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Systematic Review

Reirradiation of locally recurrent rectal cancer: A systematic review

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ABSTRACT

Background: Many patients with rectal cancer receive radiotherapy as a component of primary multimodality treatment. Although local recurrence is infrequent, reirradiation may be needed to improve resectability and outcomes. This systematic review investigated the effects of reirradiation in terms of feasibility, toxicity, and long-term outcomes. *Methods:* A Medline, Embase and Cochrane search resulted in 353 titles/abstracts. Ten publications describing seven prospective or retrospective studies were included, presenting results of 375 patients reirradiated for rectal cancer. *Results:* Median initial radiation dose was 50.4 Gy, median 8–30 months before reirradiation. Reirradiation was mostly administered using hyperfractionated (1.2–1.5 Gy twice-daily) or 1.8 Gy once-daily chemoradiotherapy. Median total dose was 30–40 Gy to the gross tumour volume with 2–4 cm margins. Median survival was 39–60 months in resected patients and 12–16 months in palliative patients. Good symptomatic relief was reported in 82–100%. Acute toxicity with diarrhoea was reported in 9–20%, late toxicity was insufficiently reported. *Conclusions:* Reirradiation of rectal cancer to limited volumes is feasible. When curative resection is possible, the goal is radical resection and long-term survival, and hyperfractionated chemoradiotherapy should be preferred to limit late toxicity. Reirradiation yielded good symptomatic relief in palliative treatment.

Rectal cancer is a common disease, with an age-standardised incidence rate of 17.3 per 100,000 person-years for colorectal cancer world-wide [1]. Improved surgery with total mesorectal excision [2] and increased use of preoperative radiotherapy (RT) and chemoradiotherapy (CRT) have led to decreased recurrence rates [3–7]. Population-based studies have demonstrated increased survival of patients with rectal cancer [8,9]. Local recurrence of rectal cancer can be a devastating condition, because of morbidity with intractable pain, pelvic infection, and obstruction, with large impact on health-related quality of life (HRQOL) [10].

Although local recurrence rates have decreased, an increasing proportion of patients with local recurrence have previously received high-dose pelvic radiotherapy as part of the primary multimodality treatment, either as preoperative short-course radiotherapy (5×5 Gy) or as chemoradiotherapy to 45–50 Gy (1.8–2.0 Gy/fraction). Curative resection of the local recurrence is the most important factor for survival [11]. Reirradiation of previously irradiated patients may increase the rate of radical resection (R0) and may also provide symptom palliation for inoperable tumours [12]. It is therefore important to determine the safety and benefits of reirradiation in patients with local recurrence.

In terms of optimising radiotherapy, the tumour should receive a high total dose while sparing the surrounding normal tissue to avoid toxicity. Reirradiation is challenging, because the surrounding normal tissues may have already received doses near the organ- or endpoint-specific tolerance dose during the primary treatment. Robust clinical data on long-term normal tissue recovery and radiation tolerance doses are sparse. Therefore, radiation oncologists have been wary of reirradiation in locally recurrent rectal cancer, due to the fear of serious adverse late effects in normal tissue, particularly of the small intestine and bladder. However, there is increasing evidence in clinical studies that reirradiation is tolerable and yields good results for different tumour locations [13]. The potential morbidity caused by retreatment should be weighed against the expected benefits in terms of achieving R0 surgery and long-term survival. If potentially curative treatment is envisaged, the expectation of long survival should drive treatment planning with conformal doses, and hyperfractionation should be considered for radiobiological reasons to reduce the risk of late effects [14].

The aim of this systematic review was to investigate and evaluate the efficacy and safety in published studies describing

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the feasibility, outcomes, and toxicity of reirradiation of previously irradiated locally recurrent rectal cancer. The main focus is on external beam reirradiation, all fractionation regimens, with or without concurrent chemotherapy; reirradiation combined with other radiotherapy modalities is only briefly discussed.

Methods

This systematic review was based on a research protocol describing the aims and methods. The review is reported according to the guidelines in the PRISMA statement [15].

Search strategy

A combined search was performed in the Medline, Embase, and Cochrane databases, through December 2012, with updated search August 2013. The search strategy included terms such as (*colorectal* or *rectal* or *rectum*) and (*neoplasms* or *cancer* or *tumour*) and (*reirradiation*), with no limitations for year of publication. No reviews of this topic were found in the Cochrane database. The titles/abstracts were screened by two of the authors (MGG, CU), and full-text copies of all potentially relevant studies were obtained. Additional studies were identified from the reference lists of full-text articles, and reviewed for potential inclusion.

Eligibility criteria

Published full-text studies that evaluated reirradiation of rectal or rectosigmoid cancer were considered for inclusion. Studies of patients with locally recurrent rectal cancer were eligible if they included patients previously irradiated for rectal cancer and if they reported outcomes after additional external beam radiotherapy with or without concomitant chemotherapy. Prospective, retrospective, and randomised controlled trials were eligible. Case reports and reviews were excluded. Studies evaluating external beam reirradiation combined with other radiation techniques such as stereotactic body radiotherapy (SBRT) or intraoperative radiotherapy (IORT) were not included. Eligibility was assessed independently by three of the authors (MGG, CU, BLR), and final inclusion in the review was based on consensus.

Evaluation of studies

The three authors assessed quality of the full-text papers independently, before consensus was obtained. Evaluation criteria focused on external validity and included the relevance of the patient population, the homogeneity of the patients and treatments, and the appropriateness of the methods used, based on a revised scoring system from the Norwegian Knowledge Centre for the Health Services.

Data regarding patient characteristics, previous radiotherapy, reirradiation details, and outcomes were extracted from the studies independently by the three authors and presented in tables. Consensus was obtained on the data extracted, and data presentation and interpretation (all authors). A meta-analysis was not feasible due to heterogeneity of studies and outcomes.

Endpoints of interest

For patients treated with curative intent, the effects of reirradiation in terms of R0 resection rate, survival, and acute and late toxicity were evaluated. For patients treated with palliative intent, the effects of reirradiation on symptom palliation, survival, toxicity, and HRQOL were evaluated. The clinical implications of reirradiation in terms of total dose, target volume, and fractionation regimens, and possible recommendations for clinical practice, were discussed.

Results

The search resulted in 331 titles/abstracts; the updated yielded an additional 22, and 11 from reference lists, leading to a total of 364 titles/abstracts (Fig. 1). These titles/abstracts were screened, and 48 full-text publications were reviewed. Ten publications describing seven patient cohorts/studies met the inclusion criteria and were included in the final analysis [16–25].

There were no randomised controlled studies; all studies were prospective or retrospective (Table 1). A total of 375 patients treated with reirradiation (range 13–103) were included. The studies published up to 2006 included patients with locally recurrent rectal cancer without distant metastases. Later studies also included patients previously irradiated for other pelvic cancers [22,25]; and in the study by Ng et al., 40% of patients had metastatic disease [25]. The median age ranged from 50 to 69 years,

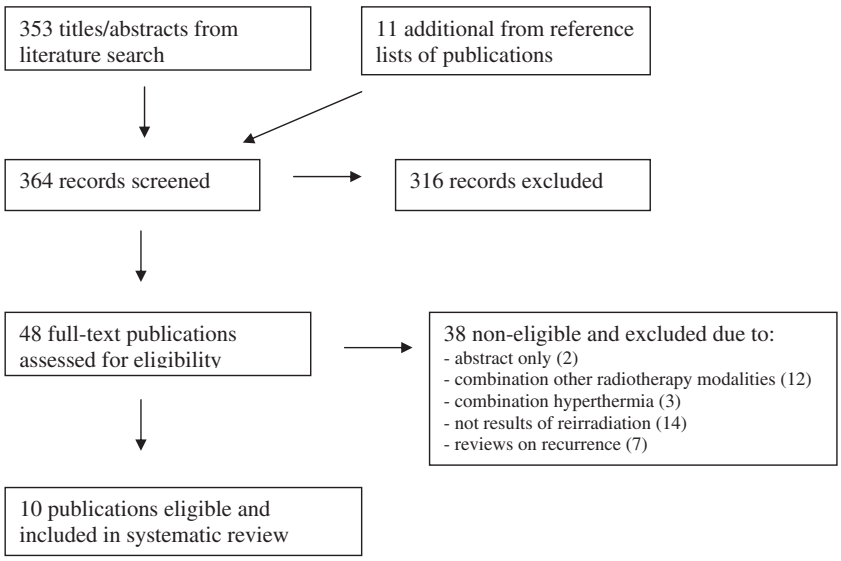

Fig. 1. Search strategy and inclusion of publications in review.