Locally recurrent rectal cancer: improving radiation treatment

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Chapter 9

Locally recurrent rectal cancer: Treatment of a second local re-recurrence

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ABSTRACT

Introduction: Little is known about the outcomes of patients with rLRRC. Understanding the impact of patient and tumour characteristics on survival and treatment success can guide therapeutic strategies. This study provides insights into the outcomes of curative versus palliative treatment for rLRRC.

Methods: A retrospective review of patients who underwent surgery for locally recurrent rectal cancer (LRRC) between 1994 and 2022 was conducted. Data were collected regarding patient demographics, primary tumour, LRRC, and rLRRC characteristics. Oncological outcomes and treatment details were compared between patients treated with curative and palliative intent.

Results: Among 512 LRRC patients, 182 developed rLRRC. Of these, 66 (36.3%) were treated with curative intent, and 116 (63.7%) with palliative intent. Surgery for rLRRC was performed in 60/66 patients, achieving a negative surgical margin (R0) in 40 cases. Three-year overall survival was 57.5% for the curative group versus 28.5% for the palliative group ($p<0.001$). For R0 resections, three-year overall survival was 76.3%, compared to 26.8% with involved margins ($p<0.001$). An interval from LRRC to rLRRC of less than 12 months, synchronous metastases, and multifocality were all factors associated with poor oncological outcome.

Conclusions: Selected rLRRC patients can be treated with curative intent. Multidisciplinary teams should carefully evaluate patient and tumour characteristics, including the likelihood of R0 resection, presence of synchronous metastases, multifocality, and interval between LRRC and rLRRC, to determine eligibility for curative treatment.

INTRODUCTION

Locally recurrent rectal cancer (LRRC) is associated with a poor prognosis. In patients eligible for curative treatment, five-year overall survival rates are approximately 30-40%.[1] At diagnosis, only 35-45% of patients with LRRC are considered eligible for treatment with curative intent. In the remaining majority, the presence of distant metastases, irresectability of the tumour or other patient related factors limit curative options.[2–5] In 22-63% of LRRC patients who underwent surgical treatment with curative intent, a local re-recurrence develops within five years, posing a difficult challenge for clinicians as re-treatment options are limited.[6–8]

It is questionable whether the potential oncological benefits of treating rLRRC with curative intent balances the impact of treatment on morbidity and quality of life.[6,9] A substantial number of patients with rLRRC already underwent extensive neoadjuvant treatment for the primary and recurrent rectal tumour, including (chemo)radiotherapy, (chemo)reirradiation and/or systemic therapy. Additionally, due to previous surgical resections and radiation-induced fibrosis, the surgical resection of local re-recurrences is considered complex.

Little is known about the management and outcomes of rLRRC patients, and it is unclear whether curative intended treatment, as opposed to palliative treatment, is beneficial in terms of oncological outcome.[10,11] Establishing the outcome of different treatment modalities, and determining factors associated with the intention of treatment and outcomes are warranted to improve patient selection in rLRRC.

This study presents a large cohort of patients with LRRC who developed rLRRC. This study assessed the oncological outcomes of patients with rLRRC based on treatment intention, and on tumour and treatment characteristics of the primary, local recurrent and local re-recurrent rectal cancer, to identify factors which may help in the selection of patients for either curative or palliative treatment.

METHODS

Patients who underwent surgical treatment for LRRC from March 1994 to June 2022 (n=512) were included in a prospectively maintained registry. All patients were followed and all details on local or distant re-recurrence were recorded. Patients who developed a local re-recurrence (rLRRC) were identified and additional characteristics of patients and treatment were retrieved. Diagnosis of rLRRC was based on thoracoabdominal CT and/or MRI of the pelvis and was defined as local re-recurrence in the lesser pelvis when it occurred after a primary resection of LRRC. Patient and treatment characteristics were

collected, including data on the primary tumour, LRRC, and rLRRC, as well as data on oncological outcomes. Follow up was completed up to 5 January 2023.

For each patient with rLRRC, the preferred treatment strategy was decided by a dedicated multidisciplinary LRRC team. If patients were considered eligible for curative treatment, neoadjuvant treatment with induction chemotherapy and/or chemoradiotherapy was considered, followed by surgical resection. When curative treatment was deemed impossible, treatment modalities with palliative intent were offered, for example best supportive care, chemotherapy, radiotherapy or a combination of these, aiming for disease and symptom control.

Overall survival (OS) was compared in patients treated with curative versus palliative intent. In rLRRC patients treated with curative intent, a comparison of characteristics of patients with an R0 resection versus those with a non-radical (R1) resection was performed. The characteristics of patients treated with curative intent who were alive three years after resection of rLRRC, were compared to patients who were not. In all patients treated with curative intent, the disease-free survival (DFS), local re-re-recurrence free survival (LrrRFS), and metastasis-free survival (MFS) were determined.
OS was calculated from the date of diagnosis of LRRC and rLRRC until the date of death or was censored at the date of last follow-up. DFS, LrrRFS and MFS were calculated from the date of diagnosis of rLRRC until the event occurred or were censored at last follow-up. Continuous data were reported as median or mean (with interquartile range or 95% confidence interval respectively), depending on parameter distribution, and categorical data as counts and percentages. Group comparisons were performed using Chi-square test, Fisher exact tests or the Mann–Whitney U test, when appropriate. Survival rates were calculated using the Kaplan–Meier method and comparisons between groups were performed using the log-rank test. All tests were two-sided. P-values $p<0.05$ were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 29.0 for Windows (IBM Corp, Armonk, NY).

RESULTS

A total of 512 patients with LRRC were included, of whom 182 patients developed a rLRRC. The median follow-up period of these patients following LRRC surgery was 35.9 months (IQR 15.2-70.9). Of the 182 rLRRC patients, 66 (36.3%) were treated with curative intent and 116 (63.7%) with palliative intent. (*Supplementary Figure S1*).

In rLRRC patients treated with curative intent, neoadjuvant therapy was administered in 59 patients (89.4%). Induction chemotherapy was administered in 37 patients (56.1%), which was followed by neoadjuvant chemoradiotherapy in 16 patients. In total, 36 patients (54.5%) received neoadjuvant radiotherapy, consisting of chemo reirradiation in 18 patients (27.3%) and full course chemoradiotherapy in 15 patients (22.7%). Sixty patients (90.9%) were deemed eligible for surgical resection of the rLRRC after neoadjuvant treatment. Six patients (9.1%) were considered ineligible for resection due to disease progression or patient preferences. A radical resection (R0) was achieved in 40 patients (66.7%). (*Table 1)*

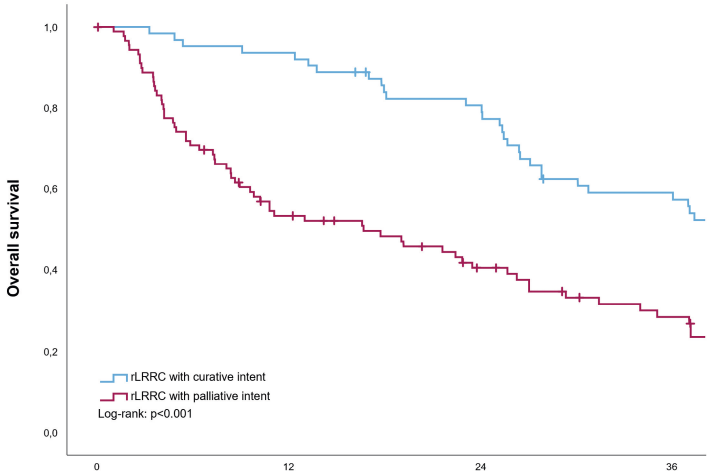
The three-year OS of 512 patients treated with curative intent for LRRC was 42.8% following surgery. Median OS after diagnosis of rLRRC of all 182 patients with rLRRC was 37.5 months (95% CI 24.0-57.3), and the three-year OS was 40.9%. In patients treated with curative intent for rLRRC, median OS was 41.6 months (95% CI 33.8-49.3) and three-year OS was 57.5%. In comparison, in patients treated with palliative intent, median OS was 16.6 months (95% CI 6.97-26.3), and three-year OS was 28.5% ($p<0.001$). (*Figure 1*) Of the patients treated with palliative intent, 47 had distant metastases at the time of diagnosis of rLRRC, while 49 patients had no distant metastases. Palliative patients without distant metastases had a median survival of 27.0 months (95% CI 14.1-39.8) and a three-year overall survival of 32.4%, while patients with distant metastases had a median survival of 12.9 months (95% CI 3.09-22.8) and a three-year overall survival of 24.4% ($p=0.235$).

Table 1. Treatment characteristics of patients treated with curative intent for rLRRC

Re-recurrence	**Curative rLRRC** *n=66 (%)*
Neoadjuvant treatment	37 (56.1)
- Induction chemotherapy	36 (54.5)
- (Chemo)radiotherapy	15 (37.8)
• Full course (50-50.4Gy)	1 (2.7)
• 5x5Gy	18 (48.6)
• Reirradiation (30-30.6Gy)	2 (8.1)
• Other	
Treatment synchronous metastases	3 (4.5)
Underwent surgical resection	60 (90.9)
Type of surgery	1 (1.5)
- Re-resection with anastomosis	15 (22.7)
- APR	2 (3.0)
- Posterior exenteration	10 (15.2)
- Total exenteration	31 (47.0)
- Tumour resection n.o.s.	
Additional resection	54 (81.8)
Intra-operative radiotherapy	31 (47.0)
HIPEC	3 (4.5)
R-status[1]	40 (60.6)
- R0	18 (27.3)
- R1/2	
Pathological complete response	4 (6.1)

[1] *missing/unknown in 2 patients*

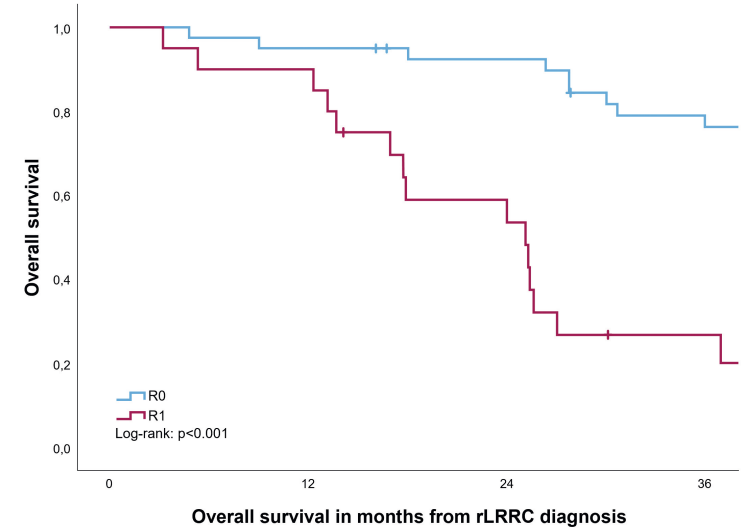
Median DFS in all patients treated with curative intent was 12.9 months (95% CI 10.7-15.2). Three-year DFS, MFS and LrrFS were 17.2%, 26.7%, and 38.1%, respectively. (*Figure 2*) In patients that had an R0 resection, three-year OS was 76.3%, versus 26.8% in case of an irradical resection (p<0.001), three-year DFS was 20.3% versus 7.5% (p=0.002), three-year MFS was 47.3% versus 26.8% (p=0.017) and three-year LrrFS was 32.3% versus 8.2% (p<0.001).



Number at risk				
Curative intent	66	64	61	53
Palliative intent	116	97	61	49

Figure 1. Kaplan-Meier analysis of OS in rLRRC patients treated with curative or palliative intent

Patients who were alive three years after resection of rLRRC had a longer interval between surgery for the first recurrence and the diagnosis of rLRRC than patients who died within three years: 19.3 months (IQR 12.4-31.4) versus 6.9 months (IQR 4.2-8.8) (p=0.004). Patients who developed a rLRRC within 12 months after the diagnosis of LRRC had inferior three-year overall survival (29.5%) compared to patients who developed a rLRRC after more than 12 months (52.2%) after the diagnosis of LRRC (OR 0.511; 95% CI 0.257-1.016, p=0.055).



Number at risk				
R0	42	42	41	38
R1	20	18	15	10

Figure 2. Kaplan-Meier analysis of OS in rLRRC patients treated with curative intent, resulting in an R0 resection versus R1 resection

rLRRC patients treated with curative intent less often received neoadjuvant chemoradiotherapy for the primary tumour compared to rLRRC patients treated with palliative intent (53.0% versus 73.3%, p=0.006). (Neo-)adjuvant chemotherapy is rarely administered in rectal cancer in the Netherlands and there was no difference in the number between patients treated with curative and palliative intent. In rLRRC patients treated with curative intent, induction chemotherapy for the primary tumour was administered in 2 patients (3.0%), versus in 6 patients (5.2%) in the palliative rLRRC group (p=0.498). In rLRRC patients treated with curative intent, patients received significant different surgical procedures (p=0.002); a sigmoidal resection was performed in 21.2% of the primary tumours compared to 3.4% in patients treated with palliative intent. A low anterior resection (LAR) was performed in 57.6% of rLRRC patients treated with curative intent and in 64.7% of rLRRC patients treated with palliative intent. (*Table 2*)

Patients treated with curative intent for rLRRC less often had a multifocal LRRC (3.0% versus 21.6%, p<0.001). In addition, rLRRC patients treated with curative intent less often underwent induction chemotherapy (18.2% versus 55.2%, p<0.001) and (chemo)radiotherapy (59.1% versus 94.0%, p<0.001) for their LRRC. In the rLRRC group treated with curative

intent, none of the patients underwent a total pelvic exenteration for their LRRC, versus 20 (17.2%) patients in the palliatively treated rLRRC group. An R0 resection of the LRRC was performed in 63.6% of rLRRC patients treated with curative intent, compared to 48.2% of rLRRC patients treated with palliative intent (p=0.060). (*Table 2*).

The median interval between treatment of LRRC and diagnosis of rLRRC was 16.1 months in rLRRC patients treated with curative intent (IQR 7.4-29.0) versus 11.3 months (IQR 5.6-22.1) in case of a palliative intent (p=0.054). rLRRC patients treated with curative intent less often had distant metastases at the time of rLRRC diagnosis when compared to rLRRC patients treated with palliative intent (6.2% versus 49.0%, p<0.001). (*Table 3)*

Table 2. Treatment history of curative treated patients with rLRRC versus palliative treated rLRRC

Primary tumour	**Curative rLRRC** ***n=66 (%)***	**Palliative rLRRC** ***n=116 (%)***	**p-value**
Male	36 (54.5)	83 (71.6)	0.020
Female	30 (45.5)	33 (28.4)	
Tumour location	51 (77.3)	110 (94.8)	<0.001
- Rectum	15 (22.7)	6 (5.2)	
- Sigmoid			
cM-stage	63 (95.5)	104 (89.7)	0.171
- cM0	3 (4.5)	12 (10.3)	
- cM1			0.498
Neoadjuvant treatment	2 (3.0)	6 (5.2)	0.006
- Induction chemotherapy	35 (53.0)	85 (73.3)	
- (Chemo)radiotherapy			
Initial surgery	38 (57.6)	75 (64.7)	0.002
- LAR/Hartmann	14 (21.2)	34 (29.3)	
- Abdominoperineal resection	14 (21.2)	4 (3.4)	
- Sigmoidal resection	0	1 (0.9)	
- Total exenteration	0	2 (1.7)	
- Other			
Intra-operative radiotherapy	4 (6.1)	11 (9.6)	0.445
R-status[1]	28 (84.8)	42 (82.4)	0.764
- R0	5 (15.2)	9 (17.6)	
- R1/2			
Metachronous metastases	5 (7.8)	15 (12.9)	0.296
Adjuvant treatment	21 (35.6)	24 (24.2)	0.126

Table 2. Continued

Primary tumour	Curative rLRRC *n=66 (%)*	Palliative rLRRC *n=116 (%)*	p-value
First Recurrence (LRRC)			
Months between primary and LRRC surgery (SD)	25.8 (34.0)	37.6 (29.4)	0.391
Multifocal recurrence	2 (3.0)	25 (21.6)	<0.001
Size of the tumour in mm, median (IQR)	31.0 (20.1-54.0)	38.0 (27.0-64.5)	0.243
cM-stage[2]			0.296
- cM0	52 (85.2)	81 (78.6)	
- cM1	9 (14.8)	22 (21.4)	
Neoadjuvant treatment	12 (18.2)	64 (55.2)	<0.001
- Induction chemotherapy	39 (59.1)	109 (94.0)	<0.001
- (Chemo)radiotherapy	11 (28.2)	23 (21.1)	0.020
• Full course (50-50.4Gy)	3 (7.7)	0	
• 5x5Gy	24 (61.5)	83 (76.1)	
• Re-irradiation (30-30.6Gy)	1 (2.6)	3 (2.8)	
• Other			
Surgery	15 (22.7)	18 (15.5)	0.004
- LAR	28 (42.4)	37 (31.9)	
- APR	2 (3.0)	8 (6.9)	
- ASR/Posterior exenteration	0	20 (17.2)	
- Total exenteration	21 (31.8)	33 (28.4)	
- Tumour resection n.o.s.			
Additional resections	55 (83.3)	115 (99.1)	<0.001
Intra-operative radiotherapy	31 (47.0)	95 (81.9)	<0.001
HIPEC	2 (3.0)	6 (5.2)	0.713
R-status[3]	35 (63.6)	55 (48.2)	0.060
- R0	20 (36.4)	59 (51.8)	
- R1/2			
Complications	7 (22.6)	14 (15.6)	0.395
- No complications at all			
- Clavien-Dindo I-IIIa	21 (67.7)	59 (65.6)	
- Clavien-Dindo IIIb-IV	3 (9.7)	17 (18.9)	

[1] missing/unknown in 89 patients, [2] missing/unknown in 18 patients, [3] missing/unknown in 13 patients

Table 3. Patient characteristics of rLRRC patients, stratified for treatment intent

Re-recurrence (rLRRC)	Curative rLRRC *n=66 (%)*	Palliative rLRRC *n=116 (%)*	p-value
Age at diagnosis rLRRC in years, mean (SD)	63.5 (9.3)	64.7 (10.1)	0.466
Months between LRRC and rLRRC, median (IQR)	16.1 (7.4-29.0)	11.3 (5.6-22.1)	0.054
Complains of rLRRC at diagnosis	16 (24.2)	34 (29.3)	0.462
Multifocality of the rLRRC[1]			
- No	44 (80.0)	44 (68.8)	0.163
- Yes	11 (20.0)	20 (31.3)	
Size of the tumour in mm, median (IQR)	37.0 (23.0-48.5)	42.0 (27.8-84.5)	0.570
cM-stage[2]	60 (93.8)	49 (51.0)	<0.001
- cM0	4 (6.2)	47 (49.0)	
- cM1			

[1] missing/unknown in 63 patients, [2] missing/unknown in 22 patients

DISCUSSION

This study shows that a select group of patients with rLRRC can be treated with curative intent. Prolonged OS may be achieved in these patients with 3-year OS rates of 57.5%. An R0 resection and an interval between diagnosis of rLRRC and treatment of LRRC of more than 12 months were associated with better oncological outcome.

Patients who were selected for treatment with curative intent were less often treated with neoadjuvant (chemo)radiotherapy for their primary tumour and LRRC, and less often underwent extensive surgical resections such as a total pelvic exenteration for their previous tumours. The absence of earlier neoadjuvant chemotherapy and radiotherapy and extensive surgical resections broaden the possibilities for neoadjuvant therapy and downstaging of the rLRRC and increase the possibilities for the surgeon to perform multivisceral resections with a chance of achieving clear resection margins.

On the other hand, patients were more often selected for palliative treatment if they had multifocal disease and/or synchronous metastases at diagnosis of rLRRC. If the presentation of the primary LRRC was multifocal, the chance for a second curative treatment was very limited. Although evidence is limited, physicians often correlate a multifocal recurrence to poor prognosis, since achieving an R0 resection is more challenging, and multifocality may be a sign of poor tumour biology. A history of a multifocal LRRC may be a reason to steer away from curative treatment.[12–14] Another factor that prompted palliative treatment of rLRRC was the presence of distant metastases, also reflecting poor tumour biology.[11,15]

Patients who were selected for palliative treatment also had shorter intervals between treatment of LRRC and the diagnosis of rLRRC. In those selected for palliative treatment, the median interval was shorter (11.3 months) than in patients treated with curative intent (16.1 months) (p=0.054).
A short interval is probably the result of poor tumour biology, which is supported by the finding that an interval between LRRC and rLRRC of less than 12 months was associated with inferior three-year OS. These factors, suggesting poor tumour biology and thereby poor oncological outcome, probably steer the patient and the multidisciplinary team away from extensive and invasive treatment strategies.

In our cohort of 182 patients diagnosed with rLRRC, 36% of patients were selected for treatment with curative intent. With adequate patient selection, the OS of these patients was found to be at least as good as in patients treated with curative intent for a first LRRC. While literature on rLRRC is scarce, Harji et al[10] previously described 30 patients that underwent resection of rLRRC. In line with our findings, an R0 resection resulted in far better survival rates than R1/R2 resections. If obtaining an R0 resection for rLRRC is not likely, an attempt for surgical resection is probably not warranted, since it is associated with poor survival. While in our cohort both median survival and OS rates were higher, it should be noted that both studies describe very heterogeneous patient groups. Any differences in these outcomes may well be explained by differences in national practice, previous treatment and patient selection.

This study is the second to describe a cohort of patients with rLRRC and represents the largest cohort described so in the literature. In addition, a major strength of our study is that all patients with rLRRC were retrieved from a prospective database of LRRC patients who were treated curatively. Therefore, we were able to identify both patients treated with curative intent and with palliative intent. A limitation of our study is the relative lack of data on the palliative treatment that patients received. This is caused by the fact that patients were often referred back to referring hospitals or their general practitioner for palliative treatment or best supportive care.
The results of this study have led us to put forward the following statements regarding the treatment of rLRRC.
(1) When patients cannot receive further neoadjuvant treatment or when previous surgery for LRRC was extensive, a radical resection (R0) of rLRRC becomes increasingly difficult, while perioperative morbidity and mortality more likely will increase. Since an irradical

resection is associated with poor survival outcomes, we advise caution in treating rLRRC patients with curative intent who already received extensive treatment for the LRRC.
(2) We consider synchronous distant metastases and a multifocal rLRRC as warning signs of poor tumour biology: extensive resections may not be warranted.
(3) In case of a short interval between treatment of the LRRC and diagnosis of the rLRRC, long term survival is unlikely. An interval of at least 12 months seems a reasonable threshold for considering treatment with curative intent.

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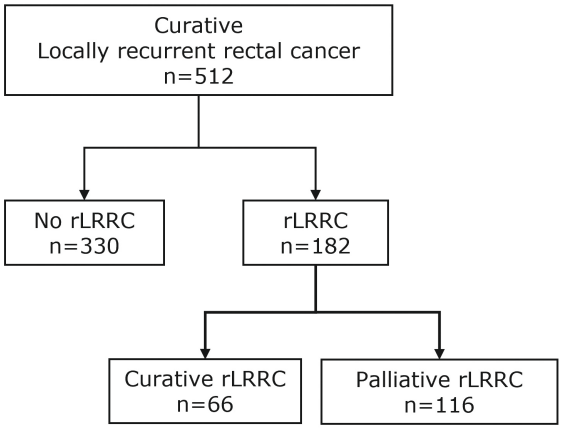
SUPPLEMENTARY DATA OF CHAPTER 9



Supplementary Figure S1. Flowchart of included patients within the study