Radiotherapy and Oncology 140 (2019) 10–19

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Systematic Review

Practical effectiveness of re-irradiation with or without surgery for locoregional recurrence of rectal cancer: A meta-analysis and systematic review

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ARTICLE INFO

Article history:
Received 25 February 2019
Received in revised form 13 May 2019
Accepted 20 May 2019
Available online 5 June 2019

Keywords:
Rectal cancer
Recurrence
Re-irradiation
Surgery
Complication

ABSTRACT

Background and purpose: Re-irradiation might yield local control (LC) or palliation for locoregionally recurrent rectal cancer (LRRC), but iatrogenic complications are a possible hindrance. We aimed to evaluate the efficacy of re-irradiation to determine optimal treatment of LRRC.
Methods: We performed a systematic review of PubMed, MEDLINE, Cochrane Library, and Embase.
Results: A total of 17 studies involving 744 patients with LRRC were included; median OS ranging from 10 to 45 months (median: 24.5 months). Pooled 1-, 2-, and 3-year OS rates for all patients were 76.1%, 49.1%, and 38.3%, respectively. For patients who underwent re-irradiation and surgery (OP group), these pooled rates were 85.9%, 71.8%, and 51.7%, respectively. For patients who underwent re-irradiation but not surgery (non-OP group), pooled 1-, 2-, and 3-year OS rates were 63.5%, 34.2%, and 23.8%, respectively. The OS difference between both groups was significant for all 3 years ($P < 0.05$). Pooled 1-, 2-, and 3-year LC rates for the OP group were 84.4%, 63.8%, and 46.9%, and for the non-OP group were 72.0%, 54.8%, and 44.6%, respectively, without significant differences. Pooled grade $\geq$3 acute and late complication rates were 11.7% and 25.5% in the OP and non-OP groups, respectively. Patients who underwent surgery had a higher risk of grade $\geq$3 late complications (odds ratio: 6.39). Pooled symptomatic palliation rate was 75.2%.
Conclusions: Re-irradiation with or without surgery for LRRC showed oncologic and palliative efficacy. Salvage treatment including re-irradiation and surgery showed higher survival, but the late complication was significantly increased with concomitant surgery.
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Multimodal treatment, including neoadjuvant chemoradiotherapy, total mesorectal excision, and adjuvant therapy have contributed to reducing locoregional failure of rectal cancer treatment [1–3]. However, a small proportion of patients with locoregionally recurrent rectal cancer (LRRC) still carry a poor prognosis, which is not confined to diminished survival but also with symptoms such as pelvic pain, fistula, bleeding, and fecal discharge [4,5].

An aggressive approach including surgery offers the best chance of successful salvage treatment, possibly leading to long-term survival [6–9]. However, surgery for LRRC is challenging because anatomical boundaries and surgical planes become distorted, and tissue fibroses from previous radiotherapy (RT) can interfere with resection. Perioperative morbidities were not negligible in previous surgical case series, and curative resection is not always feasible [9–11].

Hence, re-irradiation has been considered to be a possible local treatment modality for LRRC. Indeed, a previous systematic review found that re-irradiation of LRRC had a significant palliative effect and favorable survival outcomes when combined with surgery [12]. Increased use of developed techniques such as intensity modulated RT (IMRT) or stereotactic body RT (SBRT), which can increase the precision of RT, reduce side effects and encourage the use of re-irradiation [13,14]. Nonetheless, there is a lack of robust clinical data on long-term tissue recovery and radiation tolerance doses, making it difficult to determine clinically whether re-irradiation should be included in the treatment of LRRC [15].

Many researchers have reported their clinical experiences applying re-irradiation for LRRC to date. Our systematic review and meta-analyses aim to integrate and update the clinical information, and provide practical information for clinical decision-making regarding application of re-irradiation.

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https://doi.org/10.1016/j.radonc.2019.05.021
0167-8140/

Methods

The present meta-analysis is designed to answer the following clinical question (PICO question): '1) *Is application of re-irradiation for LRRC a feasible option? 2) Could oncologic benefit in regards to survival and palliation be achieved by applying re-irradiation for LRRC?*'. We adhered to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [16]. We systematically searched four databases, PubMed, Embase, MEDLINE, and Cochrane Library using the following terms: (''re-irradiation" OR ''re-irradiation" OR ''reRT") AND (''rectal cancer" OR ''rectal malignancy" OR ''rectal neoplasm"). No restrictions for language or time of publication were applied. Conference abstracts were not included in this meta-analysis.

Selection criteria

The following inclusion criteria were applied in the present meta-analysis. (1) Clinical trials reporting LRRC; (2) studies including at least 10 patients with rectal cancer who received re-irradiation; (3) studies reporting at least one of the following: primary objectives including overall survival (OS), and secondary objectives including complications of grade $\geq$3, tumor control rate, and symptomatic palliation rates.

An initial screening was performed using citations and titles, to filter studies duplicated among databases or studies that were not clinical trials, such as reviews, letters, editorials, and *in vivo* or *in vitro* studies. We conducted a second screening using abstracts and excluded studies with irrelevant subjects, fewer than 10 patients with rectal cancer receiving re-irradiation, and studies that were not clinical trials. We then performed a full-text review to identify studies meeting the above inclusion criteria. In cases of multiple studies from a single institution, the following criteria were applied and prioritized in the following order: (1) studies with the largest number of patients with rectal cancer who received re-irradiation, and (2) the most recent publication. Even if studies were published by the same institution, we included multiple studies if patients were clearly different among studies. The above screening processes were performed by two independent researchers, and final inclusion was confirmed upon mutual consent.

Data extraction

Data acquisition was performed by two independent researchers using a standardized form including the following: (1) general information such as authors, publication year, country, study design, patient inclusion period, number of patients with rectal cancer receiving re-irradiation, and age; (2) treatment information, including dose and regimen of previous and current re-irradiation, cumulative dose, and concomitant chemotherapy; (3) oncologic outcomes including OS, local control (LC), and symptomatic palliation; (4) treatment termination, and acute and late complications of grade 3 or higher. For missing numerical data, OS or LC rates were estimated from descriptive graphs, as available. The information regarding tumor control was collected and analyzed as rates at specific time points (e.g. 1-, 2-, and 3-year LC rates), taking into account the possible recurrence or regrowth after re-irradiation. Symptomatic palliation rates encompassed both rates of partial and complete pain relief, and descriptive statements of significant symptom reduction.

Acute complications were defined as complications occurring within 3 months of re-irradiation, or those described as acute complications in the relevant study. Late complications were defined as complications occurring 3 months after re-irradiation, or those described as late complications in the relevant study. We classified toxicities into three categories: gastrointestinal (GI; bowel obstruction, bowel perforation, diarrhea, and other GI problems); genitourinary (GU; dysuria, cystitis, ureteral stricture, and other GU problems); and skin and soft tissue (skin ulceration, wound complications, fistula formation, abscess, and other skin, wound, or soft tissue-related problems).

If discrepancies in the information were found by the two independent researchers, the difference was resolved through discussion and repeated literature review.

Quality assessment

We used the Newcastle-Ottawa scale [17] as an index of evaluation because most included studies were non-controlled and retrospective. Studies were considered to be high quality or medium quality with scores of 7–9 and 4–6, respectively, on the scale.

Statistics

As the included studies were conducted by different researchers and involved a heterogeneous group of patients, we used a random effects model [18] to perform a pooled analysis of endpoints. Cochran Q [19] test and the I^2 statistic were used to evaluate heterogeneity among included studies. Significant heterogeneity was regarded to be present with *P*-value <0.1 in the Cochran Q test and I^2 value >50%. Publication biases were evaluated using visual inspection of funnel plots and quantitative analysis using Egger's test of intercept [20]. If publication biases were present in funnel plot inspection with a two-tailed $P < 0.1$ in the Egger' test, trimmed values after corrections using Duval and Tweedie's method [21] were presented. Subgroup comparisons were performed using Q-tests based on analysis of variance and a random-effects model, and $P < 0.05$ was defined as statistically significant. All statistical analyses were conducted using Comprehensive Meta-Analysis software version 3 (Biostat Inc., Englewood, NJ, USA).

Results

An initial search identified 192 studies among the 4 databases. After excluding reviews, case reports and conference abstracts, 62 studies underwent abstract review. Among these, 15 were excluded for irrelevant subjects, 9 were unsuitable types of publication (e.g., reviews, case reports, and conference abstracts), and 2 had insufficient patients to fulfill the inclusion criteria. Full-text review was performed for 36 studies; 6 were excluded as they had irrelevant subjects and 3 had insufficient patients. Five studies were excluded because multiple studies were published from a single institution, per the abovementioned selection criteria. Another five studies were excluded as no outcomes of endpoints were provided for included patients (e.g., outcomes for all patients with LRRC were provided regardless of whether they received repeated pelvic RT). Ultimately, 17 studies involving 18 cohorts of 744 patients were included in this meta-analysis [22–38]. The study inclusion process is summarized in Fig. 1.

Most (83.3%) included studies had a retrospective study design. According to the Newcastle-Ottawa scale, all studies were categorized as having medium quality. Nine of 17 (52.9%) studies were from the US, 2 from China, 2 from South Korea, and 1 each from Australia, Germany, Italy, and the Netherlands. Previous median RT dose ranged from 45 to 54 Gy (median: 50.4 Gy), and median intervals between RT ranged from 8 to 39 months (median: 26.5 months). Median values of cumulative RT dose ranged from 66.4 to 103.3 Gy (median 85.7 Gy). As for re-irradiation, a conventional daily fractionation scheme with 1.8–2 Gy per day was used in 5 (29.4%) studies, 6 studies (35.3%) used a twice per day scheme of 1.2–1.5 Gy per fraction, 2 studies used both conventional daily and twice daily fractionation schedules, 2 studies used SBRT with

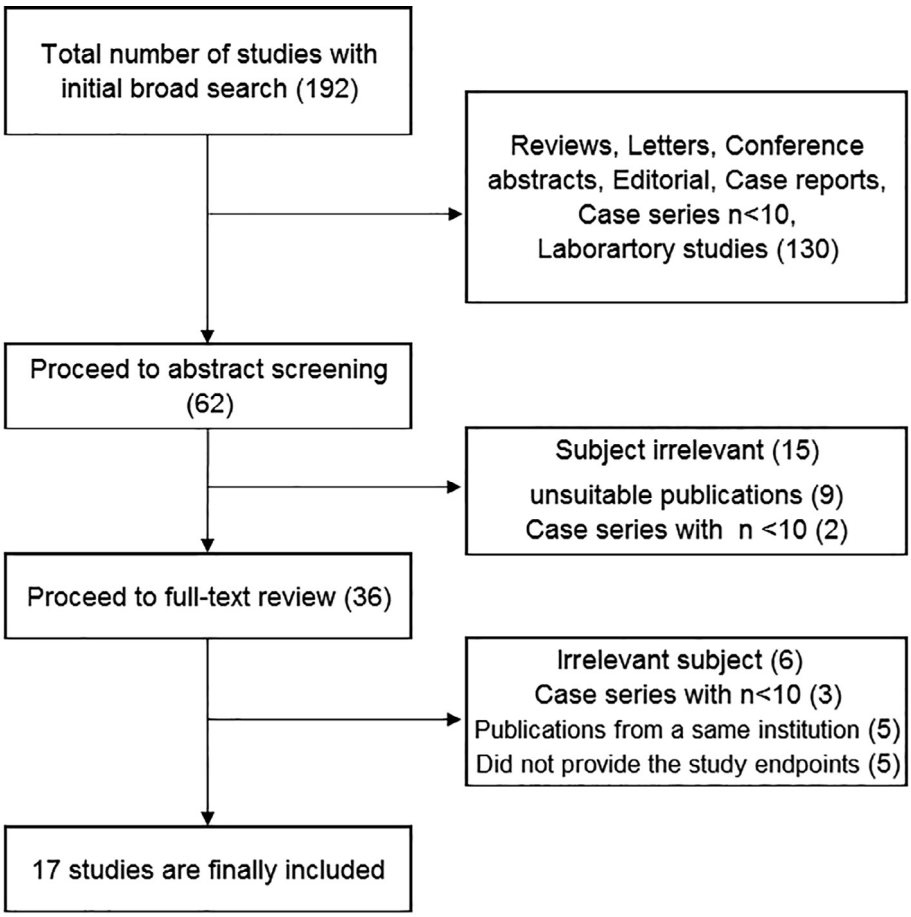

Fig. 1. Flow diagram depicting the study selection process.

a total of 4–5 fractions, 1 study used a twice weekly schedule, and 1 study performed intraoperative RT and/or additional conventional fraction external beam RT. General information of the included studies is summarized in Table 1.

Median OS was available in 14 of 17 studies, ranging from 10 to 45 months (median: 24.5 months), as shown in Table 2. For pooled analyses and comparison, OS was evaluated for all patients in the included studies and for those who underwent surgery (OP group) or did not (non-OP group), as treatment outcomes were expected to be different and results were reported separately in some studies. For all patients, results were available from 9, 15, and 10 cohorts for 1-, 2- and 3-year OS rates; pooled rates were 76.1% (95% confidence interval [CI]: 61.7–86.3%), 49.1% (95% CI: 38.5–59.7%), and 38.3% (95% CI: 30.2–47.2%), respectively. Significant heterogeneity among studies was found for all three OS rates. Trimmed values, using Duval and Tweedie's method, are presented for the 1-year OS rate, as the *P*-value of the Egger's test was less than 0.1.

For the non-OP group, 9, 9, and 7 studies had available 1-, 2-, and 3-year OS rates, respectively with pooled rates of 63.5% (95% CI: 51.1–74.4%), 34.2% (95% CI: 20.4–51.2%), and 23.8% (95% CI: 15.4–34.8%), respectively. Trimmed values are presented for the 1-year OS rate in the non-OP group. For the OP group, 7, 7, and 7 cohorts had available 1-, 2-, and 3-year OS rates, with pooled rates of 85.9% (95% CI: 74.0–92.9%), 71.8 (95% CI: 54.6–84.4%), and 51.7% (95% CI: 39.4–63.8%), respectively. Trimmed values are presented for 1- and 2-year OS rates. Significant heterogeneity among studies was found for all three OS rates of the two groups. Regarding rates in all 3 years, pooled OS rates between the OP and non-OP subgroups were significantly different ($P = 0.002$, <0.001, and 0.001, respectively); pooled OS results are summarized in Table 3.

LC results were available in fewer studies than OS results, and local progression-free survival (LPFS), rather than LC rates, was reported in some studies. Pooled analysis was performed for LC rates and not LPFS (Table 2). Pooled analyses were also performed for all patients and groups that underwent surgery and those that did not. For all patients, 3, 5, and 6 cohorts had available 1-,2-, and 3-year LC rates with pooled rates of 76.3% (95% CI: 50.5–91.0%), 51.9% (95% CI: 37.9–65.7%), and 46.4% (95% CI: 36.2–56.8%), respectively. Trimmed values are presented for the LC rates of all 3 years. Significant heterogeneity among studies was found for 2- and 3-year but not 1-year LC rates ($P = 0.144$, $I^2 = 48.4\%$). For the non-OP group, 4, 4, and 3 cohorts had available 1-, 2-, and 3-year LC rates with pooled rates of 72.0% (95% CI: 48.8–87.4%), 54.8% (95% CI: 28.6–78.5%), and 44.6% (95% CI: 16.6–76.5%), respectively. No significant publication bias was found in this analysis. Significant heterogeneity among studies was found for all three pooled analyses. For the OP group, 3, 4, and 5 cohorts had available 1-, 2-, and 3-year LC rates, with pooled rates of 84.4% (95% CI: 75.5%–90.4%), 63.8% (95% CI: 55.2%–71.5%), and 46.9% (95% CI: 39.6%–54.4%), respectively. Trimmed values are presented for 3-year LC rates. No significant heterogeneity was found for all three pooled analyses; results are summarized in Table 3.

Details of symptomatic palliation are summarized in Table 2. Overall symptomatic palliation rates were available from 12 cohorts; the pooled rate was 75.2% (95% CI: 67.3%–81.8%), which is the trimmed value. Significant heterogeneity was not found ($P = 0.085$, $I^2 = 38.4\%$) and results are summarized in Table 3.

Table 1
Study characteristics.

Author	*N*	Year	Country	Study design	Study period	Patient population	Age	Previous RT dose, Gy	Interval between RT, mo	ReRT total dose, Gy	ReRT Fx. dose, Gy	Cumulative dose, Gy	ReRT technique	CTx. Rate (%) (agent)
							median (range)							
Dagoglu	18	2015	USA	R	2006–2012	pelvic RRC or CC	68 (32–93)	50.4 (25–100.4)	22 (15–336)	mean 25 (24–40)	5	75.4	SBRT (100%)	72 (NR)
Sukso	33	2016	USA	R	2000–2014	LRRC	63 (IQR 58–70)	47	39 (IQR 25–50)	30 (18–36)	(1.8–2)	77.4 (65.4–86.4)	2D/3D RT (52%); IMRT (33%); IOERT (15%)	75 (fluoropyrimidine)
Jufferman	54	2003	Netherland	R	1990–2000	unresectable RRC	63 (38–77)	50 (25–70)	22 (4–97)	30 (24–32)	4, twice weekly	82 (57–94)	3DCRT (with hyperthermia)	
Cai	22	2014	China	P	2007–2012	unresectable RRC	53 (40–68)	48.6 (36–62)	30 (18–93)	39	1.3, bid		IMRT + hyperfractionated	81.8 (5-FU)
Tao	102	2017	USA	R	2001–2012	isolated pelvic RRC	58 (35–77)	50.4 (25–63)	30 (5–789)	39 (30–45)	1.5, bid	89.4 (55–104.5)	3DCRT (91%); IMRT (4%); others (5%) + hyperfractionated	91 (capecitabine or 5-FU or [5-FU and oxaliplatin] or [cisplatin and irinotecan])
Lingareddy	52	1997	USA	R	1987–1993	pelvic RRC	65 (37–79)	50.4 (40–70.2)	24 (3–86)	30.6 (19.8–40.8)	1.8 or 1.2, bid	84.4 (66.6–104.9)	3DCRT ± hyperfractionated	90 (5-FU)
Ng	56	2013	Australia	R	1997–2008	RRC	69 (26–88)	50.4 (21–64)	30 (8–176)	39.6 (20–39.6)	1.8	87.3 (44.4–108)	3DCRT or IMRT	80 (5-FU)
Haddock	51	2001	USA	R	1981–1994	LRRC	55 (31–73)	50.4 (27–70)	22 (9–51)	IOERT 20 (10–30)			IOERT (100%) (with preop EBRT [39%]; postop EBRT [22%]; preop and postop EBRT [12%])	47 (5-FU or 5-FU + leucovorin)
Kim	12	2010	Korea	R	2005–2008	LRRC	62 (46–77)	50.4 (45–57.6)		45	1.8	95.4	3DCRT	91.7 (NR) 100 (Capecitabine)
Sun	72	2012	China	P	2004–2008	unresectable LRRC	59 (29–78)	<50	25 (13–77)	(36–56.4)	1.2, bid		3DCRT + hyperfractionated	100 (5-FU)
Mohiuddin (1993, palliative)	15	1993	USA	R	1987–1991	LRRC	60 (31–79)	45 (41–64.8)	27 (3–79)	34.2 (19.8–47.6)	1.8	(70.6–111.6)	2D/3D RT	100 (5-FU)
Mohiuddin (1993, curative)	17							45.2 (30–66)	8 (3–456)	34.2 (19.8–40.6)	1.2, bid		2D/3D RT + hyperfractionated	
Mohiuddin (1997)	39	1997	USA	R	1987–1992	LRRC	61 (31–77)	50.4 (40–66)	18 (3–456)	36 (19.8–49.2)	1.8 or 1.2, bid	85.7 (70.6–99.8)	2D/3D RT ± hyperfractionated	100 (5-FU)
Valentini	59	2006	Italy	P	1997–2001	LRRC	62 (43–77)	50.4 (30–55)	27 (9–106)	40.8	1.2, bid		3DCRT + hyperfractionated	100 (5-FU)
Milani	24	2008	Germany	R	2000–2005	LRRC	59 (39–73)	50.4 (38–59.4)	34 (11.3–112.4)	39.6 (30.0–45.0)	1.8	(75.6 – 99.0)	3DCRT (with hyperthermia)	
Defoe	14	2011	USA	R	2003–2008	presacral RRC	65.5 (42–77)	50.4 (20–81)	NR	16 (12–36)	16 (12–18)	66.4	SBRT	

(*continued on next page*)

Table 1 (*continued*)

Author	*N*	Year	Country	Study design	Study period	Patient population	Age	Previous RT dose, Gy	Interval between RT, mo	ReRT total dose, Gy	ReRT Fx. dose, Gy	Cumulative dose, Gy	ReRT technique	CTx. Rate (%) (agent)
							median (range)							
Das	50	2010	USA	R	2001–2005	RRC	60 (32–80)	47 (25–70)	28 (5–354)	(30–39)	1.5, bid	89 (55–119)	3DCRT + hyperfractionated	96 (Capecitabine)
Koom	22	2012	Korea	R	2000–2007	LRRC	50 (33–64)	54 (45–59.4)	26 (5–72)	50.2 (30–66)	(1.8–3)	103.3 (81–119.4)	3DCRT (64%); IMRT (14%); tomotherapy (23%)	95

Abbreviations: N, number of patients; R, retrospective; P, prospective; RRC, recurrent rectal cancer; LRRC, locoregionally recurrent rectal cancer; RT, radiotherapy; Gy, gray; mo, month; ReRT, re-irradiation; Fx, fractions; 2D, two-dimensional; 3D, three-dimensional; CRT, conformal radiotherapy; IOERT, intraoperative electron beam radiotherapy; EBRT, electron beam radiotherapy; SBRT, stereotactic body radiotherapy; IMRT, intensity-modulated radiotherapy; IQR, interquartile range.

Results for complications and the risk factors for late complications among the included studies are summarized in Table 4. For acute complications with an overall grade ≥3, 11 cohorts had available data; the pooled rate was 11.7% (95% CI: 6.7–19.5%). For late complications, 15 cohorts had available data, with a pooled rate of 25.2% (95% CI: 16.7–40.0%). There was no reported treatment-related mortality. Trimmed values are presented for both acute and late overall grade ≥3 complication rates. Significant heterogeneity was found for both in pooled analyses.

As mentioned, we categorized complications according to three categories (GI, GU, and Skin and soft tissue). For acute complications, 14 cohorts had available data for GI, GU, and Skin and soft tissue complications; pooled rates were 12.7% (95% CI: 8.6–18.4%), 1.7% (95% CI: 0.9–3.4%), and 9.3% (5.2–16.0%), respectively. Trimmed values are presented for all three analyses. Significant heterogeneity among studies was not found in all three pooled analyses. For late complications, 14, 16, and 16 cohorts had available data for GI, GU, and Skin and soft tissue, with pooled rates of 13.0% (95% CI: 8.1–20.1%), 9.1% (95% CI: 5.6–14.5%), and 16.0% (95% CI: 9.9–25.1%). Trimmed values are presented for all three analyses. Significant heterogeneity was found for pooled analyses of GI, and skin and soft tissue complications.

Four studies reported results of comparison between patients who underwent surgery and those who did not. We performed pooled analysis for those studies; the odds ratio was 6.39 (95% CI: 3.2–12.7), indicating that patients who underwent surgery had much higher risk of grade ≥3 late complications. No significant heterogeneity or publication bias was found. These pooled results are summarized in Table 5.

Since several studies included in the current meta-analysis applied hyperfractionation, we performed subgroup analyses to evaluate differences regarding toxicities. However, the analyses for late toxicity ($p = 0.776$) and acute toxicity ($p = 0.578$) did not support any differences.

Discussion

Re-irradiation after previous RT for rectal cancer is generally contraindicated because re-treatment is thought to carry a high risk for severe toxicity. Despite the lack of robust clinical information on complications after re-irradiation, it is not uncommon for radiation oncologists to consider re-irradiation for LRRC in practice. The significance of our study is that we were able to integrate the latest clinical evidence, showing encouraging results with a median OS period and 2-year LC rate exceeding 2 years and 50%. These results support clinical decisions to perform re-irradiation. Also, our study confirmed the previously known benefits and harms of surgical resection for LRRC.

For patients with LRRC, attempted salvage surgical resection is the best option for cure and long-term disease control [6,7]. In our meta-analysis, surgical resection was attempted in 11 cohorts (range, 21%–100% of cases) [23,26,28–34,37], and pooled OS rates were shown to be better in the OP group than the non-OP group across all 3 years ($P < 0.05$). However, pooled LC rates between the groups showed no significant differences, although nominal values were higher in the OP group. These results should be interpreted with caution as there was high heterogeneity due to lack of control over patients selection, particularly regarding the strict criteria for surgery in each institution [7,39]. We should also consider that mortality from distant metastasis can be a competing risk in estimating LC, hence the overestimation of LC especially for non-OP group could not be ruled out. Possible heterogeneity regarding evaluation of tumor control is another limitation, as there is no standard method for evaluation of LRRC. Heterogeneity in the pooled analyses for OS was not fully resolved after subgroup com-

Table 2
Treatment outcomes after re-irradiation.

Author	*N*	Follow-up	OP rate, %	OS				LC				Symptom palliation
		Median, m (range)		Median, m	1-y	2-y	3-y	Definition of LF or LP	1-y	2-y	3-y	
Dagoglu	18	38 (6–86)	0	40	all (non-OP): 76.8%	65.9%	59.3%	Increase in sum of the longest diameter of target lesion.	100.0%	93.7%	85.9%	Pain relief 100% (15/15)
Sukso	33	13.9	42	23	all:	47.8%		Any evidence of progression in		(LPFS 15.7%)		78% (18/23): [69% (9/13) for pain;
					OP: 85.7%	64.3%	42.9%	treated area either by radiographic,				80% (4/5) for bleeding; 100% (5/5) for
					non-OP: 51.5%	36.4%	18.2%	pathologic, or clinical assessment				bowel, urinary changes]
Jufferman	54	10 (1–36)	0	10	all (non-OP): 43%	6.0%						73% (34/53): [complete palliation 17%
												good palliation 56%;]
Cai	22	17 (2–59)	0	19	all (non-OP): 85.9%	27.2%		Any evidence of progression in treated area by radiographic assessment	(LPFS 67%)	(LPFS 10.7%)		86.4% (19/22)
Tao	102	28 (1–150)	45	30	all:	61%	39%	Any pelvic recurrence or progression		51%	40%	70% (21/30) for pain, bleeding, and
					OP: 97.0%	92%	60.8%	found by imaging or endoscopy	86.8%	69.0%	47.8%	urinary obstruction
					non-OP: 73.2%	41.1%	19.6%		62.5%	35.7%	30.4%	
Lingareddy	52	16	0	12	all (non-OP):	25.0%	14.0%					80%: [bleeding 100%; pain 65%; mass effect 24%]
Ng	56	29.5	21.4	19	all: 70%	42.3%	31.4%					88% (43/49): [Rectal bleeding/ discharge 100%;
					OP: 91.7%	91.7%	58.3%					GI 100%; Pain 91%; Urinary 100% Vaginal bleeding 67%]
					non-OP: 56.8%	20.5%	13.6					
Haddock	51	30 (8–100)	100	23	all (OP): 74.9%	48.0%	28.0%	Any pelvic recurrence proven pathologically or radiologically		61.0%	45.0%	
Kim	12	34.5 (9–53)	100	NR	all (OP):		50.9%				54.6%	
Sun	72	24 (10–57)	25	32	all: 97.5%	73.7%	45.1%					Pain relief 94% (29/31)Tenesmus relief 82%
					OP: NR							(23/28)
					non-OP: NR							
Mohiuddin (1993, palliative)	15	(12–72)	0		(all, non-OP)	28.0%						Total 87% (13/15): [pain 89% (8/9); bleeding 100% (6/6); mass effect 50% (1/2)]
Mohiuddin (1993, curative)	17		100		(all, OP)	82.0%						
Mohiuddin (1997)	39	36 (24–77)	79	45	OP: 93.8%	80%	60%		85.4%	61.6%	56%	
Valentini	59	36 (9–69)	66	42	all: 87.5%		58.9%	Absence of relapse (in resected patients) or progression (without resection or with macroscopic residuals)	76.3%		46.6%	Pain relief 20/24 (83%)
					OP: NR							
					non-OP: NR							
Milani	24		0	27	all (non-OP): 87%	60.0%	30.0%		(LPFS 61%)	(LPFS 30%)	(LPFS 15%)	Pain relief 70% (12/17)
Defoe	14	16.5 (6–69)	0		all (non-OP): 90%	78.8%		20% increase in sum of the longest diameter of target lesion	90.9%	68.2%		Pain relief 4/7 (57.1%)
Das	50	25 (0–71)	36	26	all: NR	56%	39%	any pelvic recurrence of progression		44%	33%	
					OP: 94.3%	83.2%	66%	on radiographic studies or endoscopy	77.8%	61.1%	50%	
					non-OP: 59.4%	39.3%	27%		50%	28.1%	21.9%	
Koom	22	20 (7–91)	23	21	all:	50.0%		Any recurrence or progression within the RT field, by imaging or endoscopy		(LPFS 32%)		

Abbreviations: *N*, number of patients; m, months; CTx, chemotherapy; 5-FU, fluorouracil; OP, operation; RT, radiotherapy; OS, overall survival; LC, local control; y, year; LPFS, local progression-free survival; LF, local failure; LP, local progression; NR, not reported; y, year.

Table 3
Pooled analyses of oncologic outcomes.

Groups	Cohorts, (patients)	Heterogeneity analysis		Events (95% CI)	Subgroup analysis
		p	I^2		*p*
Overall survival (OS)					
1-year OS					
All	9 (370)	<0.001	82.7%	†76.1% (61.7–86.3)	
non-OP	9 (283)	0.001	70.9%	†63.5% (51.1–74.4)	**0.002**
OP	7 (473)	0.045	53.4%	†85.9% (74.0–92.9)	
2-year OS					
All	15 (602)	<0.001	81.5%	49.1% (38.5–59.7)	
non-OP	9 (274)	<0.001	82.3%	34.2% (20.4–51.20	**<0.001**
OP	7 (189)	<0.001	76.9%	†71.8% (54.6–84.4)	
3-year OS					
All	10 (496)	<0.001	70.5%	38.3% (30.2–47.2)	
non-OP	7 (245)	0.01	64.5%	23.8% (15.4–34.8)	**0.001**
OP	7 (429)	0.021	59.7%	51.7% (39.4–63.8)	
Local control (LC)					
1-year LC					
All	3 (91)	0.144	48.4%	†76.3% (50.5–91.0)	
non-OP	4 (120)	0.015	71.3%	72.0% (48.8–87.4)	0.137
OP	3 (215)	0.667	∼0.0%	84.4% (75.5–90.4)	
2-year LC					
All	5 (235)	0.023	64.6%	†51.9% (37.9–65.7)	
non-OP	4 (120)	0.001	81.9%	54.8% (28.6–78.5)	0.267
OP	4 (252)	0.849	∼0.0%	63.8% (55.2–71.5)	
3-year LC					
All	6 (292)	0.024	61.3%	†46.4% (36.2–56.8)	
non-OP	3 (106)	<0.001	87.2%	44.6% (16.6–76.5)	0.419
OP	5 (250)	0.934	∼0.0%	†46.9% (39.6–54.4)	
Symptomatic palliation					
All	12 (413)	0.085	38.4%	†75.2% (67.3–81.8)	

Abbreviations: CI, confidence interval; OP, patients underwent operation; non-OP, patients did not undergo operation.
Bold values are p-values regarded to be statistically significant (p<0.05).
† Values are corrected using Duval and Tweedie's method due to possible publication bias (*p* value of <0.1 in Egger's test).

Table 4
Complications among included studies.

Author	*N*	OP rate	≥G3 acute toxicity, overall rate	GI	GU	SWF	≥G3 late toxicity, overall rate	GI	GU	SWF	Risk factors of ≥G3 late toxicity
Dagoglu	18	0%	NR				17%	5.6%	5.6%	0.0%	
Sukso	33	42%	6.0%	0.0%	0.0%	6.0%	21%				
Jufferman	54	0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
Cai	22	0%	23.0%	14.2%	4.5%	4.5%	23%	13.6%	9.1%	0.0%	
Tao	102	45%	NR				34% (3-y)	9.8%	12.7%	19.6%	OP vs. non-OP = 54% vs. 16% (*P* = 0.001); RT interval ≤ 2-y vs. RT interval 2-y = 43% vs. 16% (*P* = 0.058)
Lingareddy	52	0%	31.0%	23.0%	0.0%	8.0%	33%	17.0%	6.0%	10.0%	hyperfractionated vs. conventional scheme = 18% vs. 47%, (*P* < 0.05)
Ng	56	21.4%	12.0%	11.0%	0.0%	5.0%	17.9%	1.8%	3.5%	12.5%	
Haddock	51	100%					48.0%	16.0%	10.0%	36.0%	IOERT doses > 20 Gy
Kim	12	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
Sun	72	25%		9.7%	0.0%	0.0%	1.4%	1.4%	0.0%	0.0%	
Mohiuddin (1993, palliative)	15	0%		13.0%	0.0%	19.0%					
Mohiuddin (1993, curative)	17	100%						6.0%	0.0%	32.0%	
Mohiuddin (1997)	39	79%		18.0%	0.0%	16.0%		23.0%	0.0%	12.8%	
Valentini	59	66%	5.0%	5.0%	0.0%	0.0%	5.0%	5.0%	0.0%	0.0%	OP vs. non-OP = 15.4% vs 5%
Milani	24	0%	12.5%	12.5%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
Defoe	14	0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	
Das	50	36%	4.0%	4.0%	0.0%	0.0%	26% (35% [3-y])	8.0%	6.0%	14.0%	OP vs. non-OP = 53% vs. 15% (*P* = 0.052); prior RT ≥ 54 Gy vs. prior RT < 54 Gy = 54% vs. 18% (*P* = 0.033)
Koom	22	23%	9.0%	9.0%	0.0%	0.0%	36.0%	18.0%	27.0%	4.5%	anterior or axial vs. post or lateral location = 64% vs. 9% (*P* = 0.024); OP vs. no OP = 80% vs. 24% (*P* = 0.039)

Abbreviations: *N*, number of patients; OP, operation; G, grade; GI, gastrointestinal; GU, genitourinary; SWF, skin, wound, and fistula; NR, not reported; y, year; Gy, gray; RT, radiotherapy; IOERT, intraoperative electron beam radiotherapy.

parisons, meaning that OS might be affected by clinical factors other than surgery. Regarding pooled analyses of LC, heterogeneity among studies for the OP group was significantly reduced but not for the non-OP group. This suggests that accompanying surgery might be a significant factor affecting LC, although LC was also affected by other factors after re-RT for LRRC. These considerations support the need for further investigation to quantify the survival benefit related to salvage surgery. Accompanying chronic toxicities

Table 5
Acute and late complications of grade 3 or higher.

Groups	Cohorts (n)	Patients (n)	*P*, He	I^2	Egger's test, *P*	Events (95% CI)
Acute complications						
Overall	11	398	0.002	64.8%	0.002	†11.7% (6.7%–19.5%)
GI	14	541	0.081	36.9%	0.001	†12.7% (8.6%–18.4%)
GU	14	541	0.998	~0.0%	0.024	†1.7% (0.9%–3.4%)
Skin and soft tissue	14	541	0.046	42.6%	<0.001	†9.3% (5.2%–16.0%)
Late complications						
Overall	15	641	<0.001	75.1%	<0.001	†25.2% (16.7%–40.0%)
GI	14	601	0.017	50.1%	0.002	†13.0% (8.1%–20.1%)
GU	16	664	0.03	44.1%	<0.001	†9.1% (5.6%–14.5%)
Skin and soft tissue	16	664	<0.001	67.2%	<0.001	†16.0% (9.9%–25.1%)
Overall late complications OP vs. non-OP						
OP vs. non-OP	4	108 (OP) 125 (non-OP)	0.806	~0.0%	0.734	OR 6.39 (3.2–12.7) OP vs. non-OP = 40.7% vs. 12.8%, $P < 0.001$

Abbreviations: GI, gastrointestinal; GU, genitourinary; OP, patients underwent operation; non-OP, patients did not underwent operation; CI, confidence interval; OR, odds ratio.
† Values are corrected using Duval and Tweedie's method due to possible publication bias (*p* value of <0.1 in Egger's test).

are a major concern when implementing re-irradiation for LRRC. Our meta-analysis showed rates of 11.7% (95% CI: 6.7–19.5%) and 25.5% (95% CI: 16.7–40.0%) for overall grade ≥ 3 acute and chronic complications, which were not negligible. Furthermore, the patients who underwent surgery had a significantly higher rate of grade ≥ 3 late toxicities, with an odds ratio of 6.39 (95% CI: 3.2–12.7). Late toxicities, such as perforation, obstruction, bleeding, and fistula might develop with time as the result of pathologic alterations after re-irradiation, such as obliterating endarteritis, abnormal vessel formation, submucosal fibrosis, and ischemic change [40–42]. Previous surgical series revealed that R0 resection was related with better survival outcomes [9,43], and our study also showed that accompanied surgery could yield better OS. However, this is a double-edged sword because although surgery could yield better OS, it may also cause significant increases in late complications.

We revealed GI, GU, and skin and soft tissue complication rates of 13%, 2%, and 9% in acute toxicity and 13%, 9%, and 16% in late toxicity, respectively. These findings might originate from the fact that the bladder can develop injuries over time as late-responding tissue whereas the bowel mucosa does not exhibit long-term recovery from acute injury [15,44]. Increased bladder and skin and soft tissue toxicity as a late complication might help us understand the radiobiological mechanisms of each organ, which is not yet clear. This information might be helpful to identify clinical candidates to undergo re-irradiation with or without accompanied surgery, as there are very few large-cohort studies regarding the type of toxicity in LRRC patients.

The limitations of the present meta-analysis should be considered. First, most of the studies included in this meta-analysis are retrospective chart-review studies (14 of 17, 82.3%) without prospectively designed follow-up protocols. Furthermore, it is practically difficult to evaluate complications (especially late complications) among patients that underwent re-irradiation for LRRC, as they commonly have short life expectancy and poor compliance. Nonetheless, most of the included studies have independently described late complications, meeting our criteria (complications occurring 3 months after re-irradiation, or those described as late complication). This implies that most radiation oncologists are aware of the clinical significance of late complications, after re-irradiation for LRRC. Future research, including prospective studies, is needed to better understand the characteristics of complications after re-irradiation of LRRC.

Some studies have indicated that advanced RT, such as IMRT and SBRT, are associated with less chronic GI toxicity than conventional RT [13,45], as IMRT involves highly conformal nonconvex dose distributions along with target boundaries [28,38,46], and SBRT enables accurate delivery with steep dose fall-off near the target [14,36]. In a few studies in our meta-analysis, SBRT was utilized for re-irradiation and some studies showed favorable LC rates [22,36]. Only one study utilized IMRT for all patients [25], but the oncologic results were not distinguishable from those of other studies. Susko et al. [23], analyzed differences of toxicity and tumor control among RT modalities, including IMRT and 2D/3D, but no significant difference was found. Dose escalation with use of IMRT for neoadjuvant re-irradiation cases [28], and selective application with smaller margins for patients with localized recurrence or who are vulnerable for toxicities (e.g. short treatment interval, re-irradiation of >2 times) can be future subjects to be studied. Haddock et al. performed intraoperative electron beam RT (IOERT) accompanied by preoperative or postoperative external beam RT, with an attempt to increase the re-irradiation dose, achieving a favorable LC rate of 61% at 2 years [29]. Multimodality approaches including IOERT have been attempted to maximize oncologic outcome; for unresectable T4 cases, 73% of R0 resection rate was reported from a large series including 417 patients [47]. For LRRC, Holman et al. reported 44% of R0 resection rate among 565 patients, and a 3-year OS rate of 52% which was comparable to that of the present meta-analysis [48]. In summary, because the number of studies using advanced techniques is still small and the clinical variation of LRRC is great, with cases that may not benefit from such precise techniques, the benefit of advanced RT techniques is yet to be determined. Future research involving LRRC patients who can benefit from advanced RT techniques is warranted to obtain better results than previous studies.

A previous systematic review by Guren et al. [12] provided valuable information for clinical decision making in the treatment of LRRC. In that study, the authors reported good palliative effects of reirradiation, supported the application of radical resection if possible, and hyperfractionation to reduce late toxicities. Our study quantitatively confirmed the efficacy of palliation, and higher survival with concomitant surgery, which can serve as a convenient reference for a multidisciplinary approach. However, we also found a higher risk of late toxicity with surgical treatment (odd ratio: 6.39). Thus, we suggest radical surgery if possible, but careful patient selection is necessary. The different incidence of toxicity according to type of complication may also serve as a useful tool for patient selection. Hyperfractionation can reduce the late effects of radiation based on the radiobiological differences between tumor and normal tissues [49]. Although significant differences regarding toxicities were not shown in the subgroup analyses, there are some limitations to our results including confounding

variables, such as use of surgery or chemotherapy, and clinical diversity among patients. Thus, the utility of hyperfractionation should not be discounted and controlled trials to evaluate toxicity difference in patients undergoing re-irradiation with hyperfractionation are warranted. Additionally, further studies to identify patients who can benefit from aggressive treatment including surgery should be performed.

Meta-analysis of observational studies is controversial, as heterogeneity among study designs and populations might affect pooled results [50]. However, in the field of oncology, robust evidence, supported by randomized controlled studies, is not always possible and clinical decisions are made by relying on multiple small studies or even clinical experiences [51]. Treating recurrent cancer is one of the most uncharted topics in oncology. Patients await new treatment schemes while doctors carefully navigate the narrow gap between side effects and treatment efficacy. A small number of studies and patients might be a limitation of this study; however, considering the scarce literature regarding re-RT for recurrent rectal cancer and the difficulty in conducting a well-designed, controlled study on this topic, our meta-analysis might offer one of the best means of evaluating the practical effectiveness of treatment.

In summary, our study showed a median survival of more than 2 years among patients with LRRC, including several long-term survivors, with application of local treatment, including re-RT. LC and symptomatic palliation can be achieved with re-irradiation, and longer OS can be expected in conjunction with surgery. Late toxicities were the most significant obstacles to local treatment, including re-RT for LRRC. We recommend future studies to identify patients who can benefit most from aggressive local treatment, including surgery, with possible use of systematic methods, such as recursive partitioning analysis or scoring models.

Acknowledgements

This work was supported by the National Research Fund of Korea [grant number NRF-2019M2D2A1A01031560].

Conflict of interest statement

The authors have declared no conflicts of interest.

References

[1] Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638–46.
[2] Camma C, Giunta M, Fiorica F, Pagliaro L, Craxi A, Cottone M. Preoperative radiotherapy for resectable rectal cancer: A meta-analysis. JAMA 2000;284:1008–15.
[3] Colorectal Cancer Collaborate Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. Lancet 2001;358:1291–304.
[4] van den Brink M, Stiggelbout AM, van den Hout WB, Kievit J, Klein Kranenbarg E, Marijnen CA, et al. Clinical nature and prognosis of locally recurrent rectal cancer after total mesorectal excision with or without preoperative radiotherapy. J Clin Oncol 2004;22:3958–64.
[5] Rasanen M, Carpelan-Holmstrom M, Mustonen H, Renkonen-Sinisalo L, Lepisto A. Pattern of rectal cancer recurrence after curative surgery. Int J Colorectal Dis 2015;30:775–85.
[6] Caricato M, Borzomati D, Ausania F, Valeri S, Rosignoli A, Coppola R. Prognostic factors after surgery for locally recurrent rectal cancer: an overview. Eur J Surg Oncol 2006;32:126–32.
[7] Saito N, Koda K, Takiguchi N, Oda K, Ono M, Sugito M, et al. Curative surgery for local pelvic recurrence of rectal cancer. Dig Surg 2003;20:192–9. discussion 200.
[8] Pacelli F, Tortorelli AP, Rosa F, Bossola M, Sanchez AM, Papa V, et al. Locally recurrent rectal cancer: prognostic factors and long-term outcomes of multimodal therapy. Ann Surg Oncol 2010;17:152–62.
[9] Rahbari NN, Ulrich AB, Bruckner T, Munter M, Nickles A, Contin P, et al. Surgery for locally recurrent rectal cancer in the era of total mesorectal excision is there still a chance for cure? Ann Surg 2011;253:522–33.
[10] Bouchard P, Efron J. Management of recurrent rectal cancer. Ann Surg Oncol 2010;17:1343–56.
[11] Westberg K, Palmer G, Hjern F, Holm T, Martling A. Population-based study of surgical treatment with and without tumour resection in patients with locally recurrent rectal cancer. Br J Surg 2019;106:790–8.
[12] Guren MG, Undseth C, Rekstad BL, Braendengen M, Dueland S, Spindler KL, et al. Reirradiation of locally recurrent rectal cancer: a systematic review. Radiother Oncol 2014;113:151–7.
[13] Gourd E. Pelvic IMRT reduces toxicity vs standard radiotherapy. Lancet 2018;19:e393.
[14] Murray LJ, Lilley J, Hawkins MA, Henry AM, Dickinson P, Sebag-Montefiore D. Pelvic re-irradiation using stereotactic ablative radiotherapy (SABR): A systematic review. Radiother Oncol 2017;125:213–22.
[15] Nieder C, Milas L, Ang KK. Tissue tolerance to reirradiation. Semin Radiat Oncol 2000;10:200–9.
[16] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336–41.
[17] Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; 2011.
[18] DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: An update. Contemp Clin Trials 2007;28:105–14.
[19] Cochran WG. The combination of estimates from different experiments. Biometrics 1954;10(1):101–29.
[20] Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Brit Med J 1997;315:629–34.
[21] Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.
[22] Dagoglu N, Mahadevan A, Nedea E, Poylin V, Nagle D. Stereotactic body radiotherapy (SBRT) reirradiation for pelvic recurrence from colorectal cancer. J Surg Oncol 2015;111:478–82.
[23] Susko M, Lee J, Salama J, Thomas S, Uronis H, Hsu D, et al. The use of re-irradiation in locally recurrent, non-metastatic rectal cancer. Ann Surg Oncol 2016;23:3609–15.
[24] Juffermans JH, Hanssens PE, van Putten WL, van Rhoon GC, van Der Zee J. Reirradiation and hyperthermia in rectal carcinoma: a retrospective study on palliative effect. Cancer 2003;98:1759–66.
[25] Cai G, Zhu J, Hu W, Zhang Z. Accelerated hyperfractionated intensity-modulated radiotherapy for recurrent/unresectable rectal cancer in patients with previous pelvic irradiation: results of a phase II study. Radiat Oncol 2014;9:278.
[26] Tao R, Tsai CJ, Jensen G, Eng C, Kopetz S, Overman MJ, et al. Hyperfractionated accelerated reirradiation for rectal cancer: an analysis of outcomes and toxicity. Radiother Oncol 2017;122:146–51.
[27] Lingareddy V, Ahmad NR, Mohiuddin M. Palliative reirradiation for recurrent rectal cancer. Int J Radiat Oncol Biol Phys 1997;38:785–90.
[28] Ng MK, Leong T, Heriot AG, Ngan SY. Once-daily reirradiation for rectal cancer in patients who have received previous pelvic radiotherapy. J Med Imaging Radiat Oncol 2013;57:512–8.
[29] Haddock MG, Gunderson LL, Nelson H, Cha SS, Devine RM, Dozois RR, et al. Intraoperative irradiation for locally recurrent colorectal cancer in previously irradiated patients. Int J Radiat Oncol Biol Phys 2001;49:1267–74.
[30] Kim TH, Kim DY, Jung KH, Hong YS, Kim SY, Park JW, et al. The role of omental flap transposition in patients with locoregional recurrent rectal cancer treated with reirradiation. J Surg Oncol 2010;102:789–95.
[31] Sun DS, Zhang JD, Li L, Dai Y, Yu JM, Shao ZY. Accelerated hyperfractionation field-involved re-irradiation combined with concurrent capecitabine chemotherapy for locally recurrent and irresectable rectal cancer. Br J Radiol 2012;85:259–64.
[32] Mohiuddin M, Lingareddy V, Rakinic J, Marks G. Reirradiation for rectal cancer and surgical resection after ultra high doses. Int J Radiat Oncol Biol Phys 1993;27:1159–63.
[33] Mohiuddin M, Marks GM, Lingareddy V, Marks J. Curative surgical resection following reirradiation for recurrent rectal cancer. Int J Radiat Oncol Biol Phys 1997;39:643–9.
[34] Valentini V, Morganti AG, Gambacorta MA, Mohiuddin M, Doglietto GB, Coco C, et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: A multicentric phase II study. Int J Radiat Oncol Biol Phys 2006;64:1129–39.
[35] Milani V, Pazos M, Issels RD, Buecklein V, Rahman S, Tschoep K, et al. Radiochemotherapy in combination with regional hyperthermia in preirradiated patients with recurrent rectal cancer. Strahlenther Onkol 2008;184:163–8.
[36] Defoe SG, Bernard ME, Rwigema JC, Heron DE, Ozhasoglu C, Burton S. Stereotactic body radiotherapy for the treatment of presacral recurrences from rectal cancers. J Cancer Res Ther 2011;7:408–11.
[37] Das P, Delclos ME, Skibber JM, Rodriguez-Bigas MA, Feig BW, Chang GJ, et al. Hyperfractionated accelerated radiotherapy for rectal cancer in patients with prior pelvic irradiation. Int J Radiat Oncol Biol Phys 2010;77:60–5.
[38] Koom WS, Choi Y, Shim SJ, Cha J, Seong J, Kim NK, et al. Reirradiation to the pelvis for recurrent rectal cancer. J Surg Oncol 2012;105:637–42.
[39] Moore HG, Shoup M, Riedel E, Minsky BD, Alektiar KM, Ercolani M, et al. Colorectal cancer pelvic recurrences: determinants of resectability. Dis Colon Rectum 2004;47:1599–606.

[40] Abusaris H, Storchi PR, Brandwijk RP, Nuyttens JJ. Second re-irradiation: efficacy, dose and toxicity in patients who received three courses of radiotherapy with overlapping fields. Radiother Oncol 2011;99:235–9.
[41] Moussa L, Usunier B, Demarquay C, Benderitter M, Tamarat R, Semont A, et al. Bowel radiation injury: complexity of the pathophysiology and promises of cell and tissue engineering. Cell Transplant 2016;25:1723–46.
[42] Sung Uk L, Young Ae K, Young-Ho Y, Yeon-Joo K, Myong Cheol L, Sang-Yoon P, et al. General health status of long-term cervical cancer survivors after radiotherapy. Strahlenther Onkol 2017;193:543–51.
[43] Yang HY, Park SC, Hyun JH, Seo HK, Oh JH. Outcomes of pelvic exenteration for recurrent or primary locally advanced colorectal cancer. Ann Surg Treat Res 2015;89:131–7.
[44] Leiper K, Morris AI. Treatment of radiation proctitis. Clin Oncol 2007;19:724–9.
[45] Vargo JA, Ward MC, Caudell JJ, Riaz N, Dunlap NE, Isrow D, et al. A multi-institutional comparison of SBRT and IMRT for definitive reirradiation of recurrent or second primary head and neck cancer. Int J Radiat Oncol Biol Phys 2018;100:595–605.
[46] Ezzell GA, Galvin JM, Low D, Palta JR, Rosen I, Sharpe MB, et al. Guidance document on delivery, treatment planning, and clinical implementation of IMRT: report of the IMRT Subcommittee of the AAPM Radiation Therapy Committee. Med Phys 2003;30:2089–115.
[47] Holman FA, Haddock MG, Gunderson LL, Kusters M, Nieuwenhuijzen GA, van den Berg HA, et al. Results of intraoperative electron beam radiotherapy containing multimodality treatment for locally unresectable T4 rectal cancer: a pooled analysis of the Mayo Clinic Rochester and Catharina Hospital Eindhoven. J Gastrointest Oncol 2016;7:903–16.
[48] Holman FA, Bosman SJ, Haddock MG, Gunderson LL, Kusters M, Nieuwenhuijzen GA, et al. Results of a pooled analysis of IOERT containing multimodality treatment for locally recurrent rectal cancer: Results of 565 patients of two major treatment centres. Radiother Oncol 2017;43:107–17.
[49] Thames Jr HD, Withers HR, Peters LJ, Fletcher GH. Changes in early and late radiation responses with altered dose fractionation: implications for dose-survival relationships. Int J Radiat Oncol Biol Phys 1982;8:219–26.
[50] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
[51] Poonacha TK, Go RS. Level of scientific evidence underlying recommendations arising from the National Comprehensive Cancer Network clinical practice guidelines. J Clin Oncol 2011;29:186–91.