Curr Colorectal Cancer Rep (2017) 13:175–182
DOI 10.1007/s11888-017-0360-y

RADIATION THERAPY AND RADIATION THERAPY INNOVATIONS IN COLORECTAL CANCER (JY WO, SECTION EDITOR)

Pelvic Reirradiation for the Treatment of Locally Recurrent Rectal Cancer

Randa Tao[1] · **Shane Lloyd**[1] · **Lindsay Burt**[1] · **Jonathan Whisenant**[2] · **Ignacio Garrido-Laguna**[2] · **Prajnan Das**[3]

Published online: 7 March 2017

Abstract
Purpose of review This study aims to summarize the literature on pelvic reirradiation for the treatment of locally recurrent rectal cancer. Symptom palliation, rates of local progression after reirradiation with or without surgery, overall survival, and toxicity outcomes are discussed.
Recent findings The majority of patients received total doses of 30–40 Gy given in 1.2 or 1.5 Gy twice-daily fractions. Treatment evolved over time to include more conformal fields. The overall rates of local control generally range from 25 to 70% and surgical salvage after reirradiation was performed in 20–79% of patients. Some studies suggest that patients treated with reirradiation may have a higher rate of a complete R0 resection, which is an important predictor of overall survival. Survival outcomes have improved over time along with increased use of reirradiation.
Summary Pelvic reirradiation can offer effective symptom palliation and be part of a curative salvage treatment strategy for locally recurrent rectal cancer.

This article is part of the Topical Collection on *Radiation Therapy and Radiation Therapy Innovations in Colorectal Cancer*

✉ Randa Tao
randa.tao@hci.utah.edu

[1] Department of Radiation Oncology, Huntsman Cancer Institute, University of Utah, 1950 Circle of Hope, Room 1570, Salt Lake City, UT 84112, USA

[2] Deparment Medical Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

[3] Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Keywords Rectal cancer · Reirradiation · Local recurrence · Hyperfractionation

Introduction

Over the past few decades, improvements in the treatment of rectal cancer have led to better survival outcomes [1]. Advances in surgery with the adoption of total mesorectal excision along with multimodality treatments with chemotherapy and radiotherapy (RT) have also led to a decreased risk of local recurrence [2–7]. However, if patients do experience local disease recurrence, it can be associated with significant symptoms and is a challenging condition for clinicians to manage. Patients often have had complex surgery and with the adoption of preoperative chemoradiation therapy and short-course RT, more and more patients have had a history of prior pelvic RT [8–10].

Radiation oncologists have often been hesitant about offering a course of reirradiation to the same pelvic site in order to treat recurrent disease because of the potential higher risk of causing toxicity. There is particular concern that the cumulative dose from reirradiation exceeds the tolerance dose of the small bowel and bladder. However, the risks of reirradiation need to be weighed with the potential benefits of symptom palliation or its role in definitive salvage therapy, which offers the only possibility of long-term survival and preservation of quality of life [11, 12]. Here we summarize the literature describing the potential risks and benefits of reirradiation for the treatment of rectal cancer with the purpose of guiding clinicians on managing this challenging condition. We describe the rationale of using hyperfractionation for retreatment and summarize the available data on symptom relief, pelvic control, survival, and toxicity outcomes.

Hyperfractionation

One strategy thought to decrease the risk of late toxicity is the use of a hyperfractionated accelerated treatment schedule for pelvic reirradiation. Delivering a total dose of RT in more fractions can potentially take advantage of the radiobiologic differences between tumor cells, which are rapidly proliferating, and the normal tissues, which have slow or absent proliferation [13]. It is thought that the alpha/beta ratio for late bowel toxicity is around 3–5 Gy [14, 15], which suggests that late bowel toxicity is sensitive to the effects of fractionation and could be spared with smaller doses per fraction. Meanwhile, accelerating the overall treatment time with twice-daily fractions can prevent tumor repopulation and deliver a meaningful total dose to the tumor while allowing normal tissue repair with a minimum 6 h inter-fraction interval [16]. Accelerated hyperfractionated treatment schedules have thus been commonly used in pelvic reirradiation for rectal cancer.

Initial Prospective Studies

The University of Kentucky reported the earliest experience on reirradiation for rectal cancer in 1993 with a phase I/II study of 32 patients [17]. They were treated to a median dose of 34.2 Gy (range, 19.8–47.66 Gy) with patients treated with curative intent receiving 1.2 Gy twice-daily treatments and palliative-intent patients receiving 1.8 Gy daily treatments. No late toxicity from RT was observed. The authors concluded that reirradiation could be performed safely without a high risk of late complications.

Valentini and colleagues in Italy then performed studies on reirradiation for rectal cancer reported in 1999 and 2006. Their initial study included a subgroup of 13 patients who were treated with reirradiation to 23.4 Gy with 1.8 Gy daily fractions [18]. They demonstrated this treatment was well-tolerated and went on to perform the only phase II multicenter prospective study of reirradiation in 59 patients with recurrent rectal cancer and disease limited to the pelvis [19]. The patients were treated to a dose of 40.8 Gy in 1.2 Gy twice-daily fractions with concurrent continuous infusion 5-FU. The authors found low rates of acute toxicity with only 5% grade 3 acute toxicity and only 12% of patients experiencing any late toxicity.

These initial prospective studies therefore established that reirradiation was feasible and well-tolerated. The majority of subsequent studies consist of retrospective reviews [20–28, 29••, 30–32] and there are no randomized controlled trials evaluating reirradiation vs. no reirradiation for recurrent rectal cancer.

Reirradiation Doses and Techniques

The majority of patients treated in reirradiation series received total doses of 30–40 Gy given in 1.2 or 1.5 Gy twice-daily fractions [17, 20–25, 32, 33]. These doses correspond to biologically equivalent doses (BEDs) of 34–47 Gy using an alpha/beta ratio of 10 for tumor effect. The dose, fractionation, target volume, and techniques used in representative studies are summarized in Table 1. In most of the studies, local fields were used to treat only the gross tumor volume (GTV) with a 2–4-cm margin. Some studies included the presacral region or

Table 1 Reirradiation dose, target, and techniques used in select studies

Authors and year	*N*	Study design	Reirradiation dose/Fx size	Target volume	Technique	Concurrent chemotherapy
Mohiuddin et al. 1993 [17]	32	Phase I/II	Median 34.2 Gy/1.8 Gy daily or 1.2 Gy twice-daily	Posterior pelvis with boost to GTV+ 2 cm	Opposed laterals	5-FU
Valentini et al. 1999 [18]	13[a]	Prospective	23.4 Gy/1.8 Gy daily	GTV + 1.5 cm + posterior pelvis	3-field or 4-field	5-FU/MMC
Mohiuddin et al. 2002 [20]	103	Retrospective	Median 34.8 Gy/1.8 Gy daily or 1.2 Gy twice-daily	GTV + 2–4 cm + presacral	Opposed laterals or 3-field	5-FU
Valentini et al. 2006 [19]	59	Prospective	40.8 Gy/1.2 Gy twice-daily (30 Gy to PTV2 + 10.8 Gy boost to PTV1)	GTV + 2 cm = PTV1 GTV + 4 cm = PTV2	3D conformal	5-FU
Haddock et al. 2011 [23]	248[b]	Retrospective	Median 27.5 Gy/NR	NR	NR	5-FU or capecitabine
Sun et al. 2012 [33]	72	Prospective	30–36 Gy/1.2 Gy twice-daily for resected pts with boost to 51.6–56.4 Gy/1.8–3 Gy daily for unresectable pts	GTV + 2 cm	3D conformal with 5–8 fields	Capecitabine
Ng et al. 2013 [26]	56	Retrospective	Median 39.6 Gy/1.8 Gy daily	GTV + 2 cm	3D conformal with 2–4 fields or IMRT	5-FU
Bosman et al. 2014 [27]	135	Retrospective	30–30.6 Gy/1.8–2 Gy daily	GTV + 2 cm	3D conformal	Capecitabine
Tao et al. 2017 [32]	102	Retrospective	30–45 Gy (median 39 Gy)/1.5 Gy twice-daily	GTV + 2–3 cm	3D conformal with 2–4 fields or IMRT	Capecitabine

N number, *Fx* fraction, *GTV* gross tumor volume, *NR* not reported, *IMRT* intensity modulated radiation therapy

[a] Forty-seven total patients with recurrent rectal cancer including 13 treated with reirradiation

[b] Six hundred seven total patients with recurrent colorectal cancer including 248 treated with reirradiation

posterior pelvis in the reirradiated volume. The majority of techniques used included 3D conformal treatment with two to four fields. Generally, no specific dose constraints were used or reported for normal tissues. Treatment evolved over time to include more conformal fields and the use of intensity modulated radiation therapy (IMRT) in select patients after 2012. All studies included concurrent 5-FU-based chemotherapy with reirradiation for the majority of patients.

Symptom Control

Studies that report outcomes related to symptom palliation show that a good portion of patients experience relief of symptoms from reirradiation [19, 20, 22, 26, 33]. The University of Kentucky also published their experience with treating patients specifically with palliative intent [22]. They included 52 patients treated with reirradiation to a median dose of 30.6 Gy with either 1.2 Gy twice-daily fractionation (22 patients) or 1.8–2 Gy daily fractions (30 patients). They found that bleeding was palliated in 100% of patients for a median duration of 10 months and 80% of patients had resolution of bleeding until death. Complete pain relief was reported in 65% of patients with 33% of patients palliated until death. Twenty-four percent of the patients had complete relief of mass effect and 64% had partial relief. Interestingly, the authors found that the patients treated with hyperfractionation experienced a significantly lower rate of late toxicity compared to those treated with daily fractions of 1.8–2 Gy (18 vs. 47%, $P < .05$).

In a recently published series on patients treated with reirradiation at MD Anderson Cancer Center, the rate of pain relief for patients treated with palliative intent was 79% for a median duration of 9 months [32]. Some patients (63%) also experienced relief of urinary obstruction after reirradiation. The proportion of patients who experience pain relief ranges from 65 to 94% in the reported literature. Bleeding has the highest rate of control when different symptom control rates are discussed with 100% control reported [20, 22, 26, 32].

Local Pelvic Control

There is a large range of reported local control rates in the literature given the heterogeneity of the patients, length of follow-up, treatment intent, and treatment modalities used. Additionally, different rates are often reported, such as actuarial vs. crude rates, and some series do not report the rate of local pelvic control separately from disease-free survival. With these factors in mind, the overall rates of local control after treatment of recurrent rectal cancer generally range from 25 to 70% [19, 30–32, 34].

In series that include patients who undergo surgical salvage after reirradiation, resection is performed in 20–79% of all patients. The rate of a complete R0 resection is in the range of 39–89%. The rates of surgical salvage and R0 resection in select studies are summarized in Table 2. Factors that help determine the resectability of recurrent tumors include the site of recurrence and the extent of tumor fixation [31, 35, 36]. A multicenter pooled analysis from the Netherlands showed that the location of the local recurrence significantly impacted the salvage rate with presacral recurrences having the worst rate of a complete R0 resection at 28% [31]. This was followed by posterolateral, perineal, anterolateral, and anterior recurrences with R0 resection rates of 45, 50, 56, and 64%, respectively. Recurrences at the surgical anastomosis had the best complete

Table 2 Proportion of patients undergoing salvage surgery after reirradiation, overall survival, and late toxicity

Authors and year	Proportion of pts undergoing surgery and R0 resection	All	Survival[a]		Late toxicity
			Resected	Unresected	
Mohiuddin et al. 1993 [17]	Surgery: 17/32 (53%); R0 NR	NR	2-year OS: 66%	14	0
Valentini et al. 1999 [18]	Surgery: 4/13 (31%); R0 NR	5-year OS: 22%[c]	NR	17	15%[c]
Mohiuddin et al. 2002 [20]	Surgery: 41/103 (40%); R0 NR	26	44	14	21%
Valentini et al. 2006 [19]	Surgery: 30/59 (51%); R0 in 70%	42	5-year OS: 65%; 67% in R0 pts	5-year OS: 22%	12%
Haddock et al. 2011 [23]	Surgery: 607/607[b] (100%); R0 in 37%	36[c]	5-year OS: 26%	N/A	37%[c]
Sun et al. 2012 [33]	Surgery: 18/72 (25%); R0 in 89%	32	NR	NR	13%
Ng et al. 2013 [26]	Surgery: 12/56 (21%); R0 in 67%	19	39	15	18%
Bosman et al. 2014 [27]	Surgery: 135/135 (100%); R0 in 56%	3-year OS: 51%	NR	NR	39%
Tao et al. 2017 [32]	Surgery: 46/102 (45%); R0 in 67%	30	47	17	27%

N number, *Fx* fraction, *Pts* patients, *OS* overall survival, *NR* not reported, *N/A* not applicable

[a] Median overall survival in months unless otherwise noted

[b] Six hundred seven total patients with recurrent colorectal cancer including 248 treated with reirradiation

[c] Survival and toxicity reported for all patients (these results were not reported separately for the reirradiation patients)

resection rate at 77% and were also associated with lower rates of local progression. The 5-year rate of local progression for presacral recurrences was 57% compared to 28% for anastomotic recurrences. Of note, 42% of the patients in this series were treated with reirradiation to 30.6 Gy and the remaining patients either received no preoperative therapy or were radiation naïve and received a full course of standard fractionation to 50.4 Gy. The authors did not report whether treatment with or without reirradiation impacted local control. They did report on the rates of R0 resection between patients treated with reirradiation or no radiation therapy and found that patients treated with reirradiation had a higher rate of R0 resection (56 vs. 36% although not statistically significant [$P = .12$]).

A separate multicenter study from the Netherlands did show that patients treated with reirradiation had a significantly higher rate of an R0 resection [30]. This study included 147 patients treated with curative-intent surgery and 39% of patients received reirradiation. The rate of an R0 resection in reirradiated patients was 65 vs. 35% in patients not treated with reirradiation ($P = .009$). This also translated into a significantly higher rate of local control observed for the patients treated with reirradiation with a 3-year rate of 49% compared to 38%.

The patients who are able to undergo surgical resection, especially those with an R0 resection, expectedly have a significantly higher rate of local control. For example, in the multicenter phase II Italian study, the 2-year local control rate was 69% for patients who underwent a complete R0 resection compared to 47% for patients who did not undergo surgery [19]. The other factor significantly associated with improved local control in this study included a longer interval of more than 2 years from surgery to initial local recurrence. Investigators from MD Anderson Cancer Center reported a 3-year local control rate of 49% for patients who underwent resection after reirradiation compared to 30% after reirradiation alone [32]. The median time to local progression for patients treated with reirradiation alone was 16 months. What is interesting from these series is that some patients can experience freedom from local progression after reirradiation alone.

In the limited reports that do include pathologic findings at the time of surgery, a small proportion of patients may achieve a pathologic complete response. The Italian study reported a pathologic complete response in 13% of their surgery patients treated to 40.8 Gy with concurrent 5-FU [19] and the MD Anderson study reported a similar 14% pathologic complete response rate after a median dose of 39 Gy with concurrent capecitabine [32]. Interestingly, this is within the range of the pathologic complete response rates reported after preoperative chemoradiation therapy for newly diagnosed rectal cancer [4, 7, 37, 38].

It is thought that reirradiation can also potentially increase the rate of surgical resection for patients initially considered to have unresectable disease. A study by investigators in China included 72 patients with unresectable locally recurrent rectal cancer [33]. These patients were treated with reirradiation to 30–36 Gy in 1.2 Gy twice-daily fractions with concurrent capecitabine and then reevaluated to determine if they could undergo surgery. A total of 18 patients (25%) underwent resection including 16 with an R0 resection. The remaining patients were treated to a higher total dose of 51.6–56.4 Gy. The authors reported a 3-year progression-free survival rate of 31% and OS rate of 45%. Local control was not reported and the authors did not separately report the outcomes for patients who underwent surgery. Nonetheless, the important finding is that reirradiation can increase resectability and most of the patients had a complete R0 resection.

Overall Survival

As expected, the overall survival rate for patients who can undergo surgical salvage is higher than patients who do not undergo surgery. The median survival for patients treated with surgery is in the range of 22–60 months, and for patients treated with reirradiation alone, it is in the range of 12–17 months. The reported median survival for patients in the select reirradiation studies is also summarized in Table 2. The 3-year overall survival rate for all patients ranges from 29 to 62% with 5-year survival generally ranging from 11 to 51%. Across different studies, an R0 resection has been associated with improved overall survival and some have found it to be the single most important predictor of long-term survival [19, 29••, 30, 34, 39].

Another study from MD Anderson Cancer Center included the subset of patients all treated with salvage surgery with curative intent and the authors found that overall survival improved significantly over the 24-year study period [29••]. In the most recent time period that included 2005–2012, the 5-year overall survival for patients treated with curative intent was 50% compared to 32% in the earlier era (1988–1996). The rate of an R0 resection also increased over time from 77 to 84% along with decreased rates of local progression. Interestingly, the authors found that the improvement in overall survival was associated with a significantly increased use of preoperative pelvic radiation in the radiation naïve and reirradiation setting. Increased use of chemotherapy after salvage surgery was also associated with improved survival over time. This improved survival in more recent studies was also found to be significant in a review paper on patients treated with curative intent that included a 20-year period from 1990 to 2010 [34].

The introduction of newer, more active chemotherapy agents may also contribute to improvements in outcomes for locally recurrent rectal cancer. Since 1996, additional systemic antineoplastic agents have been approved by the FDA in the

USA for the treatment of colorectal cancer (e.g., irinotecan, oxaliplatin, capecitabine, cetuximab, bevacizumab, panitumumab, regorafenib, aflibercept, ramucirumab, and trifluridine/tipriacil). During this time period, the median survival of patients with metastatic colon cancer has improved from approximately 12 to 30 months [40, 41], likely related to availability of these chemotherapy agents as well as more aggressive local and regional therapeutic approaches in patients with oligometastatic disease. These new systemic agents are now routinely utilized as primary therapy in patients with metastatic disease or unresectable pelvic recurrence and are contributing to survival improvements in this setting.

Toxicity

Similar to the trend of improved survival over time, the acute toxicity associated with treatment may also be decreasing over time. In the early University of Kentucky studies, treatment breaks or even termination due to acute toxicity occurred in about 30% of patients [21, 22]. This later declined to 13% in the Italian study [19] and 2–4% in others [32, 33]. The most common acute toxicities include diarrhea and skin desquamation. Grade 3–4 acute toxicity was observed in over 30% of the early University of Kentucky studies but the range reported in later studies is 4–18% [19, 24, 25, 33]. The lower rates of acute toxicity over time may be related to the use of more conformal fields in the later studies.

A bigger concern after reirradiation is the rate of late complications. Although surgery is associated with improved overall survival, most studies also find that patients who undergo surgery have a significantly higher rate of late toxicity [24–26, 32]. For example, the actuarial 3-year rate of grade 3–4 late toxicity in the MD Anderson study was 54% in the surgery patients compared to 16% in the reirradiation alone patients [32]. The most common late complications in patients who undergo surgery include wound complications, pelvic abscess formation, small bowel obstruction, urinary obstruction/hydronephrosis, anastomotic/ureteral stricture, diarrhea, and fistula. Late complications in patients who undergo reirradiation alone include small bowel obstruction, urinary obstruction/hydronephrosis, diarrhea, and fistula formation. Many of these complications are also associated with the recurrent tumor, especially in the setting of residual disease; therefore, it can be difficult to attribute symptoms as toxicity of treatment or from the disease itself. The reported rates of late toxicity are summarized in Table 2.

Other factors that may be associated with different rates of late toxicity include the initial pelvic radiation therapy dose, the length of time between the initial radiation and retreatment, and use of hyperfractionation regimens. A prior radiation dose of ≥54 Gy was found to be associated with an increased rate of grade 3–4 late toxicity in one study [25]. The total dose used for reirradiation has generally not been found to be associated with differences in late toxicity [20, 24, 32]. One study found that an interval of >24 months between the initial radiation and reirradiation significantly correlated with lower rates of late toxicity [20] and another study found this trended toward significance [32]. In the larger cohort of 103 patients from the University of Kentucky that included their palliative and curative patients, treatment with hyperfractionated twice-daily treatments was significantly correlated with lower late toxicity [20]. The rate of late toxicity was 43% in patients treated with hyperfractionation compared to 60% for patients treated with standard daily fractionation ($P < .05$).

While the University of Kentucky did report a lower rate of late toxicity with hyperfractionation using twice-daily treatments, there are two retrospective studies that reported outcomes of reirradiation using once-daily treatments that do not report higher rates of late toxicity compared to rates reported in studies that used hyperfractionation. The first study was from Peter MacCullum Cancer Center including 56 patients treated with a median reirradiation dose of 39.6 Gy in 1.8 Gy daily fractions [26]. They also found that patients who underwent surgical resection had a longer median survival and the majority of the late toxicities were observed in patients treated with surgery (9/12 patients vs. 1/43 patients treated without surgery). A larger study of 135 patients from Catharina Hospital included a majority of patients (62%) who had received prior treatment with short-course RT and reirradiation was given to 30–30.6 Gy in 1.8–2 Gy daily fractions [27]. They reported grade 3–4 toxicity in 35% of patients, including late toxicities consisting of enterocutaneous fistulas in 10% of patients, incisional hernias in 6%, and ileus in 14%. Additional studies are needed to evaluate whether once-daily treatments vs. hyperfractionated treatments result in different rates of late toxicity.

Future Directions

The aim of current and future studies for this patient population is to further optimize the therapeutic ratio of multimodality treatment. The routine use of modern imaging, such as pelvic magnetic resonance imaging and positron emission tomography, can aid in patient selection and determine which patients may have the best chance for curative therapy. Modern imaging modalities can also help in the re-evaluation of patients to determine if they have resectable disease after reirradiation and guide precise radiation treatment to target the tumor with more conformal doses.

Another method that could potentially deliver higher biologic doses to a recurrent tumor with less exit dose to the surrounding normal structures includes the use of particle therapy with protons or carbon ions. The University of Pennsylvania reported results of reirradiation with proton beam therapy in seven patients with locally recurrent rectal

cancer who received a median prior dose of 50.4 Gy [42•]. The patients received a mean dose of 61.2 Gy (range, 45–64.8 Gy) in 1.8 Gy daily fractions using a relative biological effectiveness (RBE) value of 1.1 for protons. The authors performed a dosimetric analysis comparing the IMRT vs. proton beam plans and found a significantly reduced low dose volume to the bowel using proton beam therapy. However, there was a trend toward higher intermediate doses that the bowel received with protons given that end-range uncertainties had to be accounted for, which that may have contributed to less conformal intermediate doses. The authors reported three acute grade 3 events (diarrhea and abdominal pain) that all resolved. There were three late grade 4 toxicities that included small bowel obstruction and an enterovaginal fistula, which may have been due to progressive tumor invasion. Three of the seven patients also developed evidence of further local progression. All patients experienced either complete or partial pain relief. With only seven patients, the study was not powered to determine whether toxicity was associated with the low or intermediate bowel doses. Future studies are needed to determine the normal tissue doses that are correlated with toxicity and whether these normal tissue doses can be best achieved by proton beam therapy.

Particle therapy with carbon ions has been used in Japan for over 20 years with very promising results in the treatment of recurrent rectal cancer in the radiation naïve setting [43, 44]. Due to their physical properties, carbon ions may offer an estimated RBE between 2 and 5 compared to photons [45]. The PANDORA study is an ongoing phase I/II trial based at the University Hospital of Heidelberg that is enrolling patients with inoperable locally recurrent rectal cancer to receive reirradiation with carbon ions [45]. To be eligible, patients had to receive prior photon radiation therapy to 20–60 Gy. The phase I dose escalation component of the study includes patients treated to 36 GyE up to 54 GyE all in 3 GyE fractions. The phase II part of the study includes patients treated with the maximum tolerated dose found in the phase I component with progression-free survival as the primary endpoint. The authors reported encouraging results in an initial cohort of 19 patients, including some who were not treated on protocol [46•]. The median reirradiation dose delivered with carbon ions was 36 GyE (range, 36–51 GyE) and no patients experienced grade 3 or higher toxicities after a median follow-up of 7.8 months. A total of four patients experienced further local progression and the mean local progression-free survival was 20.6 months. It will be interesting to see the mature results of the study that includes more patients and longer follow-up.

Conclusions

Reirradiation is increasingly being used as part of the multimodality treatment of locally recurrent rectal cancer. It can offer effective symptom palliation, particularly in controlling bleeding, and be part of a curative salvage treatment strategy. There are studies that show reirradiation can increase tumor resectability and increase the chance of an R0 resection, which is an important predictor of long-term survival. Overall survival has improved for this patient population over time and treatment-related toxicity is acceptable, particularly in the setting of reirradiation without surgery. Future studies are needed to further optimize the therapeutic ratio of reirradiation, such as evaluating dosimetric correlates with late toxicity, the role of particle therapy, and whether novel radiosensitizers can continue to improve outcomes.

Compliance with Ethical Standards

Conflict of Interest Randa Tao declares that she has no conflict of interest.

Shane Lloyd has received compensation from Sirtex for service on a marketing panel.

Lindsay Burt declares that she has no conflict of interest.

Jonathan Whisenant declares that he has no conflict of interest.

Ignacio Garrido-Laguna declares that he has no conflict of interest.

Prajnan Das declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. De Angelis R, Sant M, Coleman MP, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE-5—a population-based study. Lancet Oncol. 2014;15:23–34.
2. den Dulk M, Krijnen P, Marijnen CA, et al. Improved overall survival for patients with rectal cancer since 1990: the effects of TME surgery and pre-operative radiotherapy. Eur J Cancer. 2008;44:1710–6.
3. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol. 2011;12:575–82.
4. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351:1731–40.
5. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol: Off J Am Soc Clin Oncol. 2012;30:1926–33.
6. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet. 1986;1:1479–82.
7. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4

rectal cancers: results of FFCD 9203. J Clin Oncol: Off J Am Soc Clin Oncol. 2006;24:4620–5.
8. Guren MG, Undseth C, Rekstad BL, et al. Reirradiation of locally recurrent rectal cancer: a systematic review. Radiother Oncol. 2014;113:151–7.
9. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med. 1997;336:980–7.
10. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol: Off J Am Soc Clin Oncol. 2012;30:3827–33.
11. Bhangu A, Ali SM, Cunningham D, Brown G, Tekkis P. Comparison of long-term survival outcome of operative vs nonoperative management of recurrent rectal cancer. Color Dis. 2013;15:156–63.
12. You YN, Habiba H, Chang GJ, Rodriguez-bigas MA, Skibber JM. Prognostic value of quality of life and pain in patients with locally recurrent rectal cancer. Ann Surg Oncol. 2011;18:989–96.
13. 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.
14. Marzi S, Saracino B, Petrongari MG, et al. Modeling of alpha/beta for late rectal toxicity from a randomized phase II study: conventional versus hypofractionated scheme for localized prostate cancer. J Exp Clin Cancer Res. 2009;28:117.
15. Tucker SL, Thames HD, Michalski JM, et al. Estimation of alpha/beta for late rectal toxicity based on RTOG 94–06. Int J Radiat Oncol Biol Phys. 2011;81:600–5.
16. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol. 1989;62:679–94.
17. 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.
18. Valentini V, Morganti AG, De Franco A, et al. Chemoradiation with or without intraoperative radiation therapy in patients with locally recurrent rectal carcinoma: prognostic factors and long term outcome. Cancer. 1999;86:2612–24.
19. Valentini V, Morganti AG, Gambacorta MA, 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.
20. Mohiuddin M, Marks G, Marks J. Long-term results of reirradiation for patients with recurrent rectal carcinoma. Cancer. 2002;95:1144–50.
21. 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.
22. Lingareddy V, Ahmad NR, Mohiuddin M. Palliative reirradiation for recurrent rectal cancer. Int J Radiat Oncol Biol Phys. 1997;38:785–90.
23. Haddock MG, Miller RC, Nelson H, et al. Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. Int J Radiat Oncol Biol Phys. 2011;79:143–50.
24. Koom WS, Choi Y, Shim SJ, et al. Reirradiation to the pelvis for recurrent rectal cancer. J Surg Oncol. 2012;105:637–42.
25. Das P, Delclos ME, Skibber JM, et al. Hyperfractionated accelerated radiotherapy for rectal cancer in patients with prior pelvic irradiation. Int J Radiat Oncol Biol Phys. 2010;77:60–5.
26. 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.
27. Bosman SJ, Holman FA, Nieuwenhuijzen GA, Martijn H, Creemers GJ, Rutten HJ. Feasibility of reirradiation in the treatment of locally recurrent rectal cancer. Br J Surg. 2014;101:1280–9.
28. Vermaas M, Nuyttens JJ, Ferenschild FT, Verhoef C, Eggermont AM, de Wilt JH. Reirradiation, surgery and IORT for recurrent rectal cancer in previously irradiated patients. Radiother Oncol. 2008;87:357–60.
29.•• You YN, Skibber JM, Hu CY, Crane CH, Das P, Kopetz ES, et al. Impact of multimodal therapy in locally recurrent rectal cancer. Br J Surg. 2016. **This study includes 229 recurrent rectal cancer patients treated with multimodality therapy, including salvage surgery, with curative intent over a 24 year period. The authors found that salvage potential and long-term survival improved significantly over time, which was also correlated with increased adoption of preoperative pelvic reirradiation over time**.
30. Dresen RC, Gosens MJ, Martijn H, et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. Ann Surg Oncol. 2008;15:1937–47.
31. Kusters M, Dresen RC, Martijn H, et al. Radicality of resection and survival after multimodality treatment is influenced by subsite of locally recurrent rectal cancer. Int J Radiat Oncol Biol Phys. 2009;75:1444–9.
32. Tao R, Tsai C, Jensen G, Eng C, Kopetz S, Overman M, et al. Hyperfractionated accelerated reirradiation for rectal cancer: an analysis of outcomes and toxicity. Radiother Oncol. 2017
33. 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.
34. Tanis PJ, Doeksen A, van Lanschot JJ. Intentionally curative treatment of locally recurrent rectal cancer: a systematic review. Can J Surg. 2013;56:135–44.
35. Moore HG, Shoup M, Riedel E, et al. Colorectal cancer pelvic recurrences: determinants of resectability. Dis Colon Rectum. 2004;47:1599–606.
36. Bouchard P, Efron J. Management of recurrent rectal cancer. Ann Surg Oncol. 2010;17:1343–56.
37. Bosset JF, Calais G, Mineur L, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results—EORTC 22921. J Clin Oncol: Off J Am Soc Clin Oncol. 2005;23:5620–7.
38. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol: Off J Am Soc Clin Oncol. 2009;27:5124–30.
39. Harris CA, Solomon MJ, Heriot AG, et al. The outcomes and patterns of treatment failure after surgery for locally recurrent rectal cancer. Ann Surg. 2016;264:323–9.
40. Poon MA, O'Connell MJ, Moertel CG, et al. Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol: Off J Am Soc Clin Oncol. 1989;7:1407–18.
41. Venook AP, Niedzwiecki D, Lenz H-J, Innocenti F, Mahoney MR, O'Neil BH, et al. CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). ASCO Annual Meeting Proceedings; 2014. p. LBA3.
42.• Berman AT, Both S, Sharkoski T, et al. Proton reirradiation of recurrent rectal cancer: dosimetric comparison, toxicities, and preliminary outcomes. Int J Part Ther. 2014;1:2–13. **Seven patients with locally recurrent rectal cancer were treated with pelvic reirradiation with proton beam therapy in this study. The authors reported various dosimetric parameters and found that**

the volume of bowel receiving low doses of radiation was significantly improved with proton therapy compared to IMRT but there was a higher volume of bowel receiving intermediate doses from proton therapy.

43. Tsujii H, Mizoe JE, Kamada T, et al. Overview of clinical experiences on carbon ion radiotherapy at NIRS. Radiother Oncol. 2004;73 Suppl 2:S41–9.
44. Yamada S, Kamada T, Ebner DK, et al. Carbon-ion radiation therapy for pelvic recurrence of rectal cancer. Int J Radiat Oncol Biol Phys. 2016;96:93–101.
45. Combs SE, Kieser M, Habermehl D, et al. Phase I/II trial evaluating carbon ion radiotherapy for the treatment of recurrent rectal cancer: the PANDORA-01 trial. BMC Cancer. 2012;12:137.
46.• Habermehl D, Wagner M, Ellerbrock M, et al. Reirradiation using carbon ions in patients with locally recurrent rectal cancer at HIT: first results. Ann Surg Oncol. 2015;22:2068–74. **The initial experience with carbon ions in reirradiation for recurrent rectal cancer was reported for 19 patients in this study. Some of the patients were enrolled on the ongoing phase I/II PANDORA trial evaluating carbon ion reirradiation for patients with unresectable disease. Although the median follow-up was only 7.8 months, the authors found promising results with a mean local progression-free survival of 20.6 months and no cases of grade 3 or higher toxicity**.