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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,

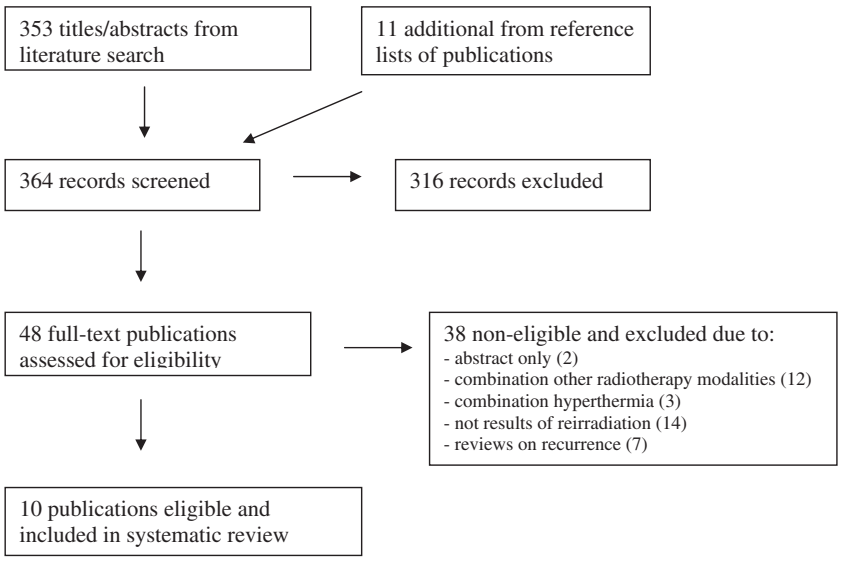

Fig. 1. Search strategy and inclusion of publications in review.

Table 1
Study characteristics, patient characteristics, and details of previous radiotherapy in the included studies.

Author and Publication year	Study design and Inclusion period	Reirradiated N	Patient population	Age median, years (range)	Previous RT dose median, Gy (range)	Time since RT median, months (range)
Ng 2013 [25]	Retrospective 1997–2008	56	RC, previous pelvic RT[b] Curative $n = 13$, Palliative $n = 43$	69 (26–88)	50.4 Gy (21–64)	30 (8–176)
Sun 2012 [24]	Prospective 2004–2008	72	Recurrent irresectable RC	59 (29–78)	<50 Gy (NR)	25 (13–77)
Koom 2012 [23]	Retrospective 2000–2007	22	Recurrent RC	50 (33–64)	54 Gy (45–59.4)	26 (5–72)
Das 2010 [22]	Retrospective 2001–2005	50	RC, previous pelvic RT[c] Primary $n = 2$, Recurrent $n = 48$	60 (32–80)	47 Gy (25–70)	28 (5–354)
Valentini 2006 [21]	Prospective phase II 1997–2001	59	Recurrent RC No extrapelvic disease	62 (43–77)	50.4 Gy (30–55)	27 (9–106)
Mohiuddin 2002 [19]	NR[a] 1987–2000	103	Recurrent RC	65 (31–79)	50.4 Gy (30–74)	19 (2–86)
Valentini 1999 [20]	Prospective 1989–1997	13 (subgroup)	Recurrent RC No metastases	NR	NR (27–59)	NR
Lingareddy 1997 [18]	NR[a] 1987–1993	52	Recurrent RC Palliative $n = 52$	65 (37–79)	50.4 Gy (40–70.2)	24 (3–86)
Mohiuddin 1997 [17]	NR[a] 1987–1992	39	Recurrent RC Curative $n = 39$	61 (31–77)	50.4 Gy (40–45) boost up to 66	18 (3–456)
Mohiuddin 1993 [16]	Phase I/II pilot 1987–1991	32	Recurrent RC Curative $n = 17$, Palliative $n = 15$	60 (31–79)	45 Gy (30–66)	Curative: 8 (3–456) Palliative: 27 (3–79)

NR = not reported in original publication; RC = rectal cancer; RT = radiotherapy.
[a] Reirradiation program.
[b] Previous RT for other cancer (7%); prostate $n = 3$, endometrial $n = 1$.
[c] Previous RT for other cancer (14%); cervical $n = 2$, prostate $n = 2$, bladder $n = 1$.

and the proportion of male patients was 52–78%. The median previous RT dose was mostly 50.4 Gy, previous fractionation regimen was rarely described, but assumed to be 1.8–2.0 Gy per fraction. The median time since previous RT varied from 8 to 30 months.

Reirradiation doses and techniques are summarised in Table 2, and estimates of the EQD_{2Gy} doses in Supplementary Table. An evolution of reirradiation over time was demonstrated. In the early series reported by Mohiuddin et al., reirradiation was administered with either 1.2 Gy twice daily or 1.8 Gy daily to approximately 30 Gy, followed by a boost of 6–20 Gy [16–19]. The median reirradiation dose given was 30.6–36 Gy, delivered by opposed lateral fields or three-field technique, encompassing the presacral region and gross tumour volume (GTV) with 2–4 cm margins, and combined to concomitant 5-fluorouracil (5-FU) continuous infusion. In the prospective study of patients with recurrent rectal cancer reported by Valentini et al., 1.2 Gy twice daily with concomitant 5-FU was given to the GTV plus a 4-cm margin to a total dose of 30 Gy; thereafter, additional CRT to a total of 40.8 Gy was given to GTV plus 2-cm margin [21]. Das et al. reported on patients who received 1.5 Gy twice daily and concomitant 5-FU. Patients with a long interval since previous treatment ($\geqslant$1 year) received a total dose of 39 Gy, and patients with shorter intervals 30 Gy [22]. The treatment was delivered to GTV with a 2–3 cm margin, mostly by three-field technique.

Koom et al. reported on a smaller series of patients treated more heterogeneously with 1.8–3.0 Gy once daily, to a median reirradiation dose of 50.2 Gy, with techniques including conformal RT, intensity-modulated radiation therapy (IMRT), and tomotherapy [23]. Sun et al. reported on patients treated with 1.2 Gy twice daily to a reirradiation dose of 30–36 Gy delivered by 5–8 fields delivered to GTV plus 2 cm, with concomitant capecitabine [24]. In non-resectable patients, the GTV was redrawn and RT continued to a total dose of 51.6–56.4 Gy, thus delivering a high reirradiation dose to patients with irresectable local recurrence.

Finally, Ng et al. reported on patients with rectal cancer who had had previous pelvic radiotherapy, of whom 40% had metastatic disease. They were treated with 1.8 Gy once daily to a reirradiation dose of 39.6 Gy, with concomitant 5-FU. The treatment volume included GTV plus a 2-cm margin; most patients were treated by three-field technique and some with IMRT [25].

To summarise the treatment given, reirradiation for rectal cancer was mostly given with hyperfractionated chemoradiotherapy to total doses of 30–40 Gy, although higher doses have been explored. Once-daily reirradiation was mostly used for palliative intent. The treatment volumes encompassed the tumour with margins, in newer studies delivered by multiple fields.

The median follow-up time ranged from 15 to 36 months (Table 3). R0 resection was obtained in 39–89% of patients who underwent tumour resection; the wide range probably reflecting differences in patient selection. Further local recurrence occurred in approximately 50% of resected patients. The median survival ranged from 39 to 60 months in resected patients and from 12 to 16 months in palliative patients.

A high proportion of patients reirradiated with palliative intent to median doses of $\geqslant$30 Gy obtained symptomatic relief (Table 3). The proportion with complete or partial pain relief ranged from 83% to 94%. Rectal bleeding resolved completely in 100% of patients. The majority (>80%) of patients experienced partial or complete symptom relief from gastrointestinal symptoms or rectal mass. The median duration of symptom relief was 8 months for mass effect, 9 months for pain, and 10 months for bleeding [18,19].

The rate of treatment interruption or termination due to toxicity was >30% in the earlier studies by Mohiuddin et al. (Table 4) [16–19] and was later reduced to 13% [20] and 4% [24,25]. This reduction in acute toxicity seems to be correlated with increasingly conformal radiotherapy and smaller margins to the GTV, and possibly better selection. The most commonly observed grade 3–4 toxicities were diarrhoea and skin reactions (Table 4), the frequency were reduced in the later studies.

Late toxicity was not prospectively evaluated probably because most studies were retrospective, follow-up was relatively short, and patients treated with palliative intent had limited life expectancy. The most commonly reported late toxicities were gastrointestinal and urinary complications such as small bowel obstruction, fistula, stricture, chronic diarrhoea, and cystitis (Table 4). Factors that influenced the development of late toxicity

Table 2
Reirradiaton treatment.

Author and Year	Planned RT regimen fraction dose/total dose	Reirradiation dose median (range)	Treatment volume	Technique	Cumulative dose median (range)	Concomitant chemotherapy
Ng 2013 [25]	1.8 Gy/39.6 Gy	39.6 Gy (20–39.6)	GTV CTV = GTV + 1 cm PTV = CTV + 1 cm	3DCRT 2–4 fields or IMRT	87.3 Gy (44.4–108)	5-FU
Sun 2012 [24]	1.2 Gy bid/30–36 Gy (n = 18) Non-resectable: redraw GTV, total 51.6–56.4 Gy (n = 54)		GTV CTV = GTV + 1 cm PTV = CTV + 1 cm	3DCRT 5–8 fields	NR	Capecitabine
Koom 2012 [23]	1.8–3 Gy/NR	50.2 Gy (30–66)	GTV + 2–3 cm	3DCRT or IMRT or tomotherapy	103.3 Gy (81–119.4)	Yes
Das 2010 [22]	1.5 Gy bid/30–39 Gy[a]	39 Gy (94%) 30 Gy (6%)	GTV + 2–3 cm	3-field	NR	Capecitabine
Valentini 2006 [21]	1.2 Gy bid/30 Gy (PTV2) +1.2 Gy bid/10.8 Gy (PTV1)	40.8 Gy	GTV + 4 cm (PTV2) GTV + 2 cm (PTV1)	3DCRT	NR	5-FU
Mohiuddin 2002 [19]	1.2 Gy bid/30 Gy + boost 6–20 Gy[b] (n = 43) or 1.8 Gy/30.6 Gy + boost 6–20 Gy (n = 60)	34.8 Gy (15–49.2)	Presacral region and GTV + 2–4 cm Boost: GTV + 2 cm	2 lateral fields or 3-field	85.8 Gy (70.6–108)	5-FU
Valentini 1999 [20]	1.8 Gy/23.4 Gy	23.4 Gy	GTV + 1.5 cm + posterior pelvis	Box or 3-field	NR	5-FU/MMC
Lingareddy 1997 [18]	1.2 Gy bid/30 Gy + boost 6–20 Gy (n = 22) or 1.8 Gy/30.6 Gy + boost 6–20 Gy (n = 30)	30.6 Gy (19.8–40.8)	Presacral region and GTV + 2–3 cm Boost: GTV + ⩽2 cm	2 lateral fields	84.4 Gy (66.6–104.9)	5-FU
Mohiuddin 1997 [17]	1.2 Gy bid/30 Gy + boost 6–20 Gy[c] (n = 21) or 1.8 Gy/30.6 Gy + boost 6–20 Gy[c] (n = 18)	36 Gy (19.8–49.2)	Presacral region and GTV + min 2 cm Boost: limited tumour volumes	2 lateral fields	85.7 Gy (70.6–99.8)	5-FU
Mohiuddin 1993 [16]	Curative: 1.2 Gy bid/30 Gy ± boost 10 Gy (n = 17) Palliative: 1.8 Gy/30 Gy ± boost 10 Gy (n = 15)	34.2 Gy (19.8–47.7)	Posterior half pelvis Boost GTV + <2 cm	2 lateral fields	NR (70.6–111.6)	5-FU

Bid: two fractions daily; GTV: gross tumour volume; CTV: clinical target volume; PTV: planning target volume; 3-field: 1 posterior and 2 lateral fields.
3DCRT: 3-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; 5-FU: 5-fluorouracil; MMC: Mitomycin C; NR: not reported.
[a] Total dose 39 Gy if time since previous RT ⩾ 1 year, 30 Gy if time since previous RT < 1 year.
[b] Higher boost dose if >1 year interval from initial RT.
[c] Boost if >1 year from initial RT.

Table 3
Treatment results after reirradiation. Radical surgery and survival after reirradiation. Symptom palliation in non-resected patients.[a]

Author year	Follow-up median, months (range)	Surgery tumour resection, n (%)	Survival[b] median, months			Symptom palliation, n (%)
			All	Resected	Palliative	
Ng 2013 [25]	15 (1–108)	Surgery 12/56 (21%) Resection 11/56 (20%) R0: 8	19	39	15	Overall RR 88%, CR 24/49 (49%) PR 19/49 (39%) Rectal bleeding/discharge 100% GI CR 50% PR 50% Pain CR 47% PR 44% Urinary CR 1/1 (100%) Vaginal bleeding CR 2/3 (67 %)
Sun 2012 [24]	24 (10–57)	Resection 18/72 (25%) R0: 16	32	–	–	Pain relief 29/31 (94%) Tenesmus relief 23/28 (82%)
Koom 2012 [23]	20 (7–91)	Resection 5/22 (23%)	21	–	–	
Das 2010 [22]	25 (0–71)	Resection 18/50 (36%) R0: 7	26	60	16	
Valentini 2006 [21]	36 (9–69)	Resection 30/59 (51%) R0: 21	42	–	–	Pain relief 20/24 (83%)
Mohiuddin 2002 [19]	24 (3–84)	Surgery 41/103 (40%) Resection 34/103 (33%)	26	44	14	Bleeding CR 21/21 (100%) Pain CR 25/46 (54%) PR 13/46 (28%) Mass effect CR 9/36 (25%) PR 23/36 (64%)
Valentini 1999 [20]	NR	Resection 4/13 (31%)	–	–	–	
Lingareddy 1997 [18]	16	NA	–	–	12	
Mohiuddin 1997 [17]	36 (24–77)	Resection 31/39 (79%) R0: 27	–	45		
Mohiuddin 1993 [16]	NR (12–72)	Surgery 17/32 (53%) Resection 15/32 (49%)	–	–	14	

Operated: number of patients operated; Reirradiated: number of patients reirradiated.
R0: number of patients with microscopic radical resection; NR: not reported; RR: response rate; CR: complete response; PR: partial response.
[a] Data from selected studies where palliation was reported, and median reirradiation dose was ⩾30 Gy. The publications by Mohiuddin et al. [16] and Lingareddy et al. [18] also reported on symptom palliation, but these patients are included in the publication by Mohiuddin et al. [19].
[b] Survival: either median *survival* or *overall survival* was reported.

Table 4
Acute and late toxicity after reirradiation.

Author year	Acute toxicity[a] grade 3 or 4	Treatment break or termination (toxicity)	Late toxicity, *n*
Ng 2013 [25]	Skin 5% Gastrointestinal 9% Mucositis 2%	Termination 4%	Infection/abscess/drainage/discharge 4/12, fistula 1/12, urinary infection/retention 2/12, small bowel obstruction 1/12, delayed wound healing 1/12, skin ulceration 1/43
Sun 2012 [24]	Diarrhoea 10% Granulocytopenia 8%	Termination 4%	Skin fibrosis 4/72, urinary incontinence/dysuria 4/72, small bowel obstruction 1/72
Koom 2012 [23]	Diarrhoea 9%	–	Grade 3–4 toxicity 8/22 – small bowel obstruction, fistula, urinary stricture, haematologic
Das 2010 [22]	Nausea/vomiting 4%	–	Grade 3 toxicity 12/50 – small bowel obstruction, wound complication, abscess, fistula, ureteral stricture/leakage, haemorrhage, joint disease, nausea Grade 4 toxicity 1/50 – cystitis
Valentini 2006 [21]	Gastrointestinal 5%	Break 10% Termination 3%	Skin fibrosis 2/59, impotence 2/59, urinary incontinence/dysuria 2/59, small bowel obstruction 1/59
Mohiuddin 2002 [19]	Diarrhoea 20% Moist desquamation 8% Mucositis 4%	Break 22% Termination 15%	Diarrhoea 8/103, small bowel obstruction 15/103, fistula (recurrence) 4/103, skin ulceration 2/103
Valentini 1999 [20]	Haematologic/ diarrhoea 8% (same patient)	–	
Lingareddy 1997 [18]	Diarrhoea 19% Perineal skin breakdown 8% Mucositis 4%	Break/termination 31%	Small bowel obstruction 9/52, cystitis 3/52, fistula 4/52, skin ulceration 1/52
Mohiuddin 1997 [17]	Diarrhoea 13% Moist desquamation 10% Mucositis 5% Delayed wound healing 6%	Break 18% Termination 13%	Chronic diarrhoea 3/39, small bowel obstruction 6/39, fistula (recurrence) 3/39, coloanal stricture 2/6
Mohiuddin 1993 [16]	Diarrhoea 13% Skin reaction 13% Pelvic abscess 6%	–	Delayed wound healing 2/17, small bowel obstruction 1/17, coloanal stricture 1/5

[a] Toxicity scored by Common Toxicity Criteria (CTC) or RTOG score.

included surgery [22,23], prior radiotherapy dose [22], interval between initial radiotherapy and reirradiation [19], tumour location within the pelvis [23], and fractionation regimen [19]. None of the studies evaluated health-related HRQOL.

Discussion

This systematic review of reirradiation for patients with locally recurrent rectal cancer revealed that reirradiation is feasible and has acceptable acute toxicity, although there is limited evidence on late toxicity. Reirradiation was delivered as hyperfractionated or once-daily regimens to total doses of 30–40 Gy to the GTV with 2–4 cm margins, and concurrent chemotherapy. The aims of the treatment were to achieve a curative resection with radical surgery, or to obtain tumour control and symptom palliation.

Radical surgery is the main predictor for increased survival [11,26]. Thus, an aggressive multimodal and surgical approach is justified if R0 resection may be possible. Surgery of local recurrence is challenging, since the normal anatomical boundaries and surgical planes have been distorted and previous radiotherapy may have induced fibrosis, and because recurrence often involves other pelvic organs or structures [11]. Reirradiation may downsize the tumour and increase the chance of an R0 resection [26], although it is not clear whether all patients benefit from reirradiation. Patients who underwent tumour resection experienced a longer median survival than patients with inoperable disease [19,21,22,25], however more toxicity was reported in patients who underwent surgery [23,25]. It was difficult to know whether late toxicity was due to radiotherapy, surgery, or symptoms from further recurrence. Future studies are needed to define the optimal curative treatment for previously irradiated patients with recurrent rectal cancer.

The distinction between curative and palliative intent is often not clear, and in several studies reviewed this depended on whether patients were eligible for curative resection after reirradiation. Patients reirradiated with palliative intent had a shorter median survival, but reported good symptom palliation of bleeding, pain, and gastrointestinal symptoms [16,18,19,21,24,25]. This is in line with a recent review of palliative radiotherapy for rectal cancer, reporting good symptomatic relief [27], and a review reporting efficacy of reirradiation for bone metastases [28]. The need for symptom palliation and the expected benefits of reirradiation must be weighed against the expected survival.

The main organs at risk are the small bowel and the bladder. Clinical evidence concerning reirradiation tolerance is lacking [29], and dose constraints are not given. For small bowel, there are suggestions for constraints in the literature to minimise acute toxicity [30], and experimental evidence suggests consequential chronic damage; however, a correlation with late toxicity has not been established. For bladder, experimental studies suggest no late toxicity recovery, and a strong consequential component [14], but reliable tolerance data are not known. Surgery following reirradiation is often extensive and may result in colostomy and urostomy. Furthermore, complications such as perforation, obstruction, bleeding, incontinence, and fistula are also associated with persistent or recurrent disease [19,22]. Reirradiation should be given to limited volumes using small margins and highly conformal therapy, thereby reducing small bowel and bladder doses [14,30].

HRQOL was not reported in any of the reirradiation studies, but in disease-free patients after radiotherapy and surgery for recurrent rectal cancer, acceptable HRQOL has been described even after pelvic exenteration [31,32]. On the other hand, significant deterioration occurs in patients with progressive disease [10]. Future trials should address patient-reported outcomes and HRQOL after reirradiation for recurrent rectal cancer.

Most studies included in this review used hyperfractionated radiotherapy, administered in 1.2–1.5 Gy fractions twice daily, at least for curative treatment [16–22,24]. Once-daily fractions of 1.8 Gy were mostly an option for palliative treatment or patient preference [16–19,23,25]. The fractionation regimens were probably chosen due to radiobiological rationale, extrapolation from other tumour sites, and feasibility. Although several studies used different regimens, patients were not randomised, making comparison between schedules difficult.

The rationale for hyperfractionated, accelerated therapy is that small fraction doses increases the therapeutic ratio by exploiting the difference in fractionation sensitivity between tumour (high α/β) and late-reacting normal tissue (low α/β) [33]. Reirradiation doses can be recalculated to equivalent doses delivered with 2 Gy fractions (EQD_{2Gy}) for comparison of fractionation schemes ($EQD_{2Gy} = n * d * ((d + \alpha/\beta)/(2 + \alpha/\beta))$). A total dose of 39.6 Gy delivered with 1.2 Gy/fraction gives EQD_{2Gy} = 33.3 Gy for late-reacting tissue (α/β = 3 Gy), and a higher EQD_{2Gy} = 37.0 Gy for tumour (α/β = 10 Gy), assuming adequate time between the fractions to allow normal tissue recovery. Repair half-times for human small bowel are not certain, but assuming an incomplete repair factor of 0.063 based on animal models [14], normal tissue has full recovery by 6 h.

Hyperfractionated reirradiation should theoretically be the preferred treatment for patients with curative intent. It may also be considered in patients with inoperable tumour with a relatively long life expectancy, with the aim of durable local control. Although some patients with metastatic disease have long survival with combination chemotherapy, many patients with disseminated disease or poor performance status have a short life expectancy, and the risk of late effects is less relevant. For these patients, once-daily reirradiation has been shown to be feasible and effective [12,25] and should in our opinion be considered the preferred treatment regimen, considering convenience and patient preference.

Although treatment techniques have become more sophisticated with time, the treatment principles remained the same. In earlier studies, computed tomography (CT) was probably not used for treatment planning; the target volume was the gross tumour with margins of 2–4 cm and the presacral space, given by opposed lateral fields to spare the anteriorly situated small bowel [16–20]. In recent studies, the GTV was delineated and margins of 1 cm to the clinical target volume (CTV) and 1 cm to the planning target volume (PTV) were added [21–25]. Treatment was delivered by conformal radiotherapy or IMRT [23,25], in order to deliver high tumour doses with acceptable small intestine and bladder doses. There was a trend towards less acute and late toxicity in the recent studies, probably due to better conformal treatment.

The total dose administered was mostly at the level of 30–40 Gy; however, some studies administered a higher dose to a smaller volume, depending on time elapsed since previous radiotherapy [19] or in inoperable patients [24]. One study showed that reirradiation doses >50 Gy increased the infield progression-free survival [23]. For patients with inoperable disease, it seems that higher doses can be administered safely, especially with conformal CRT or IMRT, provided sufficiently low normal tissue doses. Escalated doses to 51.6–56.4 Gy (hyperfractionated, shrinking-field after 36 Gy) with 5–8 fields were administered in one study, with dose limitation to the bladder of 30 Gy and to the small intestine 10 Gy for <50% of volume [24]. A short time interval since previous radiotherapy may result in worse radiation tolerance [19,22]. Modern imaging (i.e., magnetic resonance imaging and positron emission tomography) and radiotherapy techniques (e.g., conformal RT and IMRT) permit more precise target delineation, accurate dose distribution, and narrow margins (e.g., cone beam CT and image-guided radiotherapy), increasing accuracy and allowing for individualised treatment.

Reirradiation has been combined with IORT, where high radiation doses are delivered to the tumour bed while organs at risk are displaced or shielded from the radiation field. Large retrospective institutional series from experienced centres have been published in which subgroups received reirradiation to 30–30.6 Gy followed by resection and IORT [26,34–36]. Good local control and survival was shown, and results after reirradiation were as good as after conventional preoperative irradiation [36]. Reirradiation has been combined with hyperthermia [37,38] and has also been delivered with brachytherapy [39] in patient series. SBRT for reirradiation poses an interesting possibility for delivering high doses to restricted volumes with very tight margins [40], although there are limited data for recurrent rectal cancer, SBRT has been used for presacral or pelvic wall recurrences [41,42].

Tumour classification according to the site of recurrence within the pelvis or according to degree of fixation, determined by preoperative imaging [11,43,44], may be helpful for decisions in the multidisciplinary team (MDT) conference. Axial tumours were most often resectable, in contrast with lateral or posterior tumours; however, more toxicity was observed, probably due to higher small bowel and bladder doses [23]. Presacral recurrence had the worst prognosis and anastomotic recurrence the most favourable prognosis [45]. Patients with higher fixation grades had worse outcomes [46]. A recent review of curative treatment of locally recurrent rectal cancer emphasised the importance of careful patient selection and optimised multimodality treatment [47]. Patients should ideally be treated by experienced clinicians in specialist centres [48].

Future trials should aim at prospective assessment of tumour and normal tissue doses, investigate the optimal fractionation regimen, and the acute and late toxicity including patient-reported outcomes and HRQOL. Central review of CTV delineation in rectal cancer may increase the CTV uniformity, and can be used for quality assurance for radiation treatment [49,50]. Methods for standardised data collection in rectal cancer has been described as a tool to aid personalised medicine [51].

In summary, although treatment of previously irradiated patients with recurrent rectal cancer is a challenge, several studies have shown that reirradiation is feasible, safe, and effective in terms of achieving radical resection or palliation. Retreatment is likely to be even safer with modern staging and radiotherapy techniques, allowing for increased accuracy and individualised radiotherapy. Patients should undergo adequate diagnosis and MDT discussion in experienced centres, and ideally be included in prospective trials. When the intent is curative treatment, patients should undergo hyperfractionated chemoradiotherapy followed by radical surgery. If the intent is clearly palliative and life expectancy is short, patients are probably best treated by once-daily chemoradiotherapy.

Conflict of interest statement

The authors declare that no conflicts of interest exist.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2014.11.021.

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