

Scientific Article

# Treatment of primary rectal adenocarcinoma after prior pelvic radiation: The role of hyperfractionated accelerated reirradiation

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## Abstract

**Purpose:** Previous studies have reported that hyperfractionated accelerated reirradiation can be used as part of multimodality treatment of locally recurrent rectal cancer with acceptable toxicity and promising outcomes. The purpose of this study was to evaluate the outcomes and toxicity of hyperfractionated accelerated reirradiation for patients with primary rectal adenocarcinoma and a history of prior pelvic radiation for other primary malignancies.

**Methods and materials:** We identified 10 patients with a prior history of pelvic radiation for other primary malignancies who were treated with hyperfractionated accelerated reirradiation for primary rectal adenocarcinoma. Radiation therapy was administered with 1.5 Gy twice daily fractions to a total dose of 39 Gy to 45Gy.

**Results:** The median follow-up time was 3.2 years (range, 0.6-9.0 years). Seven of 10 patients received surgery after reirradiation. The 3-year freedom-from-local-progression rate was 62% for all patients and 80% for patients who underwent surgery. The 3-year overall survival rate was 100%, with 3 deaths occurring at 4.7, 6.5, and 9.0 years after reirradiation. One patient had an acute

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Grade 3 toxicity of diarrhea, and 1 patient experienced a late Grade 3 toxicity of sacral insufficiency fracture.

**Conclusions:** Hyperfractionated accelerated reirradiation was well tolerated with promising rates of freedom from local progression and overall survival in patients with primary rectal cancer with a history of prior pelvic radiation therapy. This approach, along with concurrent chemotherapy and surgery, appears to be a viable treatment strategy for this patient population.

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## Introduction

Rectal cancer makes up approximately 13% of gastrointestinal tumors, with 39,220 estimated new cases in 2016.<sup>1</sup> The standard of care for the treatment of locally advanced rectal cancer includes preoperative chemoradiation therapy or short-course radiation therapy (RT), followed by surgery.<sup>2–8</sup> However, some patients with rectal cancer have a prior history of pelvic radiation therapy, and the role of further radiation therapy in these patients has not been established.

Reirradiation has been demonstrated as safe and feasible in prior retrospective and phase 1 and 2 studies for the treatment of locally recurrent rectal cancer.<sup>9–14</sup> Reirradiation for recurrent rectal cancer can potentially increase the ability to achieve a complete R0 resection, which is associated with improved overall survival (OS) and improved local control and quality of life.<sup>15,16</sup> Many published series on pelvic reirradiation have used a hyperfractionated accelerated radiation schedule to increase the therapeutic ratio by maximizing tumor control while minimizing the risk of normal tissue toxicity.<sup>10,17–19</sup> We recently published our long-term experience with a hyperfractionated accelerated regimen for the treatment of locally recurrent rectal cancer, and showed that reirradiation resulted in acceptable rates of toxicity along with promising rates of local pelvic control.<sup>20</sup>

The goal of this study was to evaluate toxicity and outcomes of hyperfractionated accelerated reirradiation in patients with rectal adenocarcinoma with a prior history of pelvic radiation for other malignancies.

## Methods and materials

This study was approved by the MD Anderson institutional review board. We identified 10 patients with primary rectal adenocarcinoma and a history of prior pelvic RT who were treated with hyperfractionated accelerated reirradiation of 1.5 Gy twice daily fractions between 2001 and 2015. Patients who received reirradiation with other fractionation schemes or with interstitial brachytherapy were not included in the study.

Patients were staged using the criteria for rectal cancer staging in accordance with the American Joint Committee on Cancer 7th Edition staging system. Follow-up and toxicity information was obtained from hospital records and clinic notes. Patients were followed regularly by the multidisciplinary team with follow-up visits every 3 months for the first year, at least every 6 months for the next 2 years, and then yearly afterward. At the discretion of the treating physicians, patients were evaluated during the follow-up period with a repeat endoscopy, computed tomography, or magnetic resonance imaging (MRI) of the pelvis. Local progression was defined as any recurrence or disease progression in the pelvis found on imaging studies or by endoscopy.

The institutional tumor registry, which collects information on patients annually through letters and phone calls, was also used to obtain follow-up information on patients. Toxicity data were retrospectively drawn from patient charts and graded per the Common Terminology Criteria for Adverse Events version 4. The statistical analysis was performed with IBM SPSS Statistics 21. Freedom from local progression (FFLP), freedom from any progression, and OS rates were estimated with the Kaplan-Meier method.

## Results

### Patient characteristics

Patient characteristics and course are shown in [Table 1](#). The median age at the time of diagnosis of the primary rectal cancer was 56 years. The median time from completion of pelvic radiation to reirradiation was 15.4 years. The initial pelvic radiation was administered for prostate cancer in 6 patients, cervical cancer in 2 patients, bladder cancer in 1 patient, and uterine leiomyosarcoma in 1 patient. The prior external beam radiation doses delivered ranged from 40 Gy to 81 Gy (median: 50 Gy). Brachytherapy was used in the prior treatment of 3 patients with prostate cancer and 2 patients with cervical cancer.

For the staging of the primary rectal cancer, the tumor classification was T3 in 7 patients and T4 in 3 patients.

**Table 1** Patient characteristics and treatment course

Patient no.	Age <sup>a</sup> and sex	Rectal cancer stage	Prior malignancy	Prior EBRT, dose (Gy)	Prior brachytherapy, dose (Gy)	Time to re-RT (yrs)	Re-RT dose (Gy) <sup>a</sup>	Indication	Re-RT technique	Re-RT fields	Surgery	Margin	FFLP (yrs)	OS (yrs)
1	71F	T3N0M0	Cervical	Y, 40	Y, 31	43.7	45	Preop	3 field	Pelvic nodal	Declined		0.6 <sup>b</sup>	0.6 <sup>b</sup>
2	67M	T3N0M0	Prostate	Y, 76	N	12.4	39	Definitive	IMRT	Pelvic nodal	Poor candidate		1.2	1.8 <sup>b</sup>
3	70M	T3N0M0	Prostate	N	Y, 144	5.6	42	Preop	IMRT	Pelvic nodal	Declined		0.7	3.6 <sup>b</sup>
4	67F	T3N0M0	Uterine leiomyosarcoma	Y, 48	N	36.6	39	Preop	3 field	Partial nodal	APR	R0	4.7 <sup>b</sup>	6.5
5	65M	T3N0M0	Bladder	Y, 50	N	23.2	39	Preop	3 field	Tumor only	LAR	R0	4.0 <sup>b</sup>	4.7
6	75M	T3N0M0	Prostate	Y, 70	N	20.3	39	Preop	IMRT	Pelvic nodal	APR	R0	2.8 <sup>b</sup>	2.8 <sup>b</sup>
7	68F	T4N0M0	Cervical	Y, 45	Y, 20	18.1	39	Preop	3 field	Tumor only	APR, IORT, 15 Gy	R1	5.6 <sup>b</sup>	9.0
8	80M	T4N0M0	Prostate	N	Y, unknown	12.6	45	Preop	IMRT	Pelvic nodal	APR	R0	2.4	3.7 <sup>b</sup>
9	67M	T3N1M1	Prostate	Y, 81	N	1.7	39	Preop	2 field	Partial nodal	Proctectomy w/ coloanal anastomosis	R0	1.7 <sup>b</sup>	1.7 <sup>b</sup>
10	76M	T4bN2M0	Prostate	N	Y, unknown	10.9	39	Preop	3 field	Pelvic nodal	TPE	R0	2.3 <sup>b</sup>	2.3 <sup>b</sup>

APR, abdominoperineal resection; EBRT, external beam radiation therapy; F, female; FFLP, freedom from local progression; IMRT, intensity modulated radiation therapy; IORT, intraoperative radiation therapy; LAR, low anterior resection; M, male; N, no; OS, overall survival; preop, preoperative; re-RT, reirradiation; TPE, total pelvic exenteration; Y, yes; yrs, years

<sup>a</sup> At the start of reirradiation

<sup>b</sup> Local progression or death has not occurred by that time.

Two patients were node-positive, and 1 patient had a distant metastasis to the liver. Therefore, a total of 6 patients had stage IIA, 2 patients had stage IIB, 1 patient stage IIIC, and 1 patient had stage IVA disease.

### Treatment characteristics

All patients were treated with a hyperfractionated accelerated radiation schedule that consisted of 1.5 Gy fractions delivered twice daily with a minimum 6-hour interval between the fractions. The median radiation dose was 39 Gy (range, 39–45 Gy) delivered in 26 fractions. The radiation fields included the full pelvic nodal volume in 6 patients, a partial pelvic nodal volume in 2 patients, and only the primary tumor in 2 patients. Patients were treated with a 3-field technique with posterior-anterior and lateral fields ( $n = 5$ ), 2 lateral fields ( $n = 1$ ), or intensity modulated RT ( $n = 4$ ). All patients received capecitabine concurrently with RT.

Nine patients were treated with preoperative intent. However, 2 patients later declined surgery because of patient concerns about the surgery. One patient who was not treated with preoperative intent was deemed a poor surgical candidate because of extensive comorbidities. Thus, a total of 7 patients underwent surgery after reirradiation. The surgeries included a low anterior resection in 1 patient, abdominal perineal resection in 4 patients (1 in conjunction with a vaginectomy), total pelvic exenteration in 1 patient, and a proctectomy with coloanal anastomosis in 1 patient. One patient was administered intraoperative RT (IORT) with a dose of 15 Gy. Among the patients who underwent surgery, 6 of 7 patients (86%) had R0 resections.

### Toxicity

Chemoradiation was well tolerated, and only 1 patient had grade  $\geq 3$  acute toxicity consisting of diarrhea, which required intravenous fluid replacement. One patient had a grade 2 postoperative wound complication. One patient experienced a grade 3 late toxicity of sacral insufficiency fracture 1 year after the second course of RT and 3 years after the first course of RT.

### Outcomes

The median follow-up time was 3.2 years (range, 0.6–9.0 years). There were 3 local progressions at 0.7, 1.2, and 2.4 years after reirradiation, of which 2 occurred in patients who did not undergo surgery. The 3-year FFLP was 62% in all patients and 80% for patients who underwent surgery. The 3-year freedom from any progression (local or distant) was 36% in all patients and 46% for patients who underwent surgery.

At the time of the analysis, 3 patients had died (at 4.7, 6.5, and 9.0 years after reirradiation); thus, the median OS was not reached. The 3-year OS rate was 100% for all patients.

### Discussion

To our knowledge, this is one of the only series reported in the literature on reirradiation for primary rectal cancer in the context of prior pelvic radiation. Patients with primary rectal cancer were often not included in prior reirradiation studies that focused on locally recurrent rectal cancer. Das et al. included 2 patients with primary rectal cancer in their initial study of hyperfractionated accelerated reirradiation, and Ng et al. included 4 patients with primary rectal cancer that was reirradiated with once-daily fractionation.<sup>19,21</sup> However, outcomes that are specific to the subset of patients with primary rectal cancer were not reported in either study. Primary rectal cancer after prior RT for other pelvic malignancies can be a challenging clinical situation. Our study provides useful information on the clinical management of these patients.

We found that patients with primary rectal cancer who were treated with hyperfractionated accelerated reirradiation had high rates of FFLP and OS. Understandably, the rates of FFLP and OS were much higher compared with those of patients who were treated with reirradiation for recurrent rectal cancer, which carries a worse prognosis. In a recent study, we reported a 3-year FFLP rate of 40%, and a 3-year OS rate of 39% in 102 patients who were treated with reirradiation for recurrent rectal cancer.<sup>20</sup> However, the rates of FFLP and freedom from any progression appear to be lower than those typically expected for de novo rectal cancer. Inferences are difficult to draw from a small series such as this, but our results do raise the question of whether rectal cancer in the setting of prior pelvic radiation carries a worse prognosis. The rectal cancers in our series may represent secondary malignancies that arise in a previously irradiated field with inherently different tumor biology.

Toxicity remains a concern for reirradiation, but the rates described in the literature for reirradiation are generally acceptable, with acute grade 3 to 4 toxicity rates of 4% to 20%, and late toxicity rates of 12% to 39%.<sup>10,13,19,21–23</sup> Toxicity in this study was relatively low, with only 1 acute and 1 late grade 3 toxicity. The lower rates of toxicity in this setting may be explained by the longer interval between the initial RT and reirradiation for primary rectal tumors compared with those for recurrent tumors. The median retreatment interval in this series was 15.4 years compared with 2.5 years in our recurrent rectal cancer experience.

We have previously advocated for the use of limited RT fields (tumor + 2–3 cm margin) for reirradiation in the setting of recurrent rectal cancer.<sup>19,20</sup> However, in the

current series, 8 of 10 patients were given reirradiation to an elective nodal volume in addition to the primary tumor. Our rationale was that primary rectal cancer after other malignancies is a very different clinical entity compared with recurrent rectal cancer and the pattern of failure is likely to be locoregional for primary rectal cancer and local for recurrent rectal cancer. Hence, we felt that treatment of elective nodal volumes was warranted for primary rectal cancer after other malignancies. Some patients in this series had received only prostate brachytherapy in the past, which caused no major overlap with the elective nodal volume for rectal cancer. Moreover, there was a prolonged interval between the 2 RT courses in this series, which made the inclusion of a nodal volume more tolerable.

Of the 7 patients who underwent surgery in our series, 1 patient received IORT because of concern for positive margins during surgery. There is evidence from retrospective series that IORT in addition to external beam RT (EBRT) can improve disease control in primary and locally recurrent rectal cancer.<sup>24,25</sup> In patients with locally recurrent rectal cancer and prior radiation, outcomes using IORT alone are poor and substantially improved with the addition of EBRT.<sup>26,27</sup> The patient who received IORT after EBRT reirradiation was the only patient in our series who had an R1 resection. However, the patient ultimately did not experience local disease progression.

This was a small, retrospective study with certain inherent limitations. The main limitation of the study was the limited number of patients. General conclusions are difficult to draw on the basis of a series of 10 patients, and we were not able to find factors that significantly correlated with outcomes given the small sample size. Toxicity was assessed on the basis of a retrospective review of hospital and departmental records, and some toxicity may not have been captured. Patients received multimodality therapy, and drawing firm conclusions with regard to how much reirradiation contributed to the overall outcomes is difficult.

On the other hand, this disease entity and treatment paradigm is not well reported in the literature. We have described multidisciplinary management strategies and outcomes for these patients, which contributes to the literature and may provide guidance to clinicians who manage patients with these challenging diseases.

## Conclusions

Hyperfractionated accelerated irradiation for primary rectal cancer in patients with prior pelvic radiation is associated with low rates of toxicity and excellent local control, particularly when patients also undergo surgery. Therefore, patients with newly diagnosed rectal cancer with a history of prior pelvic RT can be considered for preoperative reirradiation. Prior pelvic RT, especially

when given many years prior, is not necessarily a contraindication for the multimodality management of primary rectal cancer.

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