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FULL PAPER

Standard fractionation external beam radiotherapy with and without intraoperative radiotherapy for locally recurrent rectal cancer: the role of local therapy in patients with a high competing risk of death from distant disease

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Objective: We sought to evaluate the effectiveness and safety of utilizing radiotherapy (RT) with standard fractionation, with or without intraoperative RT (IORT), to treat locally recurrent rectal cancer (LRRC).

Methods: Retrospective review of 25 patients with LRRC treated with standard fractionation RT from 2005 to 2011. 15 patients (60%) had prior pelvic RT and 10 (40%) had synchronous metastases. The median equivalent dose in 2-Gy fractions was 30 and 49.6 Gy in patients with and without prior RT, respectively. 23 patients (92%) received concurrent chemotherapy and 16 (64%) underwent surgical resection. Eight patients (33.3%, four with and four without prior RT) received IORT. A competing risks model was developed to estimate the cumulative incidence of local failure with death treated as a competing event.

Results: Median follow-up was 36.9 months after the date of local recurrence. 3-year rates of overall survival (OS), local control (LC) and death with LC were 51.6%, 73.3% and 69.2%, respectively. On multivariable analysis, surgical resection was significantly predictive of improved OS ($p < 0.05$). If surgical resection were removed from the multivariable model, given the collinearity between IORT delivery and surgical resection, then IORT also became a significant predictor of OS ($p < 0.05$). Systemic disease at the time of local recurrence was not associated with either LC or OS. No patient had grade ≥3 acute or late toxicity.

Conclusion: RT with standard fractionation is safe and effective in the treatment of patients with LRRC, even in patients with significant risk of systemic disease and/or history of prior RT.

Advances in knowledge: The utility of RT with standard fractionation, generally with chemotherapy, in the treatment of LRRC is demonstrated. In this high-risk cohort of patients with a 40% incidence of synchronous metastatic disease, surgical resection of the recurrence was the major predictor of OS, though a benefit to IORT was also suggested. No patients had grade ≥3 acute or late toxicity, though 40% had undergone prior RT, underscoring the tolerability of standard fractionation RT in this setting.

INTRODUCTION

Following treatment with a multimodality approach involving total mesorectal excision integrated with chemoradiation, local control (LC) rates for clinically localized rectal cancer range between 92% and 96%.[1] While infrequent in incidence, locally recurrent rectal cancer (LRRC) is associated with significant morbidity by virtue of causing pain, bleeding and impaired continence.[2,3] LRRC also portends a poor prognosis: up to 50% have synchronously diagnosed distant metastases, and without treatment, the median overall survival (OS) ranges from 3 to 8 months.[4–6] Achieving an R0 resection remains the single most important therapeutic intervention for LRRC, particularly in the absence of metastatic disease, and the

chance of obtaining an R0 resection is significantly improved with neoadjuvant radiotherapy (RT).[1,7,8] However, in patients who are poor surgical candidates, RT may be the sole modality for achieving LC.[3]

Because multimodality treatment for primary rectal cancer has become widespread, many patients with LRRC have had prior RT. Despite early concerns about the toxicity of reirradiation, particularly with respect to the bladder and small bowel, several investigators reported favourable toxicity outcomes.[9–20] Many groups have employed hyperfractionation, wherein the use of smaller fractional dose of RT allows for selective dose escalation to the tumour while minimizing late normal tissue effects.[9–14,18,20–22] Hyperfractionation, however, can be logistically challenging and the advent of more sophisticated radiation planning and delivery techniques may allow for safe reirradiation with standard fractionation. Beyond the routine use of three-dimensional conformal RT (3D-CRT), modern RT protocols may involve intensity-modulated radiation therapy (IMRT), which utilizes steep dose gradients to conform the dose to target volumes, thus limiting dose to organs at risk.[23–26] Two recent studies employing standard fractionation RT (with most treatments using 3D-CRT) showed median OS ranging from 20 to 30 months and rates of late toxicity ranging from 16% to 36%.[16,17] Another showed no difference in toxicity, LC or OS with hyperfractionation or standard fractionation when IMRT was employed.[27] Notably, many of these studies did not include patients with metastatic disease at the time of local recurrence.

Another strategy for optimizing LC when managing LRRC is intraoperative RT (IORT), typically either delivered with electrons or with high-dose-rate brachytherapy. Numerous institutions have reported improved outcomes with IORT;[3,7,28–38] however, other reports suggest that the advantage of routine IORT is unclear.[39,40]

Adding to the complexity in managing these patients is the interplay between the morbidity of the local recurrence itself, the toxicity of any local intervention (particularly an aggressive intervention) and the high rate of systemic disease, with the latter being the main driver of mortality in these patients.[1,3] The continual improvements in systemic therapy have improved the control of metastatic disease, and therefore the role of local therapy has become more prominent even in patients with metastatic disease at the time of recurrence. We sought to evaluate the effectiveness and safety of RT with standard fractionation, with or without surgical resection and/or IORT, in a modern cohort of 25 patients with LRRC who received RT at a tertiary academic medical centre. We included patients with and without prior RT and patients with and without metastatic disease.

METHODS AND MATERIALS

Patient characteristics

The study population for this institutional review board-approved study included 25 patients treated with RT for LRRC at the Massachusetts General Hospital between August 2005 and July 2011 with standard fractionation RT. Patient and original treatment characteristics are shown in Table 1 while re-treatment parameters are shown in Table 2. All patients received oncologic surgery upfront, with 52% receiving no additional therapy. Nine patients (36%) received RT as part of their initial management, with a median RT dose expressed in equivalent doses in 2-Gy fractions (EQD_2) of 49.6 Gy (range, 44.3–50 Gy) with respect to tumour control (*i.e.* $\alpha/\beta = 10$). Another patient had previously received post-prostatectomy RT (EQD_2 of 58.4 Gy). Overall, the median interval between treatment of the original rectal cancer and the recurrence in question was 29.3 months. As per the Guillem classification,[41] 45.8% of recurrences were axial, 25% were posterior and 25% were lateral. 10 patients (40%) had distant metastases at the time of recurrence, and for 1 patient (4%), the recurrence being treated was actually a second local recurrence.

Details of radiation for local recurrence

Details on recurrence treatment characteristics are presented in Table 2. All patients underwent CT-based stimulation. For patients with no prior RT, radiation treatment fields were standard three-dimensional conformal fields or utilized standard IMRT contouring guidelines.[42] For patients with prior RT, treatment volumes included gross disease alone. IMRT was used significantly more frequently in patients with prior RT (50% *vs* 6.7%, $p < 0.001$ by χ^2 test). Among the 15 patients with no prior RT, all were treated with 1.8 Gy per fraction with a median cumulative equivalent dose in 2-Gy fractions (EQD_2) of 49.6 Gy, assuming an α/β ratio of 10 for the tumour. Among those with prior RT, fraction sizes ranged from 1.8 to 2.5 Gy and the median tumour EQD_2 was 30.0 Gy (range, 16–46.9 Gy). Assuming an α/β ratio of 3 for late-reacting normal tissues, the median EQD_2 values were 49.6 and 47.9 Gy, respectively, for patients without prior RT. Corresponding values were 79.6 and 77.8 Gy, respectively, for those with prior RT.

Concurrent chemotherapy was delivered in 23 patients (92%; 15 without prior RT and 8 with prior RT) and consisted of either capecitabine or 5-fluorouracil. Adjuvant chemotherapy was given in all but three patients, and most patients were treated with regimens containing oxaliplatin and/or bevacizumab.

Surgical resection

16 patients (64.0%) underwent surgical resection for their local recurrence within 6–8 weeks of RT. For the nine patients for whom surgery was not performed, six had technically unresectable lesions as determined by the operating surgeon due to likely adherence to the bony pelvis and three refused surgery. Of the four patients with prior RT who underwent surgery, one underwent low anterior resection, one underwent abdominoperineal resection and two underwent *en bloc* exenterations. Among the 12 patients without prior RT who had surgical resection of their local recurrences, 3 underwent low anterior resections, 6 underwent abdominoperineal resections and 3 underwent *en bloc* exenterations. For patients undergoing *en bloc* exenterations, viscera removed included the bladder and rectum, as well as the prostate in male patients and the vagina, cervix, uterus, fallopian tubes and ovaries in female patients. Nine patients had a pathological complete response (one with prior RT, eight without prior RT).

Table 1. Patient and original treatment characteristics

Variable or parameter	No prior RT	Prior RT	p-value[a]	Overall
n	15	10		25
Age at Dx, years	56.00 [45.00, 79.00] (15)	50.50 [34.00, 78.00] (10)	0.405	55.00 [34.00, 79.00] (25)
Age at treated LR	60.00 [46.00, 88.00] (15)	53.50 [35.00, 81.00] (10)	0.578	57.00 [35.00, 88.00] (25)
Sex				
Female	3/15 (20.0%)	5/10 (50.0%)	0.194	8/25 (32.0%)
Male	12/15 (80.0%)	5/10 (50.0%)		17/25 (68.0%)
ECOG PS				
0	14/15 (93.3%)	7/10 (70.0%)	0.249	21/25 (84.0%)
1	1/15 (6.7%)	2/10 (20.0%)		3/25 (12.0%)
2	0/15 (0.0%)	1/10 (10.0%)		1/25 (4.0%)
Stage, on presentation				
0	0/15 (0.0%)	1/10 (10.0%)	0.004[b]	1/25 (4.0%)
1	8/15 (53.3%)	0/10 (0.0%)		8/25 (32.0%)
2	1/15 (6.7%)	5/10 (50.0%)		6/25 (24.0%)
3	4/15 (26.7%)	2/10 (20.0%)		6/25 (24.0%)
4	2/15 (13.3%)	2/10 (20.0%)		4/25 (16.0%)
Original treatment				
Surgery alone	12/15 (80.0%)	1/10 (10.0%)	0.001[b]	13/25 (52.0%)
Neoadjuvant chemo-RT ± chemotherapy	0/15 (0.0%)	3/10 (30.0%)		3/25 (12.0%)
Adjuvant chemo-RT	0/15 (0.0%)	3/10 (30.0%)		3/25 (12.0%)
Perioperative chemotherapy	3/15 (20%)	3/10 (30.0%)		6/25 (12.0%)
Original surgical procedure				
LAR	10/15 (66.7%)	8/10 (80.0%)	0.335	18/25 (72.0%)
APR	1/15 (6.7%)	0/10 (0.0%)		1/25 (4.0%)
Other	4/15 (26.7%)	8/10 (80.0%)		6/25 (24.0%)
Original RT EQD_2 (tumour) [median, range]	N/A	49.6 [44.3, 58.4]	N/A	49.6 [44.3, 58.4]
Original RT EQD_2 (late-reacting normal tissue) [median, range]	N/A	47.88 [43.2, 57.0]	N/A	47.88 [43.2, 57.0]

APR, abdominoperineal resection; Dx, diagnosis; ECOG PS, ECOG performance score; EQD_2, equivalent doses in 2-Gy fractions; LAR, low anterior resection; LR, local recurrence; N/A, not applicable; RT, radiotherapy.
[a]When appropriate, analysis of variance tests were performed for categorical variables and *t*-tests for quantitative variables. Non-parametric equivalents were performed for the following variables: age at Dx, age at treated LR and original RT EQD_2.
[b]Denotes statistical significance at the 0.05 level.

Intraoperative radiotherapy

Eight patients (33.3%), four without and four with prior RT, received IORT. In all cases, IORT was performed due to intraoperative concern for unclear margin status and was delivered *via* electron beam. The median doses were 16 Gy (range, 14–17 Gy) and 12 Gy (range, 8–13 Gy) for those without and with prior RT, respectively.

Follow-up

Follow-up information was obtained from the hospital and radiation oncology departmental electronic medical record systems. The median follow-up interval was 36.9 months. Acute and late toxicity were graded using the Common Terminology Criteria with Adverse Events v. 3.0.

Statistical analyses

Descriptive statistics are reported as medians and ranges for continuous variables and counts/frequencies for categorical variables using, respectively, the Mann–Whitney–Wilcoxon exact test and Fisher or likelihood ratio tests for comparison of groups. The cumulative incidence of local failure after re-treatment was estimated using the method of Prentice et al[43] with death considered as a competing event. The primary analysis was planned for quantifying and testing the effect of a limited number of variables on local recurrence, accounting for death as a competing event. The following variables were tested in a series of univariate analyses using Fine–Gray proportional hazards model for subdistribution of time to local

Table 2. Recurrence treatment characteristics

Variable or parameter	No prior RT	Prior RT	p-value[a]	Overall
n	15	10		25
First or second LR being treated				
First	14/15 (93.3%)	7/10 (70.0%)	0.267	21/25 (84.0%)
Second	1/15 (6.7%)	3/10 (30.0%)		4/25 (16.0%)
Re-treatment dose/Fx [median, range]	1.8 [1.8, 1.8]	2.0 [1.8, 2.5]	<0.001[b]	1.8 [1.8, 2.5]
Re-treatment EQD_2 (tumour) [median, range]	49.6 [44.3, 49.6]	30.0 [16.0, 46.9]	<0.001[b]	49.6 [16.0, 49.6]
Re-treatment EQD_2 (late-reacting normal tissue) [median, range]	47.9 [43.2, 47.9]	30.0 [20, 49.5]	<0.001[b]	47.88 [20–49.5]
Total EQD_2 (tumour) [median, range]	49.6 [44.3, 49.6]	79.6 [69.6, 96.5]	<0.001[b]	49.6 [44.3, 96.5]
Total EQD_2 (late-reacting normal tissue) [median, range]	47.9 [43.2, 47.9]	77.8 [67.9, 97.4]	<0.001[b]	47.9 [43.2, 97.4]
Re-treatment RT technique				
3D-CRT	14/15 (93.3%)	5/10 (50.0%)	0.023[b]	19/25 (76.0%)
IMRT	1/15 (6.7%)	5/10 (50.0%)		6/25 (24.0%)
Surgery				
None	3/15 (20.0%)	6/10 (60.0%)	0.202	9/25 (36.0%)
LAR	3/15 (20.0%)	1/10 (10.0%)		4/25 (16.0%)
APR	6/15 (40.0%)	1/10 (10.0%)		7/25 (28.0%)
Other	3/15 (20.0%)	2/10 (20.0%)		5/25 (20.0%)
IORT	4/15 (26.7%)	4/10 (40.0%)	0.667	8/25 (32.0%)
IORT dose [median, range]	16.00 [14.00, 17.00] (4)	12.00 [8.00, 13.00] (6)	0.019[b]	13.50 [8.00, 17.00] (10)

3D-CRT, three-dimensional conformal radiotherapy; APR, abdominoperineal resection; EQD_2, equivalent doses in 2-Gy fractions; Fx, fraction; IMRT, intensity-modulated radiation therapy; IORT, intraoperative radiotherapy; LAR, low anterior resection; LR, local recurrence; RT, radiotherapy.
[a]When appropriate, analysis of variance tests were performed for categorical variables and t-tests for quantitative variables. Non-parametric equivalents were performed for the following variables: re-treatment dose/Fx, re-treatment EQD_2 and IORT dose.
[b]Statistical significance at the 0.05 level.

recurrence:[44] prior radiation, current radiation EQD_2, surgical resection of the recurrence, initial Stages III or IV, systemic disease at the time of local recurrence, IORT and IORT dose. The same set of variables was tested in multivariate analyses using the Fine–Gray model. However, due to multicollinearity among predictor variables, two separate multivariate analyses were performed: one excluding IORT use and one excluding resection at recurrence. Coefficients and p-values from the Wald test in the univariate and multivariate Fine–Gray models are reported for all tested comparisons. Univariable and multivariable regression analyses were used to determine the association between the aforementioned variables and either LC or OS. Coefficients and p-values from the Wald test in a Fine–Gray from all tested comparisons are reported. All analyses were performed in R v. 3.3.1, using the survival and cmprsk packages.[45]

RESULTS

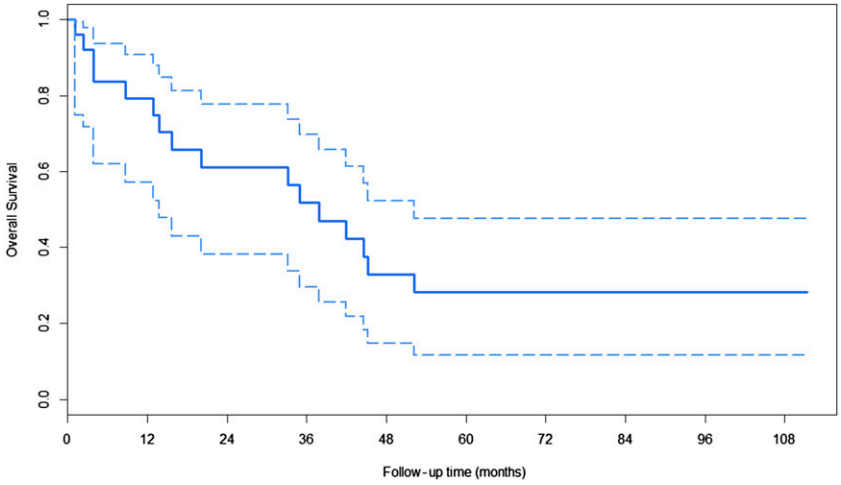
Local control and overall survival

At the time of this analysis, 9 patients (36.0%) remained alive, whereas the remaining 16 (64.0%) had died from rectal cancer. All patients who died of rectal cancer died as a result of progressive systemic disease. Seven patients (28%) were alive with no evidence of disease at last follow-up. Of the remaining two patients, one remained free of local disease but had developed distant metastases, and the other had both local and distant disease.

The Kaplan–Meier OS curve for the total cohort is shown in Figure 1. The median OS was 35.8, with 3-, 4- and 5-year OS rates of 51.6%, 32.9% and 28.2%, respectively. A cumulative incidence estimate of local failure and death without local failure, using a competing risk analysis, is shown in Table 3 and Figure 2. 3-, 4- and 5-year LC rates were 73.3%, 68.6% and 68.6%, respectively, whereas 3-, 4- and 5-year rates of death with LC rates were 69.2%, 59.8% and 55.0%, respectively.

The results of univariable and multivariable analyses for risk factors for local recurrence and OS are shown in Tables 4–7. On univariable analysis, higher IORT dose was associated with improved LC [hazard ratio (HR) 0.56, $p < 0.01$]. On multivariable analysis, however, no factors were associated with improved LC. Receiving prior RT was significantly associated with worsened OS on univariable analysis (HR 3.10; $p < 0.05$), whereas having the recurrence surgically resected was associated with improved OS (HR 0.03; $p < 0.05$ for both). Owing to the significant correlation between surgical resection of the

Figure 1. Kaplan–Meier curve for overall survival. The solid line indicates the Kaplan–Meier survival curve, with the dashed lines indicating the upper and lower bounds of the 95% confidence interval.



recurrence and receiving IORT (because all patients receiving IORT underwent surgical resection), three multivariable analyses for predictors of OS were developed: one with IORT excluded as a variable, one with surgical resection excluded a variable and one with both included. When IORT was excluded, surgical resection was significantly associated with improved OS (HR 0.03, $p < 0.01$); and when surgical resection was excluded, IORT was significantly associated with improved OS (HR 0.21, $p = 0.03$). When both variables were included, only surgical resection remained significantly associated with OS (data not shown).

Table 3. Cumulative incidence estimates of competing risks for local failure *vs* death without local failure (with 95% confidence intervals)

Months	Local failure	Death
0	0.000 (NA)	0.000 (NA)
6	0.084 (0.014, 0.238)	0.122 (0.029, 0.284)
12	0.172 (0.052, 0.352)	0.166 (0.050, 0.341)
18	0.219 (0.076, 0.408)	0.213 (0.074, 0.399)
24	0.267 (0.104, 0.462)	0.261 (0.101, 0.454)
30	0.267 (0.104, 0.462)	0.261 (0.101, 0.454)
36	0.267 (0.104, 0.462)	0.308 (0.131, 0.506)
42	0.314 (0.133, 0.513)	0.355 (0.162, 0.555)
48	0.314 (0.133, 0.513)	0.402 (0.195, 0.602)
54	0.314 (0.133, 0.513)	0.450 (0.230, 0.648)
60	0.314 (0.133, 0.513)	0.450 (0.230, 0.648)
66	0.314 (0.133, 0.513)	0.450 (0.230, 0.648)
72	0.314 (0.133, 0.513)	0.450 (0.230, 0.648)
84	0.314 (0.133, 0.513)	0.450 (0.230, 0.648)
96	0.314 (0.133, 0.513)	0.450 (0.230, 0.648)
108	0.314 (0.133, 0.513)	0.450 (0.230, 0.648)

NA, not applicable.

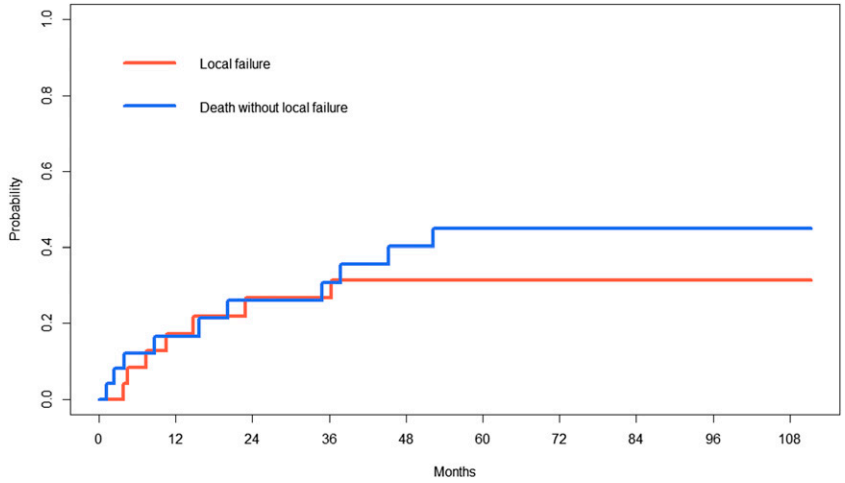
Toxicity

No patients developed grade ≥3 acute or late toxicity (Table 5). However, grades 1–2 acute toxicities were fairly common. Three patients (12.0%) did develop grade 2 proctitis. No grade 3 or 4 late toxicities were reported in this cohort. No significant differences in toxicity profiles were found between patients with prior RT and those without prior RT, or between those treated with IMRT *vs* 3D-CRT. Of note, significantly more patients with prior RT received IMRT (Table 8).

DISCUSSION

Albeit rare in the setting of modern surgical techniques and multimodality therapy, LRRC presents a significant therapeutic challenge. While many patients have synchronous metastatic disease, local recurrences are associated with significant morbidity and local therapy is often indicated for symptomatic relief alone. With improved systemic control options, however, aggressive local therapy may also influence overall prognosis. Surgical resection remains the gold standard of therapy, but neoadjuvant chemoradiation with or without IORT can help improve clinical outcomes. As more patients receive RT in the upfront setting, the challenging situation of reirradiation can present itself when dealing with local recurrences. However, because patients with LRRC have a high competing risk of developing and ultimately perishing from metastatic disease and because any local therapy carries a risk of added toxicity, the benefit of aggressive local treatment must be assessed carefully. In this cohort of 25 patients who received RT as part of the management of their LRRC, we found a favourable 3-year OS rate of 51.6% despite the fact that 40% of patients had synchronous metastatic disease. On competing risk analysis, the 3-year LC rate was 63.3% while the 3-year rate of death with LC was 30.8%. Furthermore, on multivariable analysis, having synchronous metastatic disease at the time of local recurrence was not significantly associated with OS, whereas surgical resection and IORT use were significantly associated with improved OS. Taken together, these data suggest that aggressive local therapy is indicated in patients with LRRC, even in the presence of systemic disease and/or even in those at high risk of

Figure 2. Cumulative incidence plot for local recurrence and mortality without local recurrence following re-treatment. Local failure incidence is depicted in red, whereas death without failure incidence is depicted in blue.



systemic progression. Importantly, despite the use of standard fractionation, no grade ≥3 acute or late toxicities were observed, perhaps due to the fact that 60% of reirradiation cases were treated with IMRT.

This favourable toxicity profile is particularly notable given that the estimated median cumulative EQD_2 was 77.8 Gy for late-reacting normal tissue in patients with prior RT. In order to minimize late normal tissue toxicity from reirradiation, many investigators have utilized hyperfractionated RT. Historically, median OS after hyperfractionated reirradiation has ranged from 26 to 42 months, with predicted 5-year OS rates of up to 39.3% and rates of late toxicity ranging from 10% to 20%.[9,11,13,18,20] Mohiuddin et al reported the outcomes of 103 patients undergoing reirradiation, 43 of whom received 1.2 Gy b.i.d. to 34.8 Gy with concurrent 5-fluorouracil. In that cohort, 28% of all patients developed grade ≥3 acute toxicity and 21% developed grade ≥3 late toxicity.[11] Valentini et al[13] conducted a multicentre Phase II trial in which 59 patients were treated with 1.2 Gy b.i.d. to 40.8 Gy, with concomitant 5-FU. Only 5% of patients had grade ≥3 acute toxicity and 12% had grade ≥3 late toxicity. 5-year OS was 39% for all patients and 67% in patients with an R0 resection. Das et al[9] treated 50 patients (48 with recurrent rectal cancer) with 1.5 Gy b.i.d. to 39 Gy, with concurrent chemotherapy in 96% (mainly capecitabine). 3-year OS was 39% for the entire cohort and 66% in those undergoing surgery. Grade ≥3 acute toxicity was 4%, whereas grade ≥3 late toxicity was higher at 26%, ostensibly due to higher rates of morbid surgical resection. Sun et al treated 70 patients with 1.2 Gy b.i.d to 36 Gy with concurrent capecitabine; 18 patients proceeded to surgery while the rest continued chemoradiation to 51.6–56.4 Gy.[18] Median survival was 35.8 months and 3-year OS was 45.12%. Severe acute toxicities occurred in 9.7% of patients and severe late toxicities in 1.4%. Importantly, none of these studies included patients with synchronous metastases; regardless, our 3-year OS rate of 53.4% compares favourably to these reports.

The ability to deliver more conformal RT in the modern era raises the possibility of utilizing standard fractionation, rather than hyperfractionation, even in patients with a history of prior RT. Three recent series have also utilized standard fractionation for reirradiation.[16,17,27] Koom et al[16] treated 22 patients (3 of whom had synchronous distant metastases) with 1.8–3 Gy per

Table 4. Univariable analysis of risk factors for local recurrence

Variable or parameter	HR	95% CI	*n*	*p*-value
Prior RT	4.36	(0.93, 20.50)	25	0.06
Current EQD_2	0.97	(0.92, 1.02)	25	0.19
Surgical resection of recurrence	0.37	(0.09, 1.55)	25	0.17
Stage = III/IV	0.45	(0.10, 2.14)	25	0.32
Systemic disease (at time of study LR)	1.05	(0.26, 4.17)	25	0.95
IORT	2.80	(0.67, 11.70)	25	0.16
IORT dose	0.56	(0.37, 0.85)	8	0.01[a]

CI, confidence interval; EQD_2, equivalent doses in 2-Gy fractions; HR, hazard ratio; IORT, intraoperative radiotherapy; LR, local recurrence.
HRs, CIs and *p*-values are results from Wald test in a Fine–Gray proportional hazard models for the local recurrence of rectal cancer, treating death as a competing risk.

Table 5. Univariable analysis of risk factors for overall survival

Variable or parameter	HR	95% CI	*n*	*p*-value
Prior RT	3.10	(1.15, 8.37)	25	0.03[a]
Current EQD_2	0.97	(0.93, 1.01)	25	0.10
Surgical resection of recurrence	0.03	(0.003, 0.25)	25	0.001[a]
Stage = III/IV	1.13	(0.42, 3.04)	25	0.81
Systemic disease (at the time of study LR)	1.66	(0.62, 4.44)	25	0.31
IORT	0.52	(0.18, 1.52)	25	0.23
IORT dose	0.61	(0.36, 1.04)	8	0.07

CI, confidence interval; EQD_2, equivalent doses in 2-Gy fractions; HR, hazard ratio; IORT, intraoperative radiotherapy; LR, local recurrence; RT, radiotherapy. HRs, CIs and *p*-values are results from Wald test in a Fine–Gray proportional hazard models for the local recurrence of rectal cancer, treating death as a competing risk.

day, to a median dose of 50 Gy, with concurrent chemotherapy in 73%. 64% of the patients were treated with 3D-CRT and the remainder received either tomotherapy or IMRT. Only five patients had surgical resection. 2-year OS was 50%, with a median of 21 months. 9% of the patients had grade ≥3 acute toxicity and 36% had grade ≥3 late toxicity. Ng et al[17] treated 56 patients (22 of whom had synchronous distant metastases) with reirradiation in 1.8-Gy fractions to a median dose of 39.6 Gy (73% with 3D-CRT), with 80% receiving concurrent chemotherapy. Only 13 patients were treated definitively; the median OS was 39 months for those receiving surgery and 15 months for those treated with palliative intent. Nearly 12% had grade ≥3 acute toxicity and 14.2% had grade ≥3 late toxicity. Finally, Youssef et al[27] recently reported the results of 31 patients undergoing reirradiation with either accelerated hyperfractionation (39 Gy in 1.5-Gy b.i.d. fractions) or standard fractionation (median dose of 30.4 Gy). Treatment was palliative only in 20 of the patients and only 9 underwent surgery. With a median follow-up of 11.3 months, 2-year local relapse rate was 4.73%, with a 2-year OS rate of 45.4%. Toxicity outcomes were favourable, with only one patient developing grade 3 acute toxicity and one patient developing a grade 3 late toxicity. No difference in toxicity or LC was seen between patients treated with hyperfractionation *vs* standard fractionation. Our outcomes are once again comparable to these and with lower acute and late toxicity rates. Of course, the aforementioned studies focused exclusively on patients with prior RT, whereas only 40% of patients in our study had prior RT, possibly explaining the favourable toxicity profile. However, our study also included a high proportion (40%) of patients with metastatic disease at the time of treating the local recurrence in question, which is higher than in the previous studies, and regardless, our OS outcomes compare well.

The favourable OS outcomes in this study may be in part due to the high proportion of patients undergoing surgical resection

Table 6. Multivariable analysis of risk factors for local recurrence with either intraoperative radiotherapy (IORT) excluded or surgical resection excluded

Variable or parameter	HR	95% CI	*n*	*p*-value
IORT excluded				
Prior RT	2.76	(0.24, 32.10)	25	0.42
Surgical resection of recurrence	0.55	(0.04, 8.67)	25	0.67
Stage = III/IV	0.32	(0.05, 2.05)	25	0.23
Systemic disease (at time of study LR)	0.66	(0.04, 11.43)	25	0.77
Developed metastases	3.40	(0.20, 58.20)	25	0.40
Surgical resection excluded				
Prior RT	2.70	(0.11, 66.00)	25	0.54
Stage = III/IV	0.68	(0.11, 4.26)	25	0.68
Systemic disease (at time of study LR)	0.22	(0.04, 1.30)	25	0.10
IORT	4.23	(0.68, 26.25)	25	0.12
Prior RT	2.70	(0.11, 66.00)	25	0.54

CI, confidence interval; HR, hazard ratio; LR, local recurrence; RT, radiotherapy.
HRs, CIs and *p*-values are results from Wald test in a Fine–Gray proportional hazards model for the local recurrence of rectal cancer, treating death as a competing risk.

Table 7. Multivariable analysis of risk factors for overall survival with either intraoperative radiotherapy (IORT) or surgical resection excluded

Variable or parameter	HR	95% CI	*n*	*p*-value
IORT excluded				
Prior RT	1.52	(0.49, 4.70)	25	0.46
Surgical resection of recurrence	0.03	(0.002, 0.28)	25	0.002[a]
Stage = III/IV	0.86	(0.22, 3.33)	25	0.83
Systemic disease (at time of study LR)	2.38	(0.38, 14.81)	25	0.35
Surgical resection excluded				
Prior RT	3.04	(0.77, 11.97)	25	0.11
Stage = III/IV	0.84	(0.23, 3.13)	25	0.80
Systemic disease (at time of study LR)	0.84	(0.19, 3.80)	25	0.82
IORT	0.21	(0.05, 0.87)	25	0.03[a]

CI, confidence interval; HR, hazard ratio; LR, local recurrence; RT, radiotherapy.
HRs, CIs and *p*-values are results from Wald test in a Cox proportional hazard models for overall survival.

Table 8. Maximum Common Terminology Criteria with Adverse Events v. 3.0 toxicity grades

Variable or parameter	Summary statistics
Anorexia	
1	2/25 (8.0%)
Diarrhoea	
1	9/25 (36.0%)
2	6/25 (24.0%)
Nausea	
1	3/25 (12.0%)
Vomiting	
1	3/25 (12.0%)
Constipation	
1	1/25 (4.0%)
Incontinence	
1	0/25 (0.0%)
Proctitis	
1	4/25 (16.0%)
2	3/25 (12.0%)
Fatigue	
1	14/25 (56.0%)
2	4/25 (16.0%)
Highest grade	
1	12/25 (48.0%)
2	11/25 (44.0%)
Highest grade (no fatigue)	
1	13/25 (52.0%)
2	9/25 (36.0%)

(64% overall). Indeed, surgical resection was predictive of increased OS, in agreement with findings in prior studies.[9,11,13,17] As a retrospective study, the possibility that this is due to the patients undergoing surgery being the healthiest subset of the patients in this cohort cannot be excluded and is a likely contributor to the finding. However, it is notable that having systemic disease at the time of local treatment was not associated with worse OS on multivariable analysis, which implies that aggressive local therapy can be beneficial even in patients with metastatic disease. We also found that, if surgical resection (which is associated with IORT delivery) is removed from the multivariable model, then IORT delivery becomes a significant predictor of OS. Interestingly, IORT dose was a significant predictor of improved LC on univariable analysis. This implies that within the high-risk subset of patients who received IORT, intensified local therapy (*i.e.* higher dose IORT) might have improved clinical outcomes. However, IORT dose was not included in the multivariable model due to smaller sample size at risk. Thus, this result should be interpreted with caution. In general, the use of IORT in LRRC is generally thought to improve outcomes;[7,28–37] however, others suggest the benefit is unclear.[39,40] Few studies have included comparisons of patients receiving IORT and those not receiving IORT, though two suggested an OS benefit to IORT.[14,37,39] Additionally, a large institutional series suggested improved outcomes when including IORT as compared with a prior series from the same institution that did not include IORT.[28,36]

Most recently, investigators from the Mayo Clinic and Catharina Hospital reported pooled data of 565 patients with LRRC who underwent multimodality treatment (including IORT) between 1981 and 2010.[46] They found that R0 resection was a highly significant predictor of LC and, additionally, found that the interval from pre-operative therapy to IORT delivery was a significant predictor of LC as well. They also found that the 256 patients who had prior RT had similar survival outcomes when compared with patients who were RT naïve; repeat RT in these patients was to a median dose of 30 Gy. These data are not

directly comparable to our study as all patients received IORT, but they do underscore the principle that aggressive local treatment can be helpful even in this high-risk population.

The current study has several limitations, including the general limitations of a retrospective study. First, it is possible that only a subset of patients with LRRC was even referred to radiation oncology, and thus the results may not be generalizable to all patients with LRRC. Second, all assessments of toxicity were based purely on available documentation, and as such, it is conceivable that the very low rate of toxicity seen in this study simply reflects underreporting, particularly since patients may have sought treatment at tertiary academic medical centres but were ultimately lost to follow-up. However, with a median follow-up of 36.9 months, it is likely that a fair number of late toxicities were captured, and moreover, it would seem more likely that patients with a serious toxicity would seek follow-up than those with more limited toxicity. Finally, the sample size is limited and therefore the conclusions of our statistical analyses should be regarded as hypothesis-generating, rather than definitive.

CONCLUSION

Standard fractionation RT for LRRC was well tolerated, both in patients with and without prior RT, with no incidences of grade ≥3 toxicity in either group. Despite the fact that 40% of patients had synchronous metastatic disease, 3-, 4- and 5-year LC rates were 73.3%, 68.6% and 68.6%, respectively, whereas 3-, 4- and 5-year rates of death with LC rates were 69.2%, 59.8% and 55.0%, respectively. On multivariable analysis, surgical resection was consistently associated with improved OS, whereas systemic disease at presentation was not. IORT use was associated with improved OS as well, but only upon exclusion of surgical resection from the multivariable model. On univariable analysis, IORT dose was associated with increased LC, but this effect could not be assessed in a multivariable model due to the very small number of patients receiving IORT. Overall, these findings suggest that RT with standard fractionation should be explored in larger cohorts of patients with LRRC, even for patients with prior RT, and that the presence of synchronous metastases or having a very high risk for developing systemic disease should not be contraindications to pursuing definitive local treatment.

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