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Overview

Rectal Radiotherapy — Intensity-modulated Radiotherapy Delivery, Delineation and Doses

S. Teoh *, R. Muirhead †

* Department of Oncology, Oxford University Hospitals Trust, Oxford, UK
† The Oxford Institute for Radiation Oncology, University of Oxford, Oxford, UK

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Abstract

The use of intensity-modulated radiotherapy in rectal cancer is attractive in that it may reduce acute and late toxicities and potentially facilitate dose escalation. Intensity-modulated radiotherapy probably has a role in selected patients, but further investigation is required to identify the parameters for selection. Delineation of specific nodal groups allows maximal sparing of bladder and small bowel. In locally advanced tumours a simultaneous integrated boost allows dose escalation incorporating hypofractionation and a shorter overall treatment time. However, due to a sparsity of data on late toxicity in doses ≥60 Gy, doses at this level should be used with caution, ideally within prospective trials. Future studies investigating dose escalation must ascertain late toxicity as well as local control, as both can significantly affect quality of life and without both, the risk–benefit ratio cannot be calculated.

Key words: Dose escalation; IMRT; rectal cancer

Statement of Search Strategies and Sources of Information

A combined electronic search of Medline, Embase and Cochrane databases from January 2005 to December 2014 was carried out. The search strategy included terms such as (rectal or rectum) and (cancer or neoplasm) and (IMRT or intensity-modulated radiotherapy). There were no reviews found on this topic in the Cochrane database.

Introduction

Most external beam radiotherapy in rectal cancer is delivered before total mesorectal excision (TME) as part of radical multimodality treatment [1]. The aims of preoperative radiotherapy are to reduce local relapse in operable disease [2]; improve R0 resection and local control rates in margin threatened disease [3,4]; and to improve R0 resections, local control and cancer-specific survival in inoperable disease [5].

Since these large phase III randomised trials were completed, rectal cancer management and radiotherapy delivery techniques have changed significantly. There is routine use of magnetic resonance imaging (MRI) in staging [6,7] allowing improved visualisation and therefore targeting of threatened margins and inoperable disease; there is a move towards specialised centres carrying out more radical surgeries rendering more patients operable if threatened margins can be sterilised with preoperative radiation [8]; and there has been an increase in the use of intensity-modulated radiotherapy (IMRT) in rectal cancer, due to increased interest in the potential advantages. Currently, 18 centres in England use IMRT for selected rectal cancer cases [9–11]. Additionally, there are increasing indications for radiotherapy in rectal cancer, including single or multi-modality treatment with a view to organ salvage [12], re-irradiation incorporating standard conformal or stereotactic ablative body radiotherapy for localised relapse [13,14] and palliation of symptoms [15]. These indications will not be discussed further in this overview.

Author for correspondence: R. Muirhead, CRUK/MRC Oxford Institute of Radiation Oncology, University of Oxford, Old Road Campus Research Building, Oxford OX3 7DQ, UK. Tel: +44-7989-445591; Fax: +44-1865-235981.
E-mail address: rebecca.muirhead@oncology.ox.ac.uk (R. Muirhead).

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There exists enormous disparity in the delivery of rectal radiotherapy [16]. With the advent of IMRT, variations will probably increase. This overview aims to summarise the evidence for IMRT, target delineation and doses used in this setting to aid homogeneous implementation.

Intensity-modulated Radiotherapy

Theoretical Benefit

IMRT improves conformity of the radiation dose to the three-dimensional shape of the tumour compared with conventional, conformal radiotherapy. The potential benefit of IMRT in operable disease is to reduce the dose to small bowel and other organs at risk (OARs) and consequently reduce the acute and late toxicity of radiotherapy. In margin threatened or inoperable disease, due to the reduced toxicity achieved with IMRT, a simultaneous integrated boost (SIB) incorporating shorter overall treatment times, higher biological effective doses and hypofractionation of the boost volume could theoretically improve the response rate in an area of potential R1/R2.

Multiple radiotherapy planning studies have now shown that IMRT is able to produce highly conformal dose distributions that significantly reduce small bowel dose. Guerrero Urbano *et al.* [17] compared various IMRT plans with three-dimensional conformal plans and showed that IMRT reduced the volume of bowel receiving 45 Gy (V_{45Gy}) from 214 cm^3 to 69 cm^3, corresponding to a reduction of 64%. V_{15Gy} was not significantly different however no planning constraints were set at this level. Similarly, Mok *et al.* [18] compared the dosimetry of IMRT plans with three-dimensional conformal radiotherapy and found that despite larger treatment volumes, coverage, homogeneity and conformality were superior with IMRT, whereas doses to adjacent OARs and overall integral dose to all tissues were reduced. The mean dose to small bowel was reduced from 25.2 Gy to 18.6 Gy with similar relative reductions to bladder and pelvic bones. With V_{15Gy} constraints, they achieved a reduction in V_{15Gy} from 157 cm^3 to 138 cm^3. It also highlighted that most of the benefit was seen in a selected group of patients, with the largest volume of small bowel adjacent to the planning target volume (PTV), with others receiving negligible benefit.

Clinical Evidence

There were no randomised control trials or prospective studies comparing IMRT with three-dimensional conformal radiotherapy in rectal cancer. There are 14 prospective [19–33] and four retrospective studies [34–37] identified (Table 1). All four retrospective series compared the use of IMRT with three-dimensional conformal radiotherapy and included patients with non-curable disease.

The toxicities of the identified IMRT studies and previous large phase III randomised trials [38–42] are documented in Table 1 for comparison. Of the IMRT studies identified, one study did not use concurrent 5-flurouracil or capecitabine [20], the current standard of care [5,42]. Eight of the 17 publications investigated the use of combination chemotherapy, with the addition of oxaliplatin, irinotecan, cetuximab or bevacizumab, or a combination of the above [22–24,26,27,30,33,35]. Despite this, and the higher radiation doses used, the acute toxicity seems to be not dissimilar in comparison with historical controls. In the retrospective comparison studies, Samuelian *et al.* [37] and Jabbour *et al.* [35] both showed a statistically significant reduction in grade 3+ gastrointestinal toxicity alone with IMRT, with Yang *et al.* [36] and Parekh *et al.* [34] reporting similar findings for grade 2+ diarrhoea. Jabbour *et al.* [35] and Parekh *et al.* [34] went on to identify a reduction in treatment breaks and overall treatment time in the IMRT group. Jabbour *et al.* [35] also reported a statistically significant reduction in emergency admissions.

Few studies reported data on late toxicities. This was probably due to the relatively short follow-up time. Engels *et al.* [20] reported the largest prospective late toxicity data after treatment with IMRT and SIB. The median follow-up time was 54 months and the rates of grade 3+ gastrointestinal and genitourinary toxicities were 9% and 4%, respectively. Of note, patients in this trial did not receive concomitant chemotherapy. Huang *et al.* [25] found frequencies of grade 3+ small bowel obstruction, fistula formation and anastomotic stricture of 5.7, 5.7 and 2.9%, respectively. Long-term grade 3 side-effects of diarrhoea (3.7%), local pain (11%) and tenesmus (22%) were reported by Gasent Blesa *et al.* [30].

In terms of comparable outcomes, pathological complete response (pCR) ranged from 0 to 50%, probably reflecting the varying size of studies, concurrent chemotherapy regimens and the different radiotherapy regimens. Of those studies with a high pCR rate, Cubillo *et al.* [22] reported a phase I study investigating the use of combination chemotherapy with either irinotecan/oxaliplatin or cetuximab/bevazucimab. They reported a pCR rate of 50% with an equivalent 2 Gy per fraction dose (EQD2), delivered with an SIB dose of 60.4 Gy. The phase II study of Ballonoff *et al.* [28] reported pCR rates of 38% with single-agent capecitabine delivering an EQD2 dose of 56.1 Gy in 2.2 Gy fractions using an SIB. The phase II study by Hernando-Requejo *et al.* [21] achieved similar high pCR rates with single-agent capecitabine (31%) delivering an EQD2 dose of 60.4 Gy in 2.5 Gy fractions.

The median local control rate was 94% (75–100%) with a median follow-up of 26 months (range 17–55); the wide range represents the low resection rates in some studies. In Zhu *et al.* [24] only 14 of 32 patients underwent surgery as all patients had unresectable metastatic disease at presentation. Similarly, in Parekh *et al.* [34] only 27 of 48 patients underwent resection after an EQD2 dose of 49.4 Gy in 2 Gy fractions, probably confounded by inclusion criteria allowing entry of patients with oligometastatic disease resulting in more locally advanced tumours and the added issue of systemic control.

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