Maastricht University

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

Citation for published version (APA):

Nordkamp, S., Piqeur, F., van den Berg, K., Tolenaar, J. L., van Hellemond, I. E. G., Creemers, G.-J., Roef, M., van Lijnschoten, G., Cnossen, J. S., Nieuwenhuijzen, G. A. P., Bloemen, J. G., Coolen, L., Nederend, J., Peulen, H. M. U., Rutten, H. J. T., & Burger, J. W. A. (2023). Locally recurrent rectal cancer: Oncological outcomes for patients with a pathological complete response after neoadjuvant therapy. *British Journal of Surgery*, *110*(8), 950-957. https://doi.org/10.1093/bjs/znad094

Document status and date:
Published: 01/08/2023

DOI:
10.1093/bjs/znad094

Document Version:
Publisher's PDF, also known as Version of record

Document license:
Taverne

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy
If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Download date: 08 May. 2024

OXFORD

BJS, 2023, **110**, 950–957
https://doi.org/10.1093/bjs/znad094
Advance Access Publication Date: 27 May 2023
Original Article

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

Stefi Nordkamp[1,2,*], Floor Piqeur[3,4], Kim van den Berg[5], Jip L. Tolenaar[1], Irene E. G. van Hellemond[5], Geert-Jan Creemers[5], Mark Roef[6], Gesina van Lijnschoten[7], Jeltsje S. Cnossen[3], Grard A. P. Nieuwenhuijzen[1], Johanne G. Bloemen[1], Liën Coolen[8], Joost Nederend[8], Heike M. U. Peulen[3], Harm J. T. Rutten[1,2] and Jacobus W. A. Burger[1]

[1]Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands
[2]Faculty of Health, Medicine and Life Sciences, GROW School for Oncology and Reproduction, Maastricht University, Maastricht, the Netherlands
[3]Department of Radiation Oncology, Catharina Hospital, Eindhoven, the Netherlands
[4]Department of Radiation Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands
[5]Department of Medical Oncology, Catharina Hospital, Eindhoven, the Netherlands
[6]Department of Nuclear Medicine, Catharina Hospital, Eindhoven, the Netherlands
[7]Department of Pathology, Eurofin PAMM, Catharina Hospital, Eindhoven, the Netherlands
[8]Department of Radiology, Catharina Hospital, Eindhoven, the Netherlands

Correspondence to: Stefi Nordkamp, Department of Surgery, Catharina Hospital, Michelangelolaan 2, 5623 EJ, Eindhoven, the Netherlands (e-mail: stefi.nordkamp@catharinaziekenhuis.nl)

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 (LRRC) remain poor[1–5]. 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 treament[4,6–10].

Although the value of neoadjuvant downstaging in LRRC has yet to be determined, neoadjuvant treatment in locally advanced rectal cancer (LARC) has led to an increased rate of pCR[11,12]. Oncological outcomes of patients with a pCR in LARC are significantly better than those in patients without a pCR[13]. These beneficial outcomes have resulted in less extensive surgical procedures and allowed 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 correlation similar to that in LARC exists between outcome and pCR in LRRC[10,16]. However, as most patients with LRRC often received neoadjuvant treatment for the 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

Patients

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 studied retrospectively. The diagnosis of LRRC was based on MRI of the pelvis and thoracoabdominal CT, after which all patients were

Received: January 19, 2023. **Revised:** March 11, 2023. **Accepted:** March 21, 2023
© The Author(s) 2023. Published by Oxford University Press on behalf of BJS Society Ltd. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com

Downloaded from https://academic.oup.com/bjs/article/110/8/950/7181206 by Rijksuniversiteit Limburg user on 29 February 2024

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^2 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 χ^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

Downloaded from https://academic.oup.com/bjs/article/110/8/950/7181206 by Rijksuniversiteit Limburg user on 29 February 2024

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

	pCR (*n* = 51)	No pCR (*n* = 294)	Total (*n* = 345)	P‡
Patient characteristics				
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)	
Primary tumour characteristics				
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)	
Treatment characteristics of local recurrence				
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. ‡χ^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

Downloaded from https://academic.oup.com/bjs/article/110/8/950/7181206 by Rijksuniversiteit Limburg user on 29 February 2024

Table 3 Logistic regression analysis of factors associated with a pCR

	Univariable regression		Multivariable regression	
	HR	P	HR	P
No. of lesions				
1	1.00 (reference)			
> 1	1.47 (0.60, 3.58)	0.399		
Neoadjuvant induction chemotherapy				
No	1.00 (reference)		1.00 (reference)	
Yes	1.74 (0.96, 3.17)	0.069	2.115 (1.13, 3.97)	0.020
Neoadjuvant (chemo)radiotherapy				
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
Consolidation chemotherapy				
No	1.00 (reference)			
Yes	1.06 (0.30, 3.77)	0.930		

Values in parentheses are 95% confidence intervals.

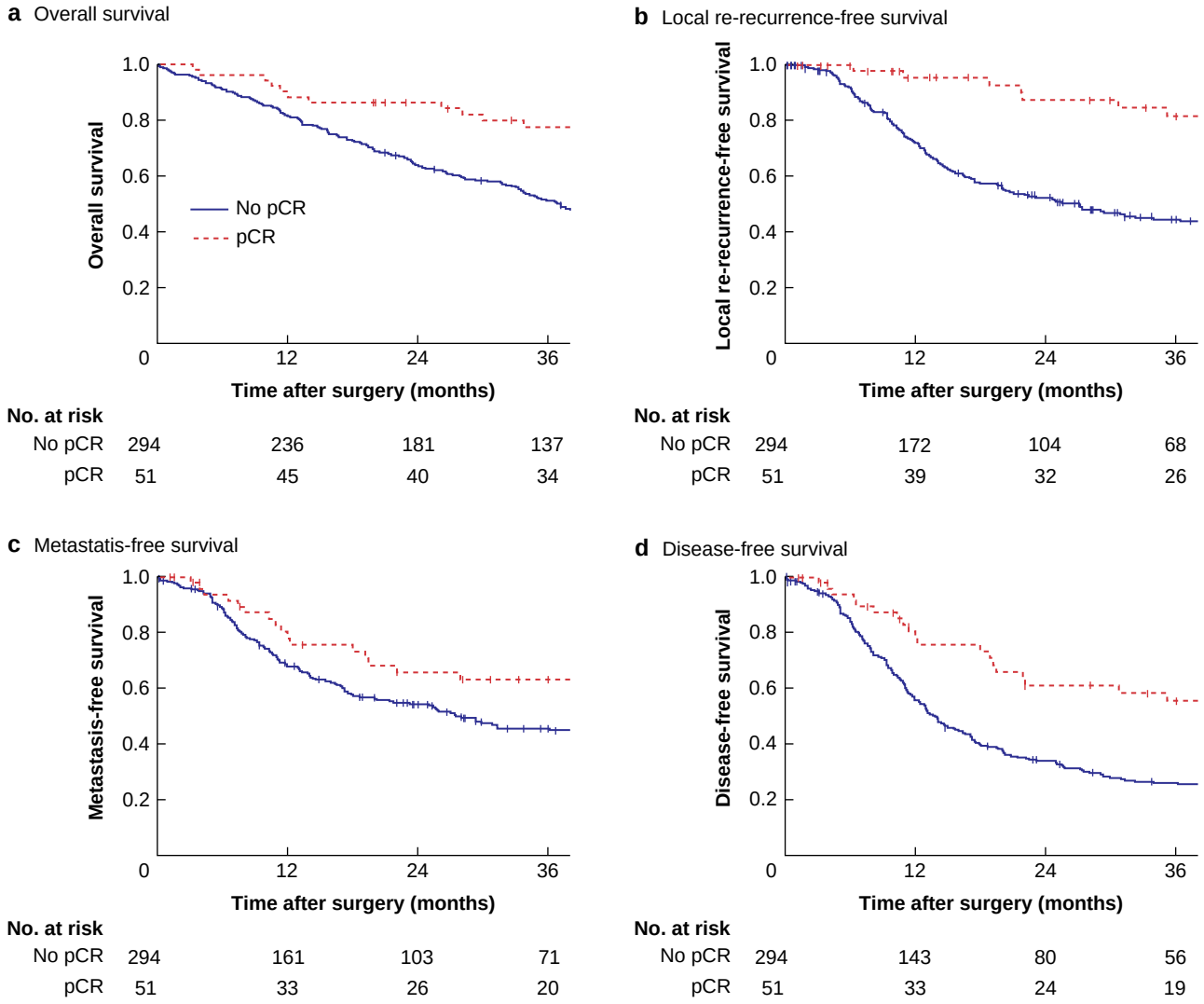

Fig. 1 Kaplan–Meier analysis of oncological outcomes in patients with and without a pCR

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

Downloaded from https://academic.oup.com/bjs/article/110/8/950/7181206 by Rijksuniversiteit Limburg user on 29 February 2024

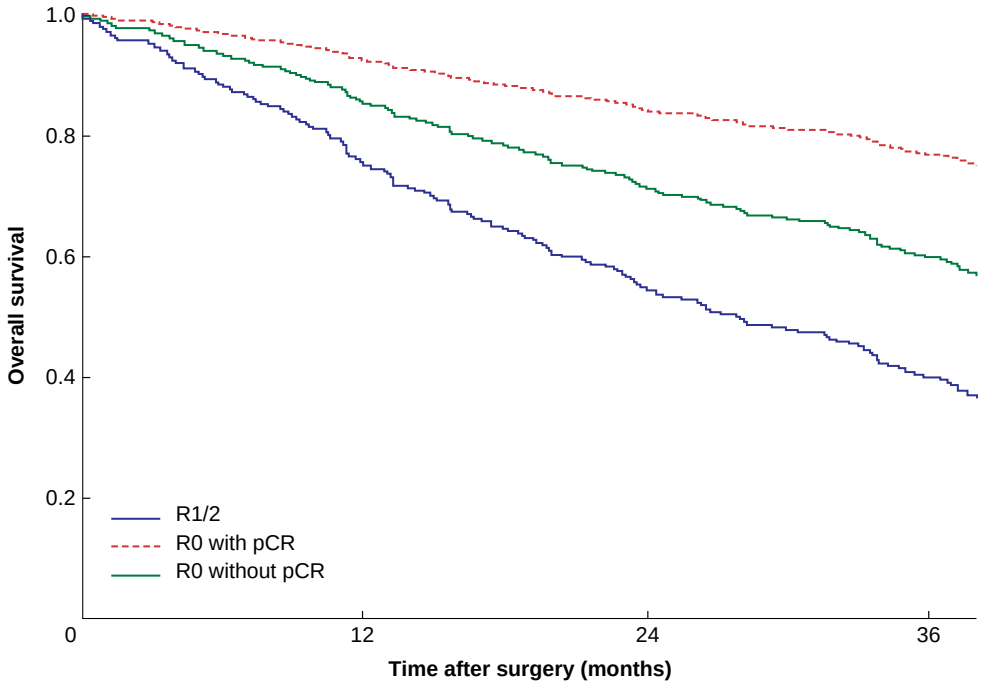

Fig. 2 Cox regression analysis of overall survival in relation to completeness of resection and pCR

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[17]. 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[7,8,18–21]. 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[22,23]. Moreover, even in the case of an increasing R0 resection rate, it is doubtful that OS will continue to improve[23].

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[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 metastasize 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 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[10,16,27]. 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[23,26]. Although a pCR is still relatively rare in patients who

Downloaded from https://academic.oup.com/bjs/article/110/8/950/7181206 by Rijksuniversiteit Limburg user on 29 February 2024

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[14,28,29]. These findings are difficult 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[30,31], 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[30]. 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[32,33].

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[10,16,27].

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[34] and GRECCAR 15[35] 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.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author contributions

Stefi Nordkamp (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing—original draft, Writing—review & editing), Floor Piqeur (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.

References

1. Tanis PJ, Doeksen A, Van Lanschot JJB. Intentionally curative treatment of locally recurrent rectal cancer: a systematic review. *Can J Surg* 2013;**56**:135–144
2. Van Der Meij W, Rombouts AJM, Bremers AJA, De Wilt JHW, Rutten H. Treatment of locally recurrent rectal carcinoma in previously (chemo)irradiated patients: a review. *Dis Colon Rectum* 2016;**59**:148–156
3. Hagemans JAW, van Rees JM, Alberda WJ, Rothbarth J, Verhoef C, Nuyttens JJME *et al.* Locally recurrent rectal cancer; long-term outcome of curative surgical and non-surgical treatment of 447 consecutive patients in a tertiary referral centre. *Eur J Surg Oncol* 2020;**46**:448–454
4. Nielsen M, Rasmussen P, Laurberg SS, Pedersen B, Hagemann-Madsen R, Lindegaard J *et al.* Early and late

Downloaded from https://academic.oup.com/bjs/article/110/8/950/7181206 by Rijksuniversiteit Limburg user on 29 February 2024

outcomes of surgery for locally recurrent rectal cancer: a prospective 10-year study in the total mesorectal excision era. *Ann Surg Oncol* 2015;**22**:2677–2684
5. van den Brink M, Stiggelbout AM, van den Hout WB, Kievit J, Klein Kranenbarg E, Marijnen CAM *et al.* Clinical nature and prognosis of locally recurrent rectal cancer after total mesorectal excision with or without preoperative radiotherapy. *J Clin Oncol* 2004;**22**:3958–3964
6. Harris CA, Dixon L, Pascoe R, Dobbs BR, Frampton CM, Frizelle FA *et al.* The outcomes and patterns of treatment failure after surgery for locally recurrent rectal cancer. *Ann Surg* 2016;**264**:323–329
7. Solomon MJ. Redefining the boundaries of advanced pelvic oncology surgery. *Br J Surg* 2021;**108**:453–455
8. Denost Q, Rullier E, Maillou-Martinaud H, Tuech JJ, Ghouti L, Cotte E *et al.* International variation in managing locally advanced or recurrent rectal cancer: prospective benchmark analysis. *Br J Surg* 2020;**107**:1846–1854
9. Romesser PB, Crane CH. Chemo-re-irradiation and salvage surgery for locally recurrent rectal cancer. *Ann Surg Oncol* 2021;**28**:4769–4771
10. Voogt ELK, Van Zoggel DMGI, Kusters M, Nieuwenhuijzen GAP, Bloemen JG, Peulen HMU *et al.* Improved outcomes for responders after treatment with induction chemotherapy and chemo(re)irradiation for locally recurrent rectal cancer. *Ann Surg Oncol* 2020;**27**:3503–3513
11. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EM *et al.* Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) *versus* preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;**22**:29–42
12. Conroy T, Bosset JF, Etienne PL, Rio E, François É, Mesgouez-Nebout N *et al.* Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;**22**:702–715
13. Maas M, Nelemans J, Marañón G, Madrid S, Glynne-Jones R, Maas M *et al.* Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 2010;**11**:835–879
14. van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL *et al.* Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet* 2018;**391**:2537–2545
15. Custers PA, Hupkens BJP, Grotenhuis BA, Kuhlmann KFD, Breukink SO, Beets GL *et al.* Selected stage IV rectal cancer patients managed by the watch-and-wait approach after pelvic radiotherapy: a good alternative to total mesorectal excision surgery? *Colorectal Dis* 2022;**24**:401–410
16. Sorrentino L, Daveri E, Sabella G, Battaglia L, Milione M, Rivoltini L *et al.* Pathologic complete response after neoadjuvant chemotherapy/(re)chemoradiation for pelvic relapse of rectal cancer undergoing complex pelvic surgery: more frequent than expected? *Int J Colorectal Dis* 2022;**37**:2257–2261
17. Guren MG, Undseth C, Rekstad BL, Brændengen M, Dueland S, Spindler KLG *et al.* Reirradiation of locally recurrent rectal cancer: a systematic review. *Radiother Oncol* 2014;**113**:151–157
18. Forsmo HM, Pfeffer F, Rasdal A, Sintonen H, Körner H, Erichsen C. Pre- and postoperative stoma education and guidance within an enhanced recovery after surgery (ERAS) programme reduces length of hospital stay in colorectal surgery. *Int J Surg* 2016;**36**:121–126
19. Thaysen HV, Jess P, Laurberg S. Health-related quality of life after surgery for primary advanced rectal cancer and recurrent rectal cancer: a review. *Colorectal Dis* 2012;**14**:797–803
20. Harji DP, Griffiths B, Velikova G, Sagar PM, Brown J. Systematic review of health-related quality of life issues in locally recurrent rectal cancer. *J Surg Oncol* 2015;**111**:431–438
21. Rogers AC, Jenkins JT, Rasheed S, Malietzis G, Burns EM, Kontovounisios C *et al.* Towards standardisation of technique for *en bloc* sacrectomy for locally advanced and recurrent rectal cancer. *J Clin Med* 2021;**10**:4921
22. Fadel MG, Ahmed M, Malietzis G, Pellino G, Rasheed S, Brown G *et al.* Oncological outcomes of multimodality treatment for patients undergoing surgery for locally recurrent rectal cancer: a systematic review. *Cancer Treat Rev* 2022;**109**:102419
23. Nordkamp S, Voogt ELK, van Zoggel DMGI, Martling A, Holm T, Jansson Palmer G *et al.* Locally recurrent rectal cancer: oncological outcomes with different treatment strategies in two tertiary referral units. *Br J Surg* 2022;**109**:623–631
24. Cady B. Basic principles in surgical oncology. *Arch Surg* 1997;**132**:338–346
25. Baird DLH, Kontovounisios C, Simillis C, Pellino G, Rasheed S, Tekkis PP. Factors associated with metachronous metastases and survival in locally advanced and recurrent rectal cancer. *BJS Open* 2020;**4**:1172–1179
26. Voogt ELK, van Zoggel DMGI, Kusters M, Nieuwenhuijzen GAP, Cnossen JS, Creemers GJ *et al.* Impact of a history of metastases or synchronous metastases on survival in patients with locally recurrent rectal cancer. *Colorectal Dis* 2021;**23**:1120–1131
27. van Zoggel DMGI, Bosman SJ, Nieuwenhuijzen GAP, Kusters M, Cnossen JS, Creemers GJ *et al.* Preliminary results of a cohort study of induction chemotherapy-based treatment for locally recurrent rectal cancer. *Br J Surg* 2018;**105**:447–452
28. Renehan AG, Malcomson L, Emsley R, Gollins S, Maw A, Myint AS *et al.* Watch-and-wait approach *versus* surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. *Lancet Oncol* 2016;**17**:174–183
29. Fernandez LM, Figueiredo NL, Sao Juliao GP, Beets GL, van der Valk MJM, Bahadoer RR *et al.* Conditional recurrence-free survival of clinical complete responders managed by watch and wait after neoadjuvant chemoradiotherapy for rectal cancer in the International Watch & Wait Database: a retrospective, international, multicentre registry study. *Lancet Oncol* 2021;**22**:43–50
30. Voogt E, Nordkamp S, van Zoggel D, Daniëls-Gooszen A, Nieuwenhuijzen G, Bloemen JG *et al.* MRI tumour regression grade in locally recurrent rectal cancer. *BJS Open* 2022;**6**:zrac033
31. van Zoggel DMGI, Voogt ELK, van Lijnschoten IG, Cnossen JS, Creemers GJ, Nederend J *et al.* Metabolic positron emission tomography/CT response after induction chemotherapy and chemo(re)irradiation is associated with higher negative resection margin rate in patients with locally recurrent rectal cancer. *Colorectal Dis* 2021;**24**:59–67
32. Tie J, Cohen JD, Wang Y, Li L, Christie M, Simons K *et al.* Serial circulating tumour DNA analysis during multimodality treatment of locally advanced rectal cancer: a prospective biomarker study. *Gut* 2019;**68**:663–671

Downloaded from https://academic.oup.com/bjs/article/110/8/950/7181206 by Rijksuniversiteit Limburg user on 29 February 2024

33. Schraa SJ, van Rooijen KL, Koopman M, Vink GR, Fijneman RJA. Cell-free circulating (tumor) DNA before surgery as a prognostic factor in non-metastatic colorectal cancer: a systematic review. *Cancers (Basel)* 2022;**14**:2218
34. Voogt E, Nordkamp S, Rutten H, Burger J; PelvEx Collaborative. Induction chemotherapy followed by chemoradiotherapy *versus* chemoradiotherapy alone as neoadjuvant treatment for locally recurrent rectal cancer: study protocol of a multicentre, open-label, parallel-arms, randomized controlled study (PelvEx II). *BJS Open* 2021;**5**:zrab029
35. Denost Q, Frison E, Salut C, Sitta R, Rullier A, Harji D *et al.* A phase III randomized trial evaluating chemotherapy followed by pelvic reirradiation *versus* chemotherapy alone as preoperative treatment for locally recurrent rectal cancer—GRECCAR 15 trial protocol. *Colorectal Dis* 2021;**23**: 1909–1918

Downloaded from https://academic.oup.com/bjs/article/110/8/950/7181206 by Rijksuniversiteit Limburg user on 29 February 2024