

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

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# 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, it is an ongoing pursuit to establish factors predicting or improving oncological outcomes. In locally advanced rectal cancer, a pCR appears to be associated with improved outcomes. The aim of this retrospective cohort study was to compare the oncological outcomes of patients with locally recurrent rectal cancer with and without a pCR.

**Methods:** Patients who underwent neoadjuvant treatment and surgery for locally recurrent rectal cancer with curative intent between January 2004 and June 2020 at a tertiary referral hospital were analysed. Primary outcomes included overall survival, disease-free survival, metastasis-free survival, and local re-recurrence-free survival, stratified according to whether the patient had a pCR.

**Results:** Of a total of 345 patients, 51 (14.8 per cent) had a pCR. Median follow-up was 36 (i.q.r. 16–60) months. The 3-year overall survival rate was 77 per cent for patients with a pCR and 51.1 per cent for those without ( $P < 0.001$ ). The 3-year disease-free survival rate was 56 per cent for patients with a pCR and 26.1 per cent for those without ( $P < 0.001$ ). The 3-year local re-recurrence-free survival rate was 82 and 44 per cent respectively ( $P < 0.001$ ). Surgical procedures (for example soft tissue, sacrum, and urogenital organ resections) and postoperative complications were comparable between patients with and without a pCR.

**Conclusion:** This study showed that patients with a pCR have superior oncological outcomes to those without a 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 (LRR) remain poor<sup>1–5</sup>. The debate regarding the most appropriate treatment strategy is still ongoing. Achievement of an R0 resection is considered the most important prognostic factor for survival, knowledge of which has led to extensive surgical approaches aiming to achieve R0 resection, with or without prior downstaging by neoadjuvant treatment<sup>4,6–10</sup>.

Although the value of neoadjuvant downstaging in LRR has yet to be determined, neoadjuvant treatment in locally advanced rectal cancer (LARC) has led to an increased rate of pCR<sup>11,12</sup>. Oncological outcomes of patients with a pCR in LARC are significantly better than those in patients without a pCR<sup>13</sup>. These beneficial outcomes have resulted in less extensive surgical procedures and allowed the development of watch-and-wait strategies<sup>14,15</sup>.

The correlation between pCR and long-term oncological outcomes is unclear in patients with LRR. It has been

postulated that a correlation similar to that in LARC exists between outcome and pCR in LRR<sup>10,16</sup>. However, as most patients with LRR often received neoadjuvant treatment for the primary tumour, neoadjuvant treatment options for LRR 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 LRR and a pCR to neoadjuvant treatment.

## Methods

### Patients

The outcomes of all patients who underwent surgical resection with curative intent for LRR at Catharina Hospital Eindhoven between January 2004 and June 2020 were studied retrospectively. The diagnosis of LRR was based on MRI of the pelvis and thoracoabdominal CT, after which all patients were

discussed by a dedicated LRRC multidisciplinary team. LRRC was defined as local recurrence of rectal cancer in the pelvis after total or partial mesorectal excision. Patients were excluded from analyses in the event of a second or third recurrence, metastases at the time of recurrence, recurrence after 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.

## Neoadjuvant treatment

In radiotherapy-naive patients, long-course chemoradiotherapy (CRT) was delivered with a cumulative dose of 50–50.4 Gy, usually with concomitant capecitabine (825 mg/m<sup>2</sup> twice daily on radiotherapy days). In patients who previously received pelvic radiotherapy in the form of long-course CRT (50–50.4 Gy) or short-course radiotherapy (25 Gy) for the primary tumour, CRT was delivered with a cumulative dose of 30–30.6 Gy, again usually with concomitant capecitabine. From 2012 onwards, selected patients with extensive disease (invasion of adjacent organs, pelvic sidewall, sacral bone, and/or vascular invasion) received induction chemotherapy (ICT) before CRT. From 2016 onwards, ICT became standard of care until the end of the study interval. 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 tolerance of the chemotherapy, one or two additional cycles were given. Adjuvant chemotherapy was not standard of care and was not offered to any patient.

## Surgery

Surgery was performed 8–14 weeks after the final cycle of CRT, generally consisting of *en bloc* resection of the tumour including involved pelvic organs and structures to achieve clear surgical margins. The procedures were categorized as: restorative rectal resection with reanastomosis; abdominoperineal resection; 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, 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 at a dose of 10–15 Gy to the area at risk (a location where the chance of a positive resection margin was deemed high by the surgeon and radiation oncologist, based on a combination of preoperative imaging and perioperative findings).

## Pathology

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

## Statistical analysis

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 are reported as median (i.q.r. or 95 per cent c.i.) and categorical data as counts with percentages. Group comparisons were performed using the  $\chi^2$  test, Fisher exact test, or Mann–Whitney *U* test, as appropriate.

Survival rates were calculated using the Kaplan–Meier method and comparisons between groups made using the log rank test. As patients with a pCR 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 of this variable was undertaken to calculate HRs. A Cox proportional hazards model was used to examine the influence of pCR on oncological outcomes. Multivariable logistic regression analysis was performed to identify predictors of pCR, using associated factors in univariable logistic regression ( $P < 0.100$ ). Potential confounders of pCR were tested for each variable separately.

Two-sided  $P < 0.050$  was considered statistically significant. All statistical analyses were carried out using SPSS® version 29.0 for Windows® (IBM, Armonk, NY, USA).

## Results

### Patient characteristics

A total of 345 patients underwent surgery with curative intent for LRRC, of whom 51 (15 per cent) had a pCR. Patient and tumour characteristics for patients with and without a pCR were comparable with respect to the rectal recurrence ([Table 1](#)) and rectal primary ([Table S1](#)). Median follow-up was 36 (i.q.r. 16–60) months.

### Type of neoadjuvant treatment

Most patients received neoadjuvant CRT (35.5 per cent long-course, 61.6 per cent reirradiation). Some 129 patients (37.4 per cent) also received ICT, of whom 30 had ICT in combination with long-course CRT, and 99 received ICT in combination with reirradiation. The median interval between the last radiotherapy fraction and surgery was 11.0 (i.q.r. 9.0–13.0) weeks for patients undergoing long-course CRT, compared with 11.0 (9.0–13.5) weeks for those having reirradiation ( $P = 0.124$ ).

Of the 30 patients who received ICT preceding long-course CRT, 9 patients had a pCR. Of the 99 patients who received ICT followed by reirradiation, 17 patients had a pCR. Of the 90 patients receiving only long-course CRT, 15 patients had a pCR. Of the 111 patients who received chemoreirradiation only, 10 patients had a pCR ([Table 2](#)). In univariable logistic regression analysis, ICT and long-course CRT were significantly associated with a pCR ([Table 3](#)).

### Oncological outcomes

The 3-year OS rate was 77 per cent in patients with a pCR, in comparison with 51.1 per cent in those without a pCR (HR 0.41, 95 per cent c.i. 0.26 to 0.63;  $P < 0.001$ ) ([Fig. 1](#)). The 1- and 3-year DFS rates were 78 and 56 per cent respectively in patients with, compared with 55.9 and 26.1 per cent in those without a pCR (HR 0.39, 0.24 to 0.61;  $P < 0.001$ ). The 1- and 3-year LRFS rates were 95 and 82 per cent respectively in patients with a pCR, compared with 71.9 and 44.4 per cent in patients without a pCR (HR 0.21, 0.10 to 0.43;  $P < 0.001$ ). Within 3 years, 37 per cent of patients with a pCR developed distant metastases, compared

**Table 1 Patient and tumour characteristics in patients with and without a pCR**

	pCR (n = 51)	No pCR (n = 294)	Total (n = 345)	P‡
<b>Patient characteristics</b>				
Age (years), mean (s.d.)	64.5 (9.4)	64.6 (9.7)	64.6 (9.6)	0.957§
Sex ratio (M : F)	36 : 15	194 : 100	230 : 115	0.520
ASA fitness grade				0.031
I	3 (6.3)	25 (9.1)	28 (8.6)	
II	31 (64.6)	215 (77.9)	246 (75.9)	
III	14 (29.2)	35 (12.7)	49 (15.1)	
IV	0 (0)	1 (0.4)	1 (0.3)	
<b>Primary tumour characteristics</b>				
Primary origin				0.873
Sigmoid	5 (9.8)	31 (10.5)	36 (10.4)	
Rectum	46 (90.2)	263 (89.5)	309 (89.6)	
Primary pathological tumour category				0.407
pT0–2	12 (26.7)	53 (21.1)	65 (22.0)	
pT3–4	33 (73.3)	198 (78.9)	231 (78.0)	
Primary pathological nodal status				0.138
pN0	17 (37.8)	123 (49.8)	104 (47.9)	
pN+	28 (62.2)	124 (50.2)	152 (52.1)	
<b>Treatment characteristics of local recurrence</b>				
No. of lesions				0.535
1	36 (83.7)	234 (88.3)	270 (87.7)	
2	5 (11.6)	18 (6.8)	23 (7.5)	
≥3	2 (4.7)	13 (4.9)	15 (4.9)	
Size of largest lesion (mm), median (i.q.r.)	40.0 (21–57)	42.0 (30–61)	42.0 (29–60.8)	0.321§
Interval between radiotherapy and surgery (weeks), median (i.q.r.)	11 (9–13)	11 (9–13)	11 (9–13)	0.456§
Main surgical procedure				0.068
Resection with reanastomosis	18 (35.3)	56 (19.0)	74 (21.4)	
Abdominoperineal resection	19 (37.3)	119 (40.5)	138 (40.0)	
Tumour resection NOS	6 (11.8)	44 (15.0)	50 (14.5)	
Total pelvic exenteration	8 (15.7)	71 (24.1)	79 (22.9)	
Additional resection: sacrum, partial or complete	12 (33.3)	89 (37.4)	101 (36.9)	0.692
Additional resection: bladder				0.777
Complete	6 (11.8)	45 (15.3)	51 (14.8)	
Partial	10 (19.6)	51 (17.3)	61 (17.7)	
Additional resection: uterus*				0.366
Uterus	0 (0)	9 (10.0)	8 (8.7)	
Uterus with adnexa	5 (38.5)	23 (25.6)	28 (27.2)	
Additional resection: vagina*				0.837
Partial without reconstruction	3 (23.1)	24 (26.4)	27 (26.0)	
Resection with reconstruction	3 (23.1)	15 (16.5)	18 (17.3)	
Additional resection: prostate†				0.483
Partial	1 (3.7)	16 (9.2)	17 (8.5)	
Complete	2 (7.4)	20 (11.5)	22 (10.9)	
Additional resection: vesicles‡				0.834
Unilateral	5 (18.5)	26 (14.9)	31 (15.4)	
Bilateral	6 (22.2)	35 (20.1)	41 (20.4)	
Intraoperative radiotherapy	44 (86.3)	257 (87.4)	301 (87.2)	0.822
Complications (Clavien–Dindo grade)				0.872
None	14 (27.5)	86 (29.4)	100 (29.1)	
I–II	22 (43.1)	115 (39.2)	137 (39.8)	
III–V	15 (29.4)	92 (31.4)	107 (31.1)	

Values are n (%) unless otherwise specified. \*Women only; †men only. NOS, not otherwise specified. ‡ $\chi^2$  or Fisher's exact test, except §Mann–Whitney U test.

**Table 2 Patients with and without a pCR stratified by type of neoadjuvant treatment**

	ICT + CRT (n = 30)	ICT + reirradiation (n = 99)	CRT alone (n = 90)	Reirradiation alone (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)
Follow-up (months), median (i.q.r.)	37.0 (23.5–49.2)	29.6 (15.0–50.1)	44.2 (22.4–85.5)	37.9 (14.9–63.1)

Values are n (%) unless otherwise specified. \*Fifteen patients received no radiotherapy. ICT, induction chemotherapy; CRT, long-course chemoradiotherapy.

with 54.3 per cent of those without a pCR (HR 0.50, 0.30 to 0.85;  $P < 0.001$ ).

Looking specifically at local control during follow-up, 20 of the 51 patients with a pCR developed recurrent disease, of whom only

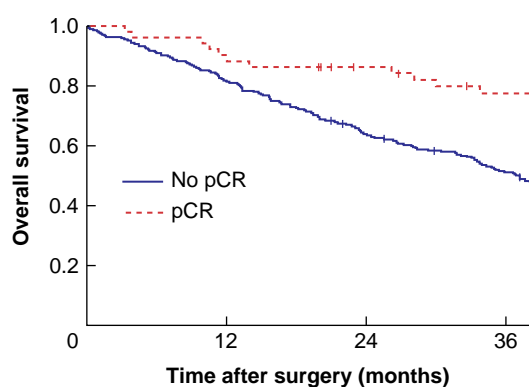
4 had a solitary local re-recurrence without distant metastasis. Of these four patients, two developed a re-recurrence in the same field as the recurrent tumour, and two developed a multifocal re-recurrence. Of the 16 patients who developed distant

Table 3 Logistic regression analysis of factors associated with a pCR

	Univariable regression		Multivariable regression	
	HR	P	HR	P
<b>No. of lesions</b>				
1	1.00 (reference)			
> 1	1.47 (0.60, 3.58)	0.399		
<b>Neoadjuvant induction chemotherapy</b>				
No	1.00 (reference)		1.00 (reference)	
Yes	1.74 (0.96, 3.17)	0.069	2.115 (1.13, 3.97)	0.020
<b>Neoadjuvant (chemo)radiotherapy</b>				
Reirradiation (30 Gy)	1.00 (reference)		1.00 (reference)	
Long-course chemoradiotherapy (45–50 Gy)	1.68 (0.92, 3.06)	0.092	2.04 (1.08, 3.84)	0.027
<b>Consolidation chemotherapy</b>				
No	1.00 (reference)			
Yes	1.06 (0.30, 3.77)	0.930		

Values in parentheses are 95% confidence intervals.

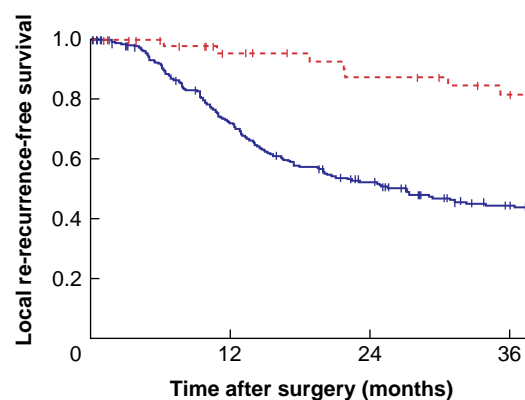
a Overall survival



No. at risk

	0	12	24	36
No pCR	294	236	181	137
pCR	51	45	40	34

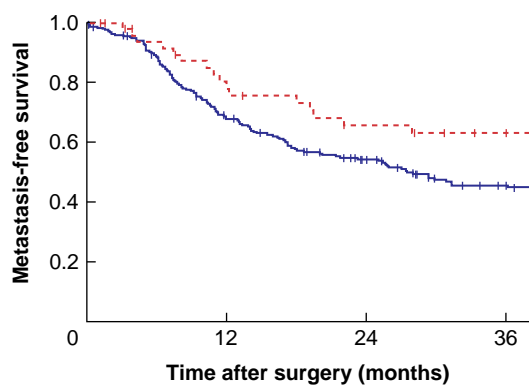
b Local re-recurrence-free survival



No. at risk

	0	12	24	36
No pCR	294	172	104	68
pCR	51	39	32	26

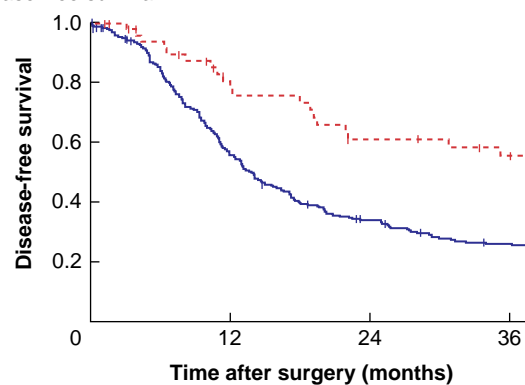
c Metastasis-free survival



No. at risk

	0	12	24	36
No pCR	294	161	103	71
pCR	51	33	26	20

d Disease-free survival



No. at risk

	0	12	24	36
No pCR	294	143	80	56
pCR	51	33	24	19

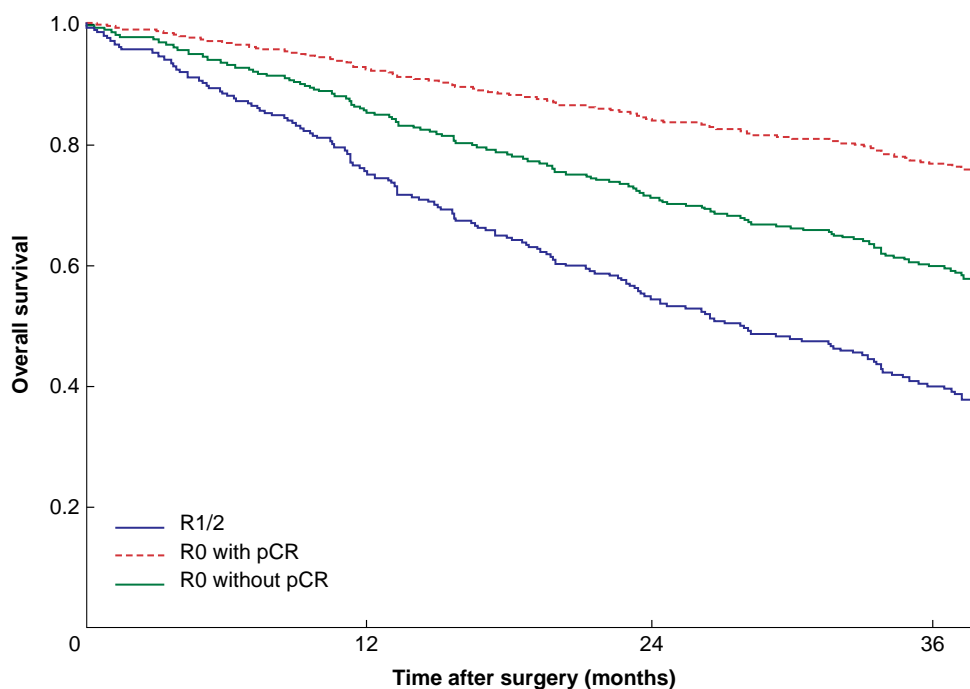
**Fig. 1** Kaplan-Meier analysis of oncological outcomes in patients with and without a pCR

a Overall, b local re-recurrence-free, c metastasis-free, and d disease-free survival. a  $P < 0.001$ , b  $P < 0.001$ , c  $P = 0.008$ , d  $P < 0.001$  (log rank test).

metastases, seven patients had pulmonary metastases and four patients had hepatic metastases.

A radical resection with microscopically clear margins (R0 resection) was achieved in 226 patients (65.5 per cent), of whom 51 (23 per cent) had a pCR. The 3-year OS, LRFs, and MFS rates

among patients with an R0 resection were significantly better than those of patients without a radical resection (R1/2) (respectively 61.9 versus 41.3 per cent,  $P < 0.001$ ; 63.7 versus 23.1 per cent,  $P < 0.001$ ; and 57.8 versus 30.7 per cent,  $P < 0.001$ ). The HR for OS in patients with an R0 compared with R1/2



**Fig. 2** Cox regression analysis of overall survival in relation to completeness of resection and pCR

R1/2: HR 1.00 (reference); R0 resection with pCR: HR 0.29 (95% c.i. 0.18 to 0.45),  $P < 0.001$ ; R0 resection without pCR: HR 0.56 (0.43 to 0.74),  $P < 0.001$ .

resection was 0.49 (95 per cent c.i. 0.38 to 0.63;  $P < 0.001$ ). The 3-year OS rate for patients with a pCR (and R0 resection by definition) was higher than that for the total group with an R0 resection, with or without a pCR (77.4 versus 61.9 per cent). The same applied to LRFS (81.6 versus 63.7 per cent) and MFS (63.3 versus 57.8 per cent). In Cox regression analysis, a variable comprising three groups was analysed: R1/2 resection, R0 with pCR, and R0 without pCR. The HR for OS was 0.56 (0.43 to 0.74;  $P < 0.001$ ) for patients with an R0 resection without a pCR versus patients with an R1/2 resection. For patients with an R0 resection with a pCR, the HR for OS was 0.29 (0.18 to 0.45;  $P < 0.001$ ) compared with patients who had an R1/2 resection (Fig. 2).

## Discussion

In this study, patients with LRRC who developed a pCR after neoadjuvant treatment had superior OS, DFS, LRFS, and MFS to patients without a pCR. The OS of such patients was also higher than that of the whole group of patients with an R0 resection, comprising both patients with and without a 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 of survival<sup>17</sup>. The pursuit of R0 resection, however, leads to extensive surgical procedures being performed, such as large multivisceral 'beyond TME' resections, *en bloc* sacrectomy, total pelvic exenteration, and hemipelvectomy. These major surgical procedures are associated with postoperative complications, functional disability, and impaired quality of life<sup>7,8,18–21</sup>. Furthermore, an R0 resection is achieved in only 30–65 per cent of these patients, and the OS of patients treated curatively for LRRC remains disappointing, with a 5-year rate of 30 per cent regardless of treatment strategy<sup>22,23</sup>. Moreover, even in the case of an increasing R0 resection rate, it is doubtful that OS will continue to improve<sup>23</sup>.

In the search of ways to improve the R0 resection rate, an important prognostic factor for oncological outcomes seems to have been disregarded: the biological behaviour of the tumour<sup>24</sup>. 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 metastasize despite local treatment<sup>24</sup>. 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<sup>15,25,26</sup>.

The OS, LRFS, and MFS rates of patients with a pCR were superior to those of patients with an R0 resection in this study. A statistical comparison of patients with a pCR versus those with an R0 resection was not appropriate, as patients with a pCR have an R0 resection by default. Looking at survival data for patients with a pCR versus those for all patients with an R0 resection, patients with a pCR appeared 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. 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 no longer make a difference and only result in more morbidity, without improving survival. Based on the present results, it is debatable whether achieving a pCR could not be a legitimate goal too.

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<sup>10,16,27</sup>. Tumour downstaging may result in less extensive surgical procedures in order to achieve an R0 resection. Surgical procedures could be postponed, allowing time for observation of the natural behaviour of the tumour, and thus avoiding upfront debilitating surgical procedures in patients who will present with metastases shortly after<sup>23,26</sup>. Although a pCR is still relatively rare in patients who

have undergone radiotherapy for the primary tumour, pCR rates seem to have increased owing to intensification of neoadjuvant treatment, and may become a significant factor in treatment decisions in the future. Ultimately, because local re-recurrences were very rare in patients with a pCR in the present study, a watch-and-wait strategy in patients with a cCR may be an appealing treatment option in the future. In LARC, watch-and-wait approaches have proven to be safe and result in oncological outcomes similar to those of surgical resection<sup>14,28,29</sup>. These findings are difficult to translate directly from LARC to LRRC, as differences in tumour biology are to be expected. Moreover, in the event of a suspected cCR in LRRC, surveillance in a watch-and-wait approach will be less straightforward because of altered anatomy and often the inability to undertake endoscopic follow-up. Therefore, comparison of repeated high-quality imaging would be the way forward. In two recently published studies from the authors' centre<sup>30,31</sup>, the response after neoadjuvant treatment on imaging was analysed and compared with the pathological response. These studies showed that response evaluation was indeed more challenging in LRRC than in LARC. For radiological assessment with MRI, there was fair-to-moderate agreement between a good clinical response and good pathological response. With a sensitivity of 46 per cent and a specificity of 99 per cent, these results seem comparable to those in the literature on response evaluation in LARC<sup>30</sup>. This implies that, in the event of a cCR on MRI, it could be safe to explore watch-and-wait strategies in selected patients in centres with dedicated radiologists specializing 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 the ability to predict a pCR and therefore aid in appropriate patient selection<sup>32,33</sup>.

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

In this study, treatment with ICT and long-course CRT was significantly associated with the achievement of a pCR. This could imply two things. Patients able to receive both options may have had more favourable tumour biology, because no neoadjuvant treatment was given to the primary rectal cancer and selection of therapy-resistant clones did not occur. It could, however, also be hypothesized that such tumours have a better outcome as they are treated more aggressively. Owing 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 RCTs that are currently recruiting, the PelvEx II<sup>34</sup> and GRECCAR 15<sup>35</sup> trials. These trials will provide prospective data on the efficacy of neoadjuvant treatment in regard to the achievement of R0 resection, but also with regard to the achievement of a pCR, compliance with therapy, toxicity due to different treatment regimens, and oncological outcomes.

This study showed that patients who developed a pCR after neoadjuvant treatment for LRRC had excellent OS and a very

low re-recurrence rate compared with 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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## Author contributions

Stefi Nordkamp (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing—original draft, Writing—review & editing), Floor Piqueur (Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing—review & editing), Kim van den Berg (Conceptualization, Investigation, Visualization, Writing—review & editing), Jip Tolenaar (Conceptualization, Investigation, Supervision), Irene van Hellemond (Investigation, Writing—review & editing), Geert-Jan Creemers (Conceptualization, Investigation, Writing—review & editing), Mark Roef (Investigation, Writing—review & editing), Ineke van Lijnschoten (Investigation, Validation, Writing—review & editing), Jeltsje Cnossen (Investigation, Writing—review & editing), Grard Nieuwenhuijzen (Investigation, Writing—review & editing), Johanne Bloemen (Conceptualization, Supervision), Liën Coolen (Conceptualization, Validation), Joost Nederend (Conceptualization, Validation, Writing—review & editing), Heike Peulen (Conceptualization, Writing—review & editing), Harm Rutten (Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization, Writing—review & editing), and Jacobus Burger (Conceptualization, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing—review & editing).

## Disclosure

The authors declare no conflict of interest.

## Supplementary material

Supplementary material is available at *BJS* online.

## Data availability

The data are available from the corresponding author upon reasonable request.

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