control in palliative patients with local and distant relapse, who have problematic local symptoms despite previous radiotherapy.
(2) To improve local control, the rate of radical resection (R0) and survival, in patients with LRRC and no, or radically treatable oligometastatic disease; or those with new locally advanced primary rectal disease on the background of previous pelvic irradiation.
(3) In isolated pelvic recurrence where a small volume of disease can be irradiated to a potentially radical dose using SABR.

The evidence base for this technique is limited to one phase I/II and two phase II studies and 23 retrospective mostly single-centre reviews. Publications reporting more than 50 patients re-irradiated are listed in Tables 1 and 2. This review aims to discuss the issues highlighted by these publications primarily in the first two clinical scenarios detailed above, with a view to considering potential avenues for research and development in this evolving subject.

Symptom Control

One phase II trial and three retrospective series have selected palliative patients, none of whom underwent surgery, and reported symptomatic response. Cai *et al.* [20] reported a phase II trial in 22 inoperable patients with LRRC who had previously received a median of 48.6 Gy (range 36–62 Gy) to the pelvis. They delivered 39 Gy in 1.3 Gy/fraction twice daily to the gross tumour volume (GTV) + 2 cm. All radiotherapy was delivered with IMRT and no concurrent chemotherapy was given. Acute grade 2 and 3 toxicity were 40.9% and 22.6%, respectively. Complete or partial symptom relief was achieved in 27.3% and 59.1%, respectively, with a median duration of 10 months (range 3–20 months). The median overall survival was 19 months. Lingareddy *et al.* [13] looked retrospectively at 52 patients receiving a median dose of 30.6 Gy (range 19.8–40.8 Gy); 90% received concurrent chemotherapy, in either 1.2 Gy/fraction twice daily or 1.8 Gy/fraction daily. They reported that bleeding was palliated in all patients, with a median duration of 10 months, a complete pain response was achieved for 65% of patients (median duration 9 months) and resolution of mass effect was seen in almost a quarter of patients. The median overall survival was 12 months. They reported almost identical results in the subsequent more heterogeneous larger series, published in 2002 [14]. Juffermans *et al.* [12] delivered 24–32 Gy in 4 Gy fractions twice weekly to 47 patients in combination with hyperthermia and no chemotherapy. They reported a good or complete palliative effect in 72% of patients, with a median duration of 6 months. The median overall survival was 10 months. Finally, Gonzalez *et al.* [21] delivered a mean dose of 31 Gy (range 24–32 Gy) in 4 Gy/fraction twice weekly with hyperthermia and no chemotherapy. Good palliation was achieved in 75% of patients, with a mean duration of 12 months. The median overall survival was 11 months. Multiple other series of more heterogeneous populations, including a number that underwent surgical resection, reported complete or partial symptomatic responses in 55.6–88% [15–17,22–24].

In summary, although late toxicity is not documented in these studies, with median overall survival rates of 10–19 months, it is likely that the significant symptom control reported will outweigh late toxicity. Daily or twice weekly radiotherapy, to a dose of approximately 30 Gy, without chemotherapy, seems to offer symptomatic benefit for most patients and should be considered.

Isolated Local Recurrence

Of all LRRC, 50–75% are isolated to the pelvis, with 65% situated within the previously irradiated field [4,25]. The optimal definitive treatment for LRRC is surgery [8–10,20]. A meta-analysis by Bhangu *et al.* [26] reported that completeness of excision is also of prognostic significance, with those that achieve R0 resection surviving 37.6 months longer than those with R1, with a hazard ratio of 2.03 (1.73–2.38), and 53 months more than those with R2, in keeping with multiple previous retrospective series. However, only 18–30% of patients with LRRC are operable at presentation [6,27] and of those who undergo surgery as a single treatment, R0 resection rates are 25–60% [8,11,28]. Therefore, strategies to downstage the disease before surgery to improve the R0 resection rate must be considered. As it is probable that most patients received adjuvant chemotherapy at initial presentation and with response rates to second-line chemotherapy ranging from 4 to 11% [29,30], chemotherapy alone is unlikely to achieve sufficient downstaging to allow surgery.

Re-irradiation is the obvious alternative and one phase I/II and one phase II trial have investigated this strategy in potentially operable patients. Valentini *et al.* [18] undertook a phase II trial involving all-comers with disease isolated to the pelvis, excluding those with bony infiltration. The median previous pelvic irradiation dose was 50.4 Gy (range 30–55 Gy). Fifty-nine patients received 30 Gy in 1.2 Gy/fraction twice daily to the GTV + 4 cm, followed by a boost of 10.8 Gy in 1.2 Gy/fraction twice daily to the GTV + 2 cm using conformal treatment delivery. Concurrent 5-fluorouracil was used continuously in all patients; 86.4% of patients completed planned treatment, although five of the eight who failed to complete treatment did so because of compliance issues rather than toxicity. The complete and partial response rates were 8.2% and 35.6%, respectively. Of the 66.1% of patients who underwent surgical resection, 35.6% achieved an R0 resection. In terms of acute toxicity, grade 2 and 3 toxicity was low (28.8% and 5.1%,

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