Locally recurrent rectal cancer: improving radiation treatment

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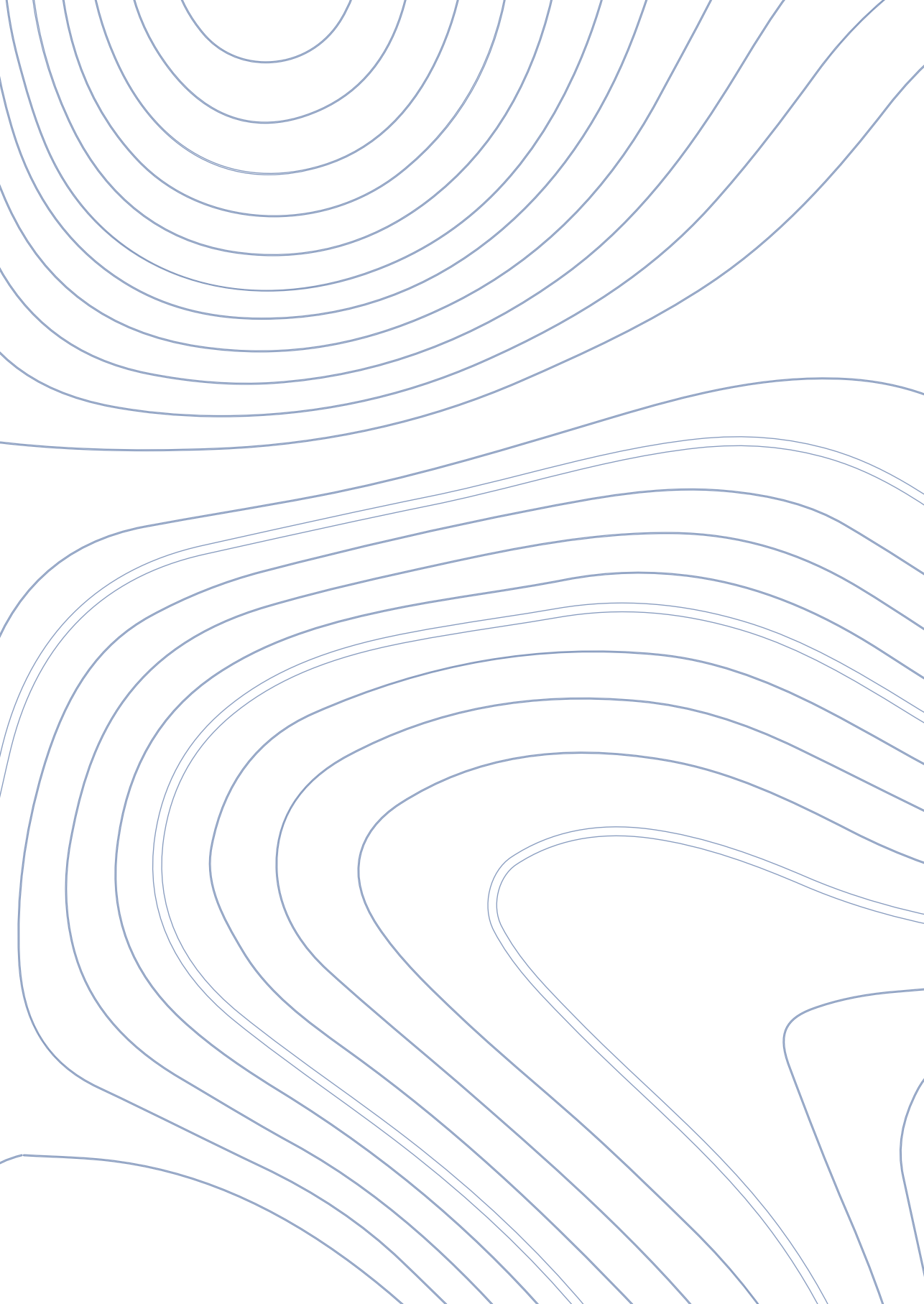
Part III

Oncological outcome of (re-)recurrent rectal cancer



Chapter 8

Locally recurrent rectal cancer: Oncological outcomes for patients with a pathological complete response after neoadjuvant therapy

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ABSTRACT

Background: For patients with locally recurrent rectal cancer (LRRC), it is an ongoing pursuit to establish factors predicting or improving oncological outcomes. In locally advanced rectal cancer, pathological complete response (pCR) appears to be associated with improved outcomes. The aim of this retrospective cohort study was to compare the oncological outcomes of LRRC patients with and without pCR.

Method: Patients who underwent neoadjuvant treatment and surgery for LRRC with curative intent between January 2004 and June 2020 at a tertiary referral hospital were analysed. Primary outcomes include overall survival, disease-free survival, metastasis-free survival, and local re-recurrence-free survival, stratified for patients with and without pCR.

Results: Of the 345 patients, 51 patients had a pCR (14.8%). Median follow-up was 36 months (IQR 16-60). The 3-year overall survival was 77.4% for patients with pCR and 51.1% for those without pCR (log-rank test; $p<0.001$). The 3-year disease-free survival was 55.6% for patients with pCR and 26.1% for those without pCR (log-rank test; $p<0.001$). The 3-year local re-recurrence-free survival was 81.6% for patients with pCR and 44.4% for those without pCR (log-rank test; $p<0.001$). Surgical procedures, including soft tissue, sacrum and urogenital organ resections, and postoperative complications were comparable between patients with and without pCR.

Conclusion: This study showed that patients with pCR have superior oncological outcomes compared to patients without pCR. It may therefore be safe to consider a watch-and-wait approach in highly selected patients, potentially improving quality of life by omitting extensive surgical procedures without compromising oncological outcomes.

INTRODUCTION

Despite substantial treatment improvements in recent decades, oncological outcomes for patients with locally recurrent rectal cancer (LRRC) remain poor.[1–5] The debate regarding the most appropriate treatment strategy is still ongoing. The achievement of an R0 resection is considered the most important prognostic factor for survival. This knowledge has led to extensive surgical approaches aiming to achieve an R0 resection, with or without prior downstaging by neoadjuvant treatment.[4,6–10]

Although the value of neoadjuvant downstaging in LRRC has yet to be determined, in locally advanced rectal cancer (LARC), neoadjuvant treatment has led to an increase in pathological complete responses (pCR).[11,12] Oncological outcomes of patients with a pCR in LARC are significantly better than in patients without a pCR.[13] These beneficial outcomes have resulted in less extensive surgical procedures allowing the development of watch and wait strategies.[14,15]

The correlation between pCR and long-term oncological outcomes is unclear in patients with LRRC. It has been postulated that a similar correlation to LARC exists between outcome and pCR in patients with LRRC.[10,16] However, as most patients with LRRC have received neoadjuvant treatment for their primary tumour, neoadjuvant treatment options for LRRC are limited, thereby potentially decreasing the chance of achieving a pCR and any associated beneficial oncological outcomes.

This study aimed to evaluate oncological outcomes of patients with LRRC and a pCR to neoadjuvant treatment.

METHODS

The outcomes of all patients who underwent surgical resection with curative intent for LRRC at Catharina Hospital Eindhoven between January 2004 and June 2020 were retrospectively studied. LRRC diagnosis was based on an MRI of the pelvis and a thoracoabdominal CT, after which all patients were discussed by a dedicated LRRC multidisciplinary team. LRRC was defined as recurrent rectal cancer in the pelvis after a total or partial mesorectal excision. Patients were excluded from analyses in case of a second or third recurrence, metastases at the time of recurrence, a recurrence after local endoscopic excision of the primary tumour, or failure of a watch and wait approach for a primary rectal cancer. Follow-up was completed until 22 February 2022.

In radiotherapy naive patients, long course chemoradiotherapy was delivered with a cumulative dose of 50-50.4Gy, usually with concomitant capecitabine (825mg/m^2 twice

daily on radiotherapy days). In patients who previously received pelvic radiotherapy by means of long course chemoradiotherapy (50-50.4Gy) or short course radiotherapy (25Gy) for the primary tumour, chemoradiotherapy was delivered with a cumulative dose of 30-30.6Gy, again usually with concomitant capecitabine. From 2012 onwards, selected patients with extensive disease (i.e. invasion of adjacent organs, pelvic sidewall, sacral bone and/or vascular invasion) received induction chemotherapy (ICT) preceding chemoradiotherapy (CRT), From 2016 onwards, ICT became standard of care until the end of the study period. ICT generally consisted of three to four cycles of CAPOX (capecitabine and oxaliplatin) or FOLFOX (leucovorin, 5-fluorouracil and oxaliplatin). Patients were restaged after three to four cycles of induction chemotherapy; in case of successful downstaging and good chemotherapy tolerance, one or two additional cycles were given. Adjuvant chemotherapy was not standard of care and was not offered to any patient.

Surgery was performed 8–14 weeks after the final cycle of chemoradiotherapy, generally consisting of an en-bloc resection of the tumour including involved pelvic organs and structures to achieve clear surgical margins. The procedures were categorised as followed: restorative rectal resection with re-anastomosis; abdominoperineal resection (APR); total pelvic exenteration, defined as resection of the rectum, bladder, and prostate with seminal vesicles or uterus with adnexa; and tumour resection "not otherwise specified" (n.o.s.), defined as an extra-anatomical, soft tissue and/or bone resection. Specific organs that were resected were identified separately as sacrum, bladder, seminal vesicles, prostate, uterus, adnexa, and vagina. Procedures could be combined with intraoperative radiotherapy (IORT) with a dose of 10–15Gy at the at-risk area (i.e. a location where the chance of a positive resection margin was deemed high by the surgeon and radiation oncologist, based on the combination of preoperative imaging and perioperative findings).

Standard pathological assessment was performed by experienced gastrointestinal pathologists with expertise in LRRC. The specimen was fixed with formalin and sampled in at least one section per centimetre of the tumour bed. In the pathology report, pCR was defined as the absence of any residual tumour in the complete specimen.

Endpoints were overall survival (OS), local re-recurrence-free survival (LRFS), distant metastasis free survival (MFS) and disease-free survival (DFS). OS was calculated from the date of surgery until the date of death from any cause or was censored at the date of last follow-up. LRFS, MFS and DFS were calculated from the date of surgery until the date

an event occurred or were censored at the date of last follow-up or death. Continuous data were reported as median or mean (interquartile range or 95% confidence interval respectively) and categorical data as counts and percentages. Group comparisons were performed using the Chi-square test, Fisher exact tests or the Mann–Whitney U test, as appropriate. Survival rates were calculated using the Kaplan–Meier method and comparisons between groups were performed using the log-rank test. As patients with pCR will have an R0 resection by definition, these variables are statistically completely dependent. A new combined variable of pCR status and R status was created, resulting in three different patient categories: R0 resection with pCR, R0 resection without pCR, and R1/2 resection. A Cox regression analysis was performed of this variable to calculate the hazard ratios (HR). A Cox proportional hazards model was used to examine the influence of pCR on oncological outcome. Multivariable logistic regression analysis was performed to find predictors for pCR, using associated factors in univariable logistic regression (p<0.10). Potential confounders for pCR were tested for each variable separately. 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 345 patients underwent surgery with curative intent for LRRC, of whom 51 had a pCR (14.8%). Patient and tumour characteristics for patients with and without pCR were comparable, as shown in *Table 1* and *Supplementary Table 1*. The median follow-up period was 36 months (IQR 16-60).

Most patients received neoadjuvant CRT (35.5% long course, 61.6% re-irradiation). One hundred and twenty-nine patients also received ICT (37.4%), of whom 30 patients received ICT in combination with long course CRT, and 99 received ICT in combination with reirradiation. The median time between the last radiotherapy fraction and surgery was 11.0 weeks (IQR 9.0-13.0) for patients undergoing long course chemoradiotherapy, and 11.0 weeks (IQR 9.0-13.5) for patients undergoing reirradiation (p=0.124).
Of the 30 patients who received ICT preceding long course CRT, nine patients had a pCR (30.0%). Out of the 99 patients who received ICT followed by reirradiation, 17 patients had a pCR (17.2%). Of the 90 patients receiving only long course CRT, 15 patients had a pCR (16.7%). Of the 111 patients receiving only chemo reirradiation, 10 patients had a pCR (9.0%) (Table 2). In the univariable logistic regression analysis, ICT and long course chemoradiotherapy were significantly associated with a pCR (Table 3).

The three-year OS was 77.4% in patients with a pCR, compared to 51.1% in patients without a pCR (HR 0.41, 95% CI 0.26-0.63; *p*<0.001). The one- and three-year DFS were 78.0% and 55.6% respectively in patients with a pCR, compared to 55.9% and 26.1% in patients without a pCR (HR 0.39, 95% CI 0.24-0.61; *p*<0.001). The one- and three-year LRFS were 95.4% and 81.6% respectively in patients with a pCR, compared to 71.9% and 44.4% in patients without a pCR (HR 0.21, 95% CI 0.10-0.43; *p*<0.001). Within 3 years, 36.7% of patients with a pCR developed distant metastases, compared to 54.3% in patients without pCR (HR 0.50, 95% CI 0.30-0.85; *p*<0.001). The oncological outcomes of patients with a pCR compared to patients without a pCR are shown in *Figure 1*.

Table 1a. Patient and tumour characteristics, stratified for patients with and without a pCR

Patient characteristics		**pCR n=51 (%)**	**No pCR n=294 (%)**	**Total n=345 (%)**	***p*-value**
Age	Mean (SD)	64.5 (59-70)	64.6 (58-72)	64.6 (59-72)	0.957
Gender ratio	M:F	36:15	194:100	36:15	0.520
ASA class	1	3 (6.3)	25 (9.1)	28 (8.6)	0.031
	2	31 (64.6)	215 (77.9)	246 (75.9)	
	3	14 (29.2)	35 (12.7)	49 (15.1)	
	4	0	1 (0.4)	1 (0.3)	
Primary origin	Sigmoid	5 (9.8)	31 (10.5)	36 (10.4)	0.873
	Rectum	46 (90.2)	263 (89.5)	309 (89.6)	
Primary tumour stage	T0-T2	12 (26.7)	53 (21.1)	65 (22.0)	0.407
In pathology	T3-T4	33 (73.3)	198 (78.9)	231 (78.0)	
Primary nodal stage	N0	17 (37.8)	123 (49.8)	104 (47.9)	0.138
In pathology	N+	28 (62.2)	124 (50.2)	152 (52.1)	
Treatment characteristics of local recurrence					
Number of lesions	1	36 (83.7)	234 (88.3)	270 (87.7)	0.535
	2	5 (11.6)	18 (6.8)	23 (7.5)	
	≥3	2 (4.7)	13 (4.9)	15 (4.9)	
Size of the largest lesion	Median (IQR) mm	40.0 (21-57)	42.0 (30-61)	42.0 (29-60.8)	0.321
Interval RT-surgery	Median (IQR) weeks	11.0 (9.0-13.0)	11.0 (9.0-13.0)	11.0 (9.0-13.0)	0.456
Surgery	LAR	18 (35.3)	56 (19.0)	74 (21.4)	0.068
	APR	19 (37.3)	119 (40.5)	138 (40.0)	
	Tumour resection n.o.s.*	6 (11.8)	44 (15.0)	50 (14.5)	

Table 1a. Continued

Patient characteristics		pCR n=51 (%)	No pCR n=294 (%)	Total n=345 (%)	*p*-value
	Total pelvic exenteration	8 (15.7)	71 (24.1)	79 (22.9)	
Sacral resection	Partial or complete	12 (33.3)	89 (37.4)	101 (36.9)	0.692
Bladder resection	Complete	6 (11.8)	45 (15.3)	51 (14.8)	0.777
	Partial	10 (19.6)	51 (17.3)	61 (17.7)	
Uterus resection	Uterus	0	9 (10.0)	8 (8.7)	0.366
Female only	Uterus with adnexa	5 (38.5)	23 (25.6)	28 (27.2)	
Vagina resection	Partial w/o reconstruction	3 (23.1)	24 (26.4)	27 (26.0)	0.837
Female only	Resection w reconstruction	3 (23.1)	15 (16.5)	18 (17.3)	
Prostate resection	Partial	1 (3.7)	16 (9.2)	17 (8.5)	0.483
Male only	Complete	2 (7.4)	20 (11.5)	22 (10.9)	
Vesicle resection	Unilateral	5 (18.5)	26 (14.9)	31 (15.4)	0.834
Male only	Bilateral	6 (22.2)	35 (20.1)	41 (20.4)	
IORT	Yes	44 (86.3)	257 (87.4)	301 (87.2)	0.822
Complications	None	14 (27.5)	86 (29.4)	100 (29.1)	0.872
Clavien-Dindo	I-II	22 (43.1)	115 (39.2)	137 (39.8)	
	III-V	15 (29.4)	92 (31.4)	107 (31.1)	

**Tumour resection not otherwise specified, i.e., a tumour resection with formal bowel resection.*
**LAR: low-anterior resection or resection with re-anastomosis*

Table 2. Patients with and without a pathological complete response stratified by type of neoadjuvant treatment [ICT: induction chemotherapy; CRT: chemoradiotherapy]

	ICT + CRT n=30 (%)	ICT + reirradiation n=99 (%)	CRT n=90 (%)	Reirradiation n=111 (%)
pCR (n=51)	9 (30.0)	17 (17.2)	15 (16.7)	10 (9.0)
No pCR (n=294*)	21 (70.0)	82 (82.8)	75 (83.3)	101 (91.0)
Median follow up (IQR)**	37.0 (23.5-49.2)	29.6 (15.0-50.1)	44.2 (22.4-85.5)	37.9 (14.9-63.1)

**15 patients received no radiotherapy*
***In months*

Table 3. Logistic regression analysis of factors correlated with a pathological complete response

		Univariable regression			Multivariable regression		
		HR	**CI**	**p-value**	**HR**	**CI**	**p-value**
Number of lesions	1	1	ref				
	>1	1.468	0.601-3.582	0.399			
Induction chemotherapy	No	1	ref		1	ref	
	Yes	1.743	0.958-3.171	0.069	2.115	1.127-3.968	0.02
Chemoradiotherapy	30Gy	1	ref		1	ref	
	45-50Gy	1.678	0.919-3.063	0.092	2.041	1.084-3.842	0.027
Consolidation chemotherapy	No	1	ref				
	Yes	1.059	0.297-3.772	0.93			

30Gy: reirradiation; 45-50Gy: Long-course chemoradiotherapy

When looking specifically at local control during the follow-up period in this cohort, 20 of the 51 patients with a pCR (39.2%) developed recurrent disease, of whom only four patients had a solitary local re-recurrence (7.8%) without distant metastasis. Of these four patients, two developed a re-recurrence in the same field as the recurrent tumour, and two patients developed a multifocal re-recurrence. Of the 16 patients that developed distant metastases, most presented with pulmonary metastases (n=7, 44.0%) or hepatic metastases (n=4, 26.0%).

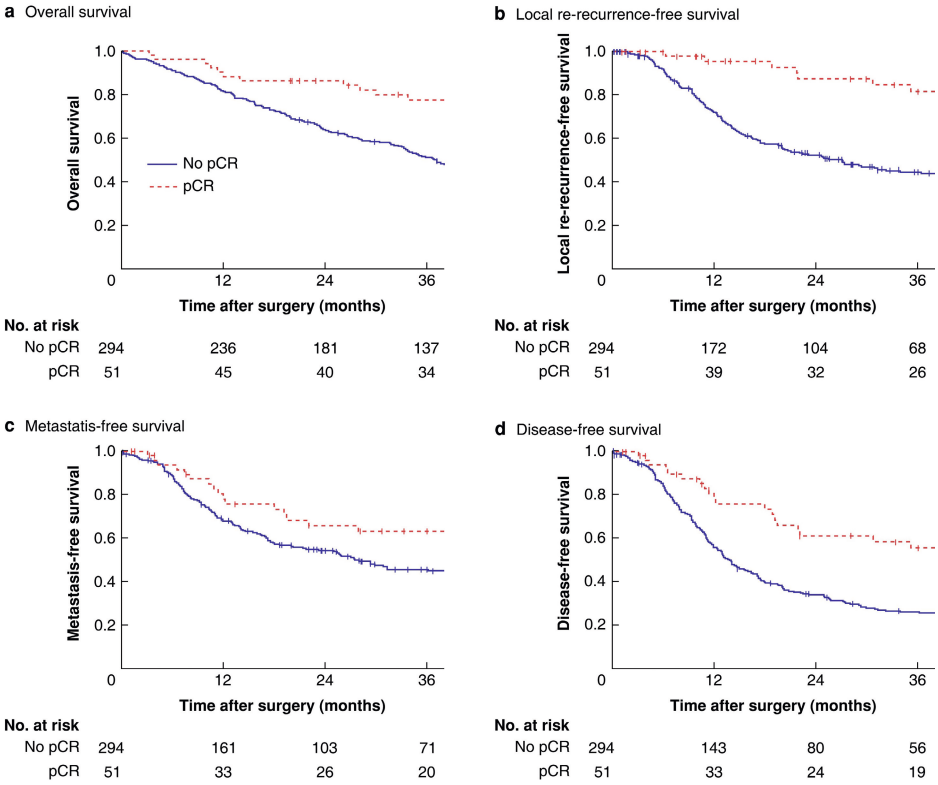

Figure 1a-d. Kaplan-Meier analysis of oncological outcomes in patients with and without a pathological complete response.

1a. Overall survival in patients with a pCR (red) and without a pCR (blue)
1b. Local re-recurrence free survival in patients with a pCR (red) and without a pCR (blue)
1c. Metastasis free survival in patients with a pCR (red) and without a pCR (blue)
1d. Disease free survival in patients with a pCR (red) and without a pCR (blue)

A radical resection with microscopically clear margins (R0 resection) was achieved in 226 patients (65.5%), of whom 51 patients had a pCR (22.6%). The 3-year OS, LRFS and MFS of patients with an R0 resection were significantly better than in patients with an irradical (R1/2) resection (61.9% vs 41.3% p<0.001, 63.7% vs 23.1% p<0.001 and 57.8% vs 30.7% p<0.001 respectively). The hazard ratio for OS in patients with an R0 resection was 0.49 (95% CI 0.38-0.63; p<0.001) compared to an R1/2 resection. In this study cohort, the 3-year OS of patients with a pCR (and R0 by definition) was higher than that of the total group of patients with an R0 resection, with or without pCR (77.4% vs. 61.9%). The same applies for LRFS (81.6% vs. 63.7%) and MFS (63.3% vs. 57.8%). In Cox regression analysis, a variable of three groups was analysed: R1/2 resection, R0 with pCR, and R0 without pCR. This

showed a hazard ratio for OS of 0.56 (95% CI 0.43-0.74; p<0.001) in patients with an R0 resection without a pCR compared to patients with an R1/2 resection. Patients with an R0 resection with pCR had a hazard ratio of 0.29 (95% CI 0.18-0.45; p<0.001) for OS compared to patients with an R1/2 resection (Figure 2).

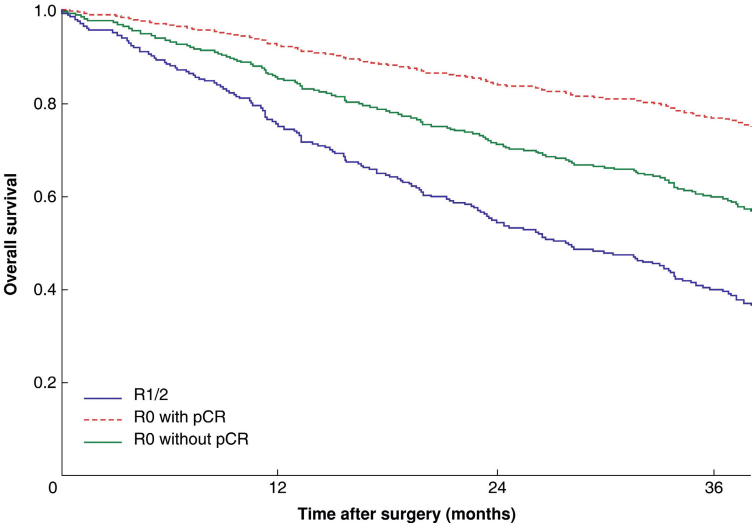

Figure 2. Cox regression analysis of overall survival, showing the curves of the combined variables; R0 resection with pathological complete response, R0 resection without pathological complete response and R1/2 resection

DISCUSSION

This study shows that patients with LRRC who achieved a pCR after neoadjuvant treatment had a superior OS, DFS, LRFS and MFS compared to patients without a pCR. The OS of patients with a pCR is also higher than that of patients with an R0 resection, where the latter group consists of both patients with and without pCR.

Achieving an R0 resection is currently the main goal in curative treatment for LRRC, as this has consistently been identified as the strongest predictor for survival.[17] The pursuit of an R0 resection, however, leads to extensive surgical procedures being performed, such as large multi-visceral "beyond TME" resections, en-bloc sacrectomy, total pelvic exenteration and hemipelvectomy. These major surgical procedures are associated with postoperative complications, functional impairment and impaired quality of life.[7,8,18–21] Furthermore, an R0 resection is only achieved in 30-65% of these patients, and the OS of patients treated curatively for LRRC remains disappointing with a 5-year OS of 30%

regardless of treatment strategy.[22,23] Moreover, even in the case of an increasing R0 resection rate, it is doubtful the overall survival will continue to improve.[23]

In search of ways to improve the R0 resection rate, an important prognostic factor for oncological outcomes seems to be disregarded: the biological behaviour of the tumour.[24] It remains questionable whether important improvements in oncological outcome in tumours with poor biology can be achieved by pushing surgical boundaries. Tumours with poor biological behaviour tend to recur and metastasise despite local treatment.[24] It seems unlikely that escalating surgical treatment would change that course. It should also be considered that patients with LRRC most often succumb to distant metastases, rather than to an overwhelming local re-recurrence.[15,25,26]

The OS, LRFS and MFS of patients with a pCR were superior to that of patients with an R0 resection in this study. A statistical comparison of patients with a pCR versus patients with an R0 resection was not suitable however, as patients with pCR have an R0 resection by default. When looking at survival data of pCR patients versus survival data of all patients with a R0 resection, patients with pCR appear to have a superior prognosis. Over time, the relatively good prognosis after an R0 resection resulted in R0 being labelled as the main goal of LRRC treatment. A favourable tumour biology and the quality of surgery enable an R0 resection. There is a certain turning point at which the extent of surgery will not make a difference anymore and only result in more morbidity while not improving survival. Based on the results of this study, it can be debated whether striving for a pCR is an alternative, legitimate goal. Increasing the pCR rate may not result in survival benefits for the entire group of patients with LRRC, but there may be other advantages to this approach.[10,16,27]

Tumour downstaging may result in less extensive surgical procedures in order to achieve an R0 resection. Surgical procedures could be postponed, thereby allowing time for observation of the natural behaviour of the tumour and thus preventing upfront debilitating surgical procedures in patients that will present with metastases shortly after.[23,26] Although a pCR is still relatively rare in patients who underwent radiotherapy for their primary tumour, pCR rates do seem to increase due to intensification of neoadjuvant treatment, and may become a significant factor in treatment decisions in the future. Ultimately, since local re-recurrences were very rare in patients with pCR, a watch and wait strategy in patients with a clinical complete response may be an appealing treatment option. In LARC,

watch and wait approaches have proven to be safe and result in similar oncological outcomes as surgical resection.[14,28,29] These findings are difficult to be translated directly from LARC to LRRC, as differences in tumour biology are to be expected. Moreover, in case of a suspected clinical complete response in LRRC, surveillance in a watch and wait approach will be less straightforward due to altered anatomy and often the inability to perform endoscopic follow-up. Therefore, the comparison of repeated high-quality imaging would be the way to move forward. In two recently published studies from our centre, response after neoadjuvant treatment on imaging was analysed and compared to pathological response.[30,31] These studies showed that response evaluation was indeed more challenging in LRRC than in LARC. For radiological assessment with MRI, a fair to moderate agreement between a good clinical response and good pathological response was observed. With a sensitivity of 46% and a specificity of 99%, these results seem comparable to literature on response evaluation in locally advanced rectal cancer.[30] This implies that in the case of a clinical complete response on MRI, it could be safe to explore watch and wait strategies in selected patients in centres with dedicated radiologists specialising in LRRC. Future developments, such as the combined interpretation of MRI with PET, the use of artificial intelligence, and possibly circulating tumour DNA may improve our ability to predict pCR and therefore aid in appropriate patient selection.[32,33]

The retrospective nature of our study means that only patients that finished curative treatment were included. There may have been patients whose disease progressed during neoadjuvant therapy, or in whom toxicity prevented further treatment. These patients are missing from our analysis, which results in selection bias. Determining correlations between specific baseline and treatment characteristics and pCR may not have been possible due to the relatively small number of patients with pCR, even though it is by far the largest cohort of patients reported in the literature.[10,16,27]

In this study, treatment with ICT and long course CRT was significantly associated with the achievement of a pCR. This could insinuate two things. It may be true that patients able to receive both options may have a more favourable tumour biology, due to the fact that no neoadjuvant treatment was given to the primary rectal cancer and selection of therapy resistant clones did not occur. It could however also be hypothesised that these tumours have a better outcome as they are treated more aggressively. Due to the small group numbers and retrospective design of the study, this cannot be investigated further.

High quality data on the efficacy of neoadjuvant treatment strategies will be generated by two randomized controlled trials that are currently recruiting, the PelvEx II and GRECCAR15 trials.[34,35] These trials will provide prospective data on the efficacy of neoadjuvant treatment in regard to the achievement of an R0 resection, but also with regard to the achievement of pCR, compliance to therapy and toxicity due to different treatment regimens, and oncological outcomes.

CONCLUSION

This study showed that patients who developed a pCR after neoadjuvant treatment for LRRC had an excellent overall survival and a very low re-recurrence rate compared to patients without a pCR. Based on these results, achieving a complete response could be a legitimate goal of treatment in patients with LRRC.

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SUPPLEMENTARY DATA OF CHAPTER 8

Table S1. Treatment details for primary rectal tumour

		pCR n=51 (%)	No pCR n=294 (%)	Total n=345 (%)	*p*-value
Neoadjuvant chemotherapy	Yes	3 (5.9)	9 (3.1)	12 (3.5)	0.326
Administered radiotherapy	No	24 (47.1)	104 (35.9)	128 (37.5)	0.045
	Short course (25Gy)	19 (37.3)	83 (28.6)	102 (29.9)	
	Long course (45-50Gy)	8 (15.7)	97 (33.4)	105 (30.8)	
	Adjuvant radiotherapy	0	6 (2.1)	6 (1.8)	
Primary surgery*	Sigmoidal resection	11 (21.6)	30 (10.2)	41 (11.9)	0.136
	Subtotal colectomy	0	3 (1.0)	3 (0.9)	
	Hartmann resection	1 (2.0)	11 (3.7)	12 (3.5)	
	Low anterior resection	30 (58.8)	152 (51.7)	182 (52.8)	
	APR	9 (17.6)	94 (32.0)	103 (29.9)	
	Posterior pelvic exenteration	0	1 (0.3)	1 (0.3)	
	Total pelvic exenteration	0	3 (1.0)	3 (0.9)	
Intra-operative radiotherapy	Yes	2 (3.9)	22 (7.5)	24 (7.0)	0.356
HIPEC**	Yes	0	2 (0.7)	2 (0.6)	0.555
Resection margin	R0	9 (17.6)	57 (19.4)	66 (19.1)	0.273
	R1	0	17 (5.8)	17 (4.9)	
	Unknown	42 (82.4)	220 (74.8)	262 (75.9)	
Adjuvant chemotherapy	Yes	4 (8.0)	53 (18.2)	57 (16.7)	0.095

**In which at least a partial mesorectal excision was performed*

***For concurrent peritoneal metastases*