Improved Outcomes for Responders After Treatment with Induction Chemotherapy and Chemo(re)irradiation for Locally Recurrent Rectal Cancer

Citation for published version (APA):

Voogt, E. L. K., van Zoggel, D. M. G., Kusters, M., Nieuwenhuijzen, G. A. P., Bloemen, J. G., Peulen, H. M. U., Creemers, G. J. M., van Lijnschoten, G., Nederend, J., Roef, M. J., Burger, J. W. A., & Rutten, H. J. T. (2020). Improved Outcomes for Responders After Treatment with Induction Chemotherapy and Chemo(re)irradiation for Locally Recurrent Rectal Cancer. *Annals of Surgical Oncology*, 27(9), 3503-3513. <https://doi.org/10.1245/s10434-020-08362-4>

Document status and date:

Published: 01/09/2020

DOI:

[10.1245/s10434-020-08362-4](https://doi.org/10.1245/s10434-020-08362-4)

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: 26 Apr. 2023

Improved Outcomes for Responders After Treatment with Induction Chemotherapy and Chemo(re)irradiation for Locally Recurrent Rectal Cancer

E. L. K. Voogt, MD¹, D. M. G. I. van Zoggel, MD², M. Kusters, MD³, G. A. P. Nieuwenhuijzen, MD¹, J. G. Bloemen, MD¹, H. M. U. Peulen, MD⁴, G. J. M. Creemers, MD⁵, G. van Lijnschoten, MD⁶, J. Nederend, MD⁷, M. J. Roef, MD⁸, J. W. A. Burger, MD¹, and H. J. T. Rutten, MD^{1,9}

¹Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands; ²Department of Surgery, Isala, Zwolle, The Netherlands; ³Department of Surgery, Amsterdam University Medical Centres, Location VUmc, Amsterdam, The Netherlands; ⁴Department of Radiotherapy, Catharina Hospital, Eindhoven, The Netherlands; ⁵Department of Medical Oncology, Catharina Hospital, Eindhoven, The Netherlands; ⁶Pathology Department, PAMM Laboratory for Pathology and Medical Microbiology, Eindhoven, The Netherlands; ⁷Department of Radiology, Catharina Hospital, Eindhoven, The Netherlands; ⁸Department of Nuclear Medicine, Catharina Hospital, Eindhoven, The Netherlands; ⁹GROW School for Oncology and Developmental Biology, Maastricht University, Maastricht, The Netherlands

ABSTRACT

Background. Despite improvements in the multimodality treatment for patients with locally recurrent rectal cancer (LRRC), oncological outcomes remain poor. This study evaluated the effect of induction chemotherapy and subsequent chemo(re)irradiation on the pathologic response and the rate of resections with clear margins (R0 resection) in relation to long-term oncological outcomes.

Methods. All consecutive patients with LRRC treated in the Catharina Hospital Eindhoven who underwent a resection after treatment with induction chemotherapy and subsequent chemo(re)irradiation between January 2010 and December 2018 were retrospectively reviewed. Induction chemotherapy consisted of CAPOX/FOLFOX. Endpoints were pathologic response, resection margin and overall survival (OS), disease free survival (DFS), local recurrence free survival (LRFS), and metastasis free survival (MFS).

Results. A pathologic complete response was observed in 22 patients (17%), a “good” response (Mandard 2–3) in 74 patients (56%), and a “poor” response (Mandard 4–5) in

36 patients (27%). An R0 resection was obtained in 83 patients (63%). The degree of pathologic response was linearly correlated with the R0 resection rate ($p = 0.026$). In patients without synchronous metastases, pathologic response was an independent predictor for LRFS, MFS, and DFS ($p = 0.004$, $p = 0.003$, and $p = 0.024$, respectively), whereas R0 resection was an independent predictor for LRFS and OS ($p = 0.020$ and $p = 0.028$, respectively). **Conclusions.** Induction chemotherapy in addition to neoadjuvant chemo(re)irradiation is a promising treatment strategy for patients with LRRC with high pathologic response rates that translate into improved oncological outcomes, especially when an R0 resection has been achieved.

Over the past decades, there have been significant improvements in the treatment of patients with rectal cancer. Due to the introduction of total mesorectal excision (TME) and the development of neoadjuvant (chemo)radiotherapy, the rate of locally recurrent rectal cancer (LRRC) has decreased from 20–30 to 6–10%.^{1–3} However, patients who develop LRRC remain to have a limited prognosis with 5-year overall survival rates of approximately 30%.^{4–7}

The most important prognostic factor influencing survival after surgery is a clear resection margin (R0 resection).^{1,2,8–11} Achieving an R0 resection is challenging

because of distorted anatomy due to previous TME surgery, the difficult distinction between fibrosis and malignant tissue after radiotherapy, and the ingrowth of the recurrent neoplasm into other structures, such as the adjacent organs, pelvic side wall, and the sacrum. To achieve downsizing of the local recurrence and consequently more R0 resections, neoadjuvant treatment with chemoradiotherapy is recommended.¹² However, a proportion of patients with locally recurrent rectal cancer have already received (chemo)radiotherapy for their primary tumor. Previous studies have shown that in these patients reirradiation with a dose of 30 Gy combined with capecitabine is safe and effective.^{2,8} Alongside an R0 resection, a pathologic complete response (pCR) may be of prognostic value in predicting long-term outcomes for LRRC patients.^{13,14} Despite neoadjuvant treatment with chemo(re)irradiation, R0 resections are achieved in only 60% of cases and pCR rates are low ($\pm 8\%$).^{7,15}

The addition of induction chemotherapy to neoadjuvant chemo(re)irradiation may improve local downsizing and thereby improve the R0 resection and pCR rates. Furthermore, induction chemotherapy may eradicate occult micrometastases. Ultimately, this may improve long-term oncological outcomes. Our preliminary results showed a promising pCR rate with this treatment regimen.¹⁶

The current study evaluated the effect of induction chemotherapy administered prior to neoadjuvant chemo(re)irradiation on the pathologic response and the R0 resection rate in an extended cohort and the predictive value of the pathological response on oncological outcomes.

PATIENTS AND METHODS

Patients

All patients with locally recurrent rectal cancer treated at the Catharina Hospital Eindhoven, a national tertiary referral center for patients with advanced rectal cancer, were prospectively collected in a database. All consecutive patients who underwent a resection between January 2010 and December 2018 after neoadjuvant treatment with induction chemotherapy followed by neoadjuvant radiotherapy or reirradiation with or without concomitant chemotherapy were retrospectively identified and reviewed. From 2010 until 2014, induction chemotherapy was mostly administered to patients with irresectable or marginally resectable disease. From 2015 onward, the administration of induction chemotherapy became more common practice and evolved to the local standard of care in 2016. The decision to administer induction chemotherapy was made during a multidisciplinary tumor (MDT)

board meeting, including experienced surgeons, medical oncologists, radiation oncologists, radiologists, and nuclear medicine specialists. The present study was approved by the medical ethics committee (registration number: W19.031).

Neoadjuvant Treatment Regimen

The general treatment regimen consisted of three cycles of CAPOX (capecitabine and oxaliplatin) or four cycles of FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin). Induction chemotherapy was followed by radiotherapy with concomitant chemotherapy.

Radiotherapy dose depended on whether the patient had received previous radiotherapy. In radiotherapy-naïve patients, full-course radiotherapy was delivered with a cumulative dose of 45–50 Gy in 25 fractions of 1.8–2 Gy. In case of previous radiotherapy, reirradiation consisted of 30–30.6 Gy in 15–17 fractions of 1.8–2 Gy. Concomitant chemotherapy agent was capecitabine (825 mg/m² bid on radiotherapy days).

All patients were assessed for radiological response 2–3 weeks after completing the induction chemotherapy and 4–6 weeks after finishing the subsequent (chemo)radiotherapy. Restaging consisted of a pelvic MRI and a thoracoabdominal CT scan with or without the addition of FDG-PET. All restaging imaging was discussed during the MDT meeting in our tertiary referral center. In case of a radiological good response to induction chemotherapy, consolidation chemotherapy during the waiting time between (chemo)radiotherapy and surgery was considered. Consolidation chemotherapy consisted of one or two cycles of CAPOX or FOLFOX.

Surgery and Pathology

The type of surgery depended on the location of the recurrence and involvement of adjacent structures and was performed by experienced surgical oncologists. In accordance with the type of reconstructions, other specialists, such as a urologist or a plastic surgeon, were consulted. When assessed as necessary and feasible, e.g., when there was tumor adherence or no adequate soft tissue margin for a clear resection margin, intraoperative electron beam radiotherapy (IOERT) was administered in a dose of 10–12.5 Gy.

Synchronous metastases were treated during the waiting time between (chemo)radiotherapy and surgery or after surgery. Treatment consisted of local resection or otherwise local therapy, including radiofrequency ablation, microwave ablation, or stereotactic radiotherapy. Hyperthermic intraperitoneal chemotherapy (HIPEC) with

mitomycin C was administered perioperative in case of limited peritoneal metastases.

Pathologic specimens were revised by a specialized pathologist. Pathologic response was scored according to the Mandard classification.¹⁷ For survival analyses, pathologic response was categorized as “complete” (Mandard 1), “good” (Mandard 2–3), or “poor” response (Mandard 4–5). An R0 resection was defined as a resection without tumor cells in any of the resection margins. An R1 resection was considered a resection with microscopically involved margins, and an R2 resection was considered a gross incomplete resection.

Study Endpoints

Endpoints were pathologic response, resection margin and overall, local recurrence free, metastasis free, and disease free survival, as well as toxicity and complications caused by the treatment regimen. Overall survival (OS) was calculated from the date of start treatment until the date of death from any cause or censored at last follow-up. Local recurrence free survival (LRFS) was calculated from the date of surgery until the date of local recurrence detected by imaging or histology or censored at last follow-up or death. Metastasis free survival (MFS) was calculated from the date of surgery until the date of histologically or radiologically proven distant metastases or censored at last follow-up or death. Disease-free survival (DFS) was calculated from the date of surgery until the date of local recurrence or distant metastases or censored at last follow-up or death. Toxicity was retrospectively scored according to the Common Toxicity Criteria of the National Cancer Institute, and complications were scored according to the Clavien–Dindo classification.^{18,19}

Statistics

Continuous data were reported as median (interquartile range) and categorical as count (percentage). Group comparisons were made using Chi-square or Mann–Whitney *U* test as appropriate. Survival analyses were performed using the (reversed) Kaplan–Meier method and comparisons were made using log-rank test. Multivariable analysis using the Cox proportional hazards model was performed on variables with a $p < 0.1$ on univariable analysis. Two-sided p values < 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 25.0 for Windows (IBM Corp, Armonk, NY).

RESULTS

Patients and Treatment Characteristics

In total, 132 patients with locally recurrent rectal cancer were treated with induction chemotherapy and subsequent (chemo)(re)irradiation and surgery between January 2010 and December 2018. Patient characteristics and characteristics about the primary tumor are presented in Table 1, and Table 2 shows the characteristics of the recurrent tumor. Most patients included had a first recurrence ($N = 116$, 88%). Twenty-nine patients (22%) had a history of metastases at time of diagnosis of the recurrence, and 35 patients were diagnosed with synchronous metastases (27%).

Induction chemotherapy consisted of CAPOX in 97 patients (73%). In 22 of 97 patients, bevacizumab was added to the induction chemotherapy. Ten patients (8%) received FOLFOX. Twenty-five (19%) patients received another chemotherapy regimen (mainly FOLFIRI). In the majority of patients, induction chemotherapy was followed by (chemo)reirradiation (82%). Consolidation chemotherapy was administered in 15% of patients.

Pathological Response, Resection Margin, and Oncological Outcomes

A pathologic complete response was observed in 22 of 132 patients (17%), Mandard 2 in 21 (16%), Mandard 3 in 53 (40%), Mandard 4 in 31 (24%), and Mandard 5 in 5 (4%) patients. A clear resection margin was achieved in 83 patients (63%), an R1 resection in 46 patients (35%), and 3 patients had an R2 resection (2%).

Median OS, DFS, LRFS, and MFS for all patients were 47, 12, 18, and 18 months, respectively. OS, DFS, LRFS, and MFS were 52, 13, 21, and 26 months for patients without synchronous metastases ($n = 97$) and 27, 7, 11, and 8 months for patients with synchronous metastases ($n = 35$) [95% confidence interval (CI) 0.792–2.968, $p = 0.205$; 95% CI 1.900–4.967, $p < 0.001$; 95% CI 0.833–2.777, $p = 0.173$; 95% CI 2.061–6.306, $p < 0.001$, respectively]. Due to the differences in oncological outcomes between these two groups, the results of patients with and without synchronous metastases will be discussed separately in the following sections.

Patients Without Synchronous Metastases

A complete pathologic response was observed in 18 patients (19%), a “good” response in 56 patients (Mandard 2–3, 58%), and a “poor” response in 23 patients (Mandard 4–5, 24%).

TABLE 1 Baseline and primary tumor characteristics

	Total (<i>N</i> = 132) <i>N</i> (%)
Gender	
Female	37 (28)
Male	95 (72)
Age (yr) ^a	
Median [IQR]	65 [58–71]
ASA ^a	
I	3 (2)
II	107 (81)
III	22 (17)
Tumor stage ^b	
T2	11 (8)
T3	92 (70)
T4	27 (21)
Nodal stage ^c	
N0	41 (31)
N1	46 (35)
N2	41 (31)
Neoadjuvant radiotherapy	
None	36 (27)
Radiotherapy	34 (26)
Chemoradiotherapy	62 (47)
Surgical procedure	
Sigmoid resection	18 (14)
LAR	67 (51)
APR	47 (36)
Adjuvant therapy ^d	
None	113 (86)
Chemotherapy	17 (13)
Radiotherapy	3 (2)

IQR interquartile range, *LAR* low anterior resection, *APR* abdominoperineal resection

^aAt time of surgery for recurrent tumor

^bMissing value in *N* = 2

^cMissing value in *N* = 4

^dOne patient received both adjuvant chemotherapy and radiotherapy

Univariable analyses are shown in Table 3. For overall survival, only resection margin remained significant after multivariable analysis ($p = 0.034$, 95% CI 1.059–4.272), with a hazard ratio (HR) of 2.1 for death after an irradical resection. Median survival for patients with an R0 resection was 54 months versus 29 months otherwise. When comparing complete responders with noncomplete responders (Mandard 2–5), multivariable analyses demonstrated a significant improved effect of complete response for OS with a 3-year OS of 92% versus 57% respectively (HR 4.706; $p = 0.045$, 95% CI 1.063–20.833; Fig. 1a, b).

TABLE 2 Characteristics recurrent tumor and treatment

	Total (<i>N</i> = 132) <i>N</i> (%)
Number local recurrence	
First	116 (88)
Second/third	16 (12)
Multifocality	
Yes	27 (20)
No	105 (80)
Lateral involvement	
Yes	69 (52)
No	63 (48)
History of metastases	
Yes	29 (22)
No	103 (78)
Synchronous metastases	
Yes	35 (27)
No	97 (73)
Type metastasis ^a	
Liver	13
Lung	10
Inguinal lymph nodes	2
Peritoneal	10
Other	3
Neoadjuvant radiotherapy	
(Chemo)radiotherapy	24 (18)
(Chemo)reirradiation	108 (82)
Surgical procedure	
LAR	14 (11)
APR	16 (12)
Multivisceral resection	50 (38)
Total pelvic exenteration	25 (19)
Resection n.o.s	27 (20)
HIPEC	
Yes	8 (4)
No	124 (96)
IOERT	
Yes	111 (84)
No	21 (16)
Time to recurrence (months) ^b	
Median [IQR]	32 [21–51]
Time radiotherapy-surgery (weeks)	
Median [IQR]	12 [10–14]
Blood loss (ml)	
Median [IQR]	2350 [1225–3500]

LAR low anterior resection, *APR* abdominoperineal resection, *Re-section n.o.s.* resection not otherwise specified, resection recurrence without bowel resection, *HIPEC* hyperthermic intraperitoneal chemotherapy, *IOERT* intraoperative electron beam radiotherapy

^aSome patients had metastases in more than one organ

^bTime between primary surgery and current recurrence

TABLE 3 Univariable analyses for risk factors for distant metastasis, local recurrence, disease free, and overall survival

Variable	Distant metastasis			Local recurrence			Disease-free survival			Overall survival		
	HR	CI	p	HR	CI	p	HR	CI	p	HR	CI	p
Age												
	1.007	0.971–1.044	0.710									
				0.989	0.957–1.021	0.491	0.997	0.970–1.026	0.856	1.013	0.974–1.053	0.514
Gender												
Female	1.00		0.642	1.00		0.349	1.00		0.522	1.00		0.785
Male	1.192	0.567–2.507		1.378	0.705–2.693		1.208	0.677–2.157		0.904	0.437–1.870	
ASA												
1–2	1.00		0.926	1.00		0.730	1.00		0.285	1.00		0.898
3	1.050	0.373–2.957		0.835	0.299–2.329		0.575	0.209–1.585		1.081	0.328–3.558	
T stage primary												
2	1.00		0.644	1.00		0.650	1.00		0.985	1.00		0.746
3	0.718	0.297–1.735		1.459	0.520–4.098		1.072	0.484–2.375		1.193	0.419–3.398	
4	0.576	0.175–1.892		1.770	0.531–5.903		1.049	0.389–2.827		0.767	0.170–3.466	
N stage primary												
0	1.00		0.792	1.00		0.034	1.00		0.150	1.00		0.366
1	1.018	0.477–2.171		0.726	0.361–1.461		0.842	0.459–1.542		0.744	0.332–1.668	
2	1.304	0.603–2.818		1.827	0.928–3.607		1.536	0.839–2.810		1.311	0.613–3.022	
Neoadjuvant RTx primary												
None	1.00		0.696	1.00		0.043	1.00		0.055	1.00		0.171
5 × 5 Gy radiotherapy	1.191	0.492–2.888		1.539	0.637–3.718		1.765	0.834–3.738		1.216	0.466–3.177	
(Chemo)radiotherapy	1.401	0.635–3.095		2.558	1.162–5.629		2.319	1.165–4.613		2.061	0.890–4.771	
Type of surgery primary												
Sigmoid resection	1.00		0.156	1.00		0.837	1.00		0.309	1.00		0.093
LAR	1.678	0.489–5.749		1.334	0.511–3.484		1.857	0.721–4.779		0.694	0.248–1.938	
APR	2.695	0.798–9.101		1.311	0.488–3.521		2.113	0.811–5.501		1.519	0.555–4.1607	
Adjuvant chemotherapy												
No	1.00		0.756	1.00		0.637	1.00		0.792	1.00		0.914
Yes	1.148	0.481–2.739		0.840	0.408–1.731		0.916	0.478–1.757		1.049	0.438–2.516	
Number local recurrence												
1st	1.00		0.241	1.00		0.917	1.00		0.462	1.00		0.588
2nd/3rd	0.241	0.152–1.606		0.952	0.376–2.411		0.729	0.314–1.692		1.302	0.501–3.383	
History metastases												
No	1.00		0.833	1.00		0.734	1.00		0.398	1.00		0.416
Yes	0.833	0.382–2.170		1.141	0.534–2.441		1.325	0.690–2.543		0.610	0.185–2.010	
Neoadjuvant radiotherapy												
			0.535			0.182			0.312			0.376

TABLE 3 continued

Variable	Distant metastasis			Local recurrence			Disease-free survival			Overall survival		
	HR	CI	p	HR	CI	p	HR	CI	p	HR	CI	p
(Chemo)radiotherapy	1.00			1.00			1.00			1.00		
(Chemo)reirradiation	0.782	0.360–1.700		1.877	0.744–4.733		1.466	0.698–3.076		1.533	0.595–3.946	
Type of surgery			0.797			0.890			0.763			0.833
LAR	1.00			1.00			1.00			1.00		
APR	0.571	0.104–3.134		1.702	0.421–6.889		1.679	0.482–5.846		0.533	0.058–4.900	
Multivisceral resection	1.145	0.393–3.331		1.451	0.508–4.143		1.662	0.651–4.244		1.228	0.417–3.617	
Resection n.o.s	1.198	0.383–3.745		1.404	0.460–4.282		1.536	0.567–4.158		1.301	0.406–4.168	
IOERT			0.848			0.866			0.542			0.682
No	1.00			1.00			1.00			1.00		
Yes	0.918	0.384–2.193		1.077	0.456–2.544		1.277	0.581–2.808		0.682	0.283–1.645	
Resection margin			0.112			< 0.001			< 0.001			< 0.001
R0	1.00			1.00			1.00			1.00		
R1/2	1.678	0.887–3.176		3.595	2.042–6.330		2.541	1.524–4.236		3.271	1.699–6.298	
Response			0.003			< 0.001			0.002			0.012
pCR	1.00			1.00			1.00			1.00		
Good response	1.689	0.627–4.552		2.893	1.112–7.526		2.278	1.053–4.927		6.236	1.461–26.624	
Poor response	4.361	1.585–12.000		6.754	2.467–18.494		4.296	1.869–9.876		9.501	2.124–42.497	

RTx radiotherapy, LAR low anterior resection, APR abdominoperineal resection, Resection n.o.s. resection not otherwise specified, resection recurrence without bowel resection, pCR pathologic complete response

FIG. 1 Pathologic response to treatment (a) and achievement of R0 resection (b) are independent prognostic variables after multivariable analysis. Combination of these variables helps to fine-tune prognosis

(c). OS overall survival; MFS metastasis-free survival; LRFS local recurrence-free survival. *Only for complete versus noncomplete responders significant ($p = 0.045$)

For disease free survival, only response remained significant after multivariable analysis (HR 2.070; 95% CI 0.904–4.736 for “good” responders and HR 3.525; 95% CI 1.388–8.951 for “poor” responders, $p = 0.024$). Median DFS for complete responders, good responders, and poor responders was 35, 14, and 11 months, respectively.

For local recurrence free survival, response (HR 2.232 95% CI 0.787–6.328 for “good” responders and HR 5.684; 95% CI 1.776–18.191 for “poor” responders, $p = 0.004$),

resection margin (HR 2.104; 95% CI 1.125–3.933; $p = 0.020$), and lymph node status of the primary tumor (HR 0.816; 95% CI 0.388–1.719 for N1 and HR 2.156; 95% CI 1.001–4.640 for N2, $p = 0.036$) remained significant after multivariable analysis (Fig. 1a, b).

For metastasis free survival, only response was significant after univariable analyses ($p = 0.003$). Hazard ratios were 2.0 and 5.0 for good and poor responders compared with complete responders. Median MFS for complete

FIG. 2 Significant linear relation between increasing Mandard score and probability of a positive resection margin. *R0* resection with clear margins; *R1/2* resection with involved margins

responders was not reached (3-year MFS 75%): 45 months for good responders, and 11 months for poor responders (Fig. 1a, b).

For all oncological outcome parameters, both response and complete resection were the most independent predictive variables. By definition, all complete responders have an *R0* resection. However, there also is a linear relation between increasing response and the rate of *R0* resections ($p = 0.026$, Fig. 2). Therefore, both variables were combined to see whether outcome prediction can be fine-tuned and may help to make treatment decisions. Five new categories were analyzed: pCR (automatically *R0*), good response and *R0* resection, poor response and *R0* resection, good response and *R1/R2* (*R+*) resection, and finally, poor response and *R+* resection. In Fig. 1c, the outcome of combining these variables is shown. Complete responders consistently demonstrate an excellent outcome for OS, MFS, and LRFS. In addition, patients with a good response and *R0* resection ($n = 45$) show an outcome almost as good as patients with a pCR for all outcome parameters. Poor responders with an *R0* resection ($n = 16$) have a less favorable metastasis free survival compared with good responders with an *R+* resection ($n = 29$). Patients with a poor response and *R0* resection have a similar LRFS compared with patients with a good response but *R+* resection.

Patients with Synchronous Metastases

Patients presenting with LRRC and synchronous metastases had overall a poor oncological outcome. None of the patients had a DFS extending beyond 2 years. An *R0* resection was a prognostic factor for overall survival and local recurrence ($p = 0.033$, HR 0.237, 95% CI 0.063–0.894 and $p = 0.016$, HR 0.236, 95% CI 0.073–0.768, respectively). Median OS was not reached for patients with an *R0* resection (3-year OS 68%) and median OS was

23 months after an irradical resection. Median LRFS was not reached for patients with an *R0* resection (3-year LRFS 72%), and median LRFS was 10 months after an *R+* resection. Median MFS was 8 months irrespective of response to treatment or resection margin.

Toxicity and Complications

Data on toxicity caused by induction chemotherapy were available for 125 of 132 patients. Grade 3–4 toxicity was observed in 12 of 125 patients (10%). No grade 5 toxicity was seen. Details on chemoradiotherapy toxicity were available for 121 of 132 patients. Grade 3–4 toxicity was reported in only 2 of 121 patients (2%), and no grade 5 toxicity was seen.

Postoperatively, the most common complications were ileus/gastroparesis ($n = 31$), urological complications ($n = 21$), pneumonia ($n = 19$), presacral abscess ($n = 17$), urinary tract infection ($n = 14$), and wound infection ($n = 13$). Major postoperative complications (Clavien Dindo ≥ 3) were observed in 41 of 132 patients (31%). There was no in-hospital mortality, but one patient died within 30 days of surgery as she refused further treatment. In the 41 patients with major postoperative complications, there were 46 complications with a Clavien Dindo ≥ 3 of which 34 complications required a surgical reintervention, 10 required an endoscopic/radiological intervention, and 3 required ICU admittance. The type of complications are shown in Table 4.

DISCUSSION

In this study, we observed a 17% pathologic complete response rate in patients with locally recurrent rectal cancer after treatment with induction chemotherapy and

TABLE 4 Complications Clavien–Dindo ≥ 3

	Total $N = 46$
Presacral abscess	13 (28)
Intraabdominal abscess	6 (13)
Urological	8 (17)
Ileus/gastroparesis	4 (9)
Wound infection	3 (7)
Wound dehiscence	3 (7)
Pneumonia	2 (4)
Anastomotic leakage	1 (2)
Colon perforation	1 (2)
Compartment syndrome lower leg	1 (2)
Metabolic acidosis	1 (2)
Other	3 (8)

chemo(re)irradiation resulting in an excellent 3-year overall survival of 92% in these patients. In addition, this study shows pathologic response to be a powerful prognostic variable of improved oncological outcomes in LRRC patients, especially when an R0 resection has been achieved.

Comparing the pathologic complete response rate with the literature is challenging, because data are limited on neoadjuvant treatment strategies for locally recurrent rectal cancer. The administration of induction chemotherapy before chemoradiotherapy has been studied to a greater extent in patients with locally advanced rectal cancer (LARC), although evidence is mainly from retrospective nature or phase II trials. When focusing only on studies that administered either neoadjuvant CAPOX or FOLFOX followed by (chemo)radiotherapy, the results are inconsistent. Some studies showed a rather disappointing pCR rate when comparing their results with the pCR rate after chemoradiotherapy alone as reported in the literature, whereas others demonstrated promising pCR rates ranging between 33 and 40%.^{20–27} The pCR rate in our study is rather low compared with the latter findings in LARC; however, it has to be noted that LRRC has proven to be relatively chemoradio-resistant. Hence, it is to be expected that pCR rates are lower in patients with recurrent disease even if treatment regimens are comparable. The pCR rate of 17% is comparable with pCR rates after chemoradiotherapy for LARC.¹⁵ When comparing our results with previously reported pCR rates in patients with LRRC, our treatment regimen with induction chemotherapy and chemoradiotherapy seems superior to treatment with neoadjuvant chemoradiotherapy alone as pCR rates are 17 versus 4–9% respectively.^{14–16} The current findings are in line with the results published earlier by our group in which a 17% pCR rate was observed after treatment with induction chemotherapy followed by reirradiation.¹⁶ Another study performed by our group demonstrated a 31% pCR rate, but it has to be noted that in this study only lateral recurrences were included, and these recurrences may represent a different etiology.²⁸

The 92% 3-year OS for patients with a pCR in this study is superior to the survival rates reported for patients with LRRC after treatment with solely neoadjuvant (chemo)radiotherapy. For R0 resections, 3-year OS varies between 40 and 55%.^{1,10,11,29,30} Data on survival for LRRC patients with a pCR are limited. Wiig et al. showed a 80% 3-year survival for LRRC after pCR.¹⁴ Our preliminary results also showed a 3-year survival of 92% for patients with a pCR.¹⁶ Notably, more than half of complete responders had recurrent disease at 3 years.

Although patients with a pCR have excellent oncological outcomes, patients with a good response (Mandard 2–3) also showed improved outcomes. There have been no

previous reports about the prognostic value of response on neoadjuvant treatment in patients with locally recurrent rectal cancer. There have been several studies assessing the prognostic value of tumor regression in patients with LARC. Most studies showed that the extent of response was a significant independent prognostic factor for long-term oncological outcomes, which supports the findings in our study.^{31–35} Together with the observation that there is a significant linear relation between the degree of response and the R0 resection rate, this underlines the necessity of adequate neoadjuvant treatment in patients with LRRC. Potential bias caused by whether or not patients received neoadjuvant treatment for the primary tumor was investigated by chi-square (data not shown) and showed no correlation, suggesting that induction chemotherapy is sufficient for tumor downstaging regardless of prior treatment. Future research to establish whether a correlation exists between radiological and pathologic response could help to identify patients in whom a different treatment approach may be justified.

The R0 resection rate in this study was 63%, which is consistent compared with the findings in the literature after treatment with neoadjuvant chemoradiotherapy alone. However, in this study 21% of the included patients were considered irresectable at primary staging.

For patients with synchronous metastases the story seems different. LRRC patients with synchronous metastases clearly have a more aggressive biological behavior of their tumor, which is characterized by rapid progression and decreased disease-free survival. For these patients, a different approach and different counseling may be indicated.

This study is limited by its retrospective character. Many patients underwent their preoperative treatment in the referring hospitals and therefore data on toxicity of treatment are not complete. Besides, drop-out rates during neoadjuvant treatment were not available as progressive disease under induction chemotherapy may have occurred and these patients have never been referred back for surgery. Nevertheless, the available data on toxicity implicates that treatment was well tolerated. Furthermore, neoadjuvant treatment regimen combining induction chemotherapy with chemoradiotherapy resulted in major postoperative morbidity in 32% of the patients. This percentage is comparable to the literature, suggesting that the addition of induction chemotherapy does not lead to more postoperative complications when comparing it with the current standard treatment of neoadjuvant chemoradiotherapy.^{4,36}

The retrospective character of this study also leads to heterogeneity regarding oncological history and manifestation of the local recurrence of the patients included in this study. This study is however a good representation of the clinical practice and is, to our knowledge, the largest series

to date of patients treated with induction chemotherapy and subsequent chemo(re)irradiation for locally recurrent rectal cancer.

CONCLUSIONS

This study shows a high pCR rate in patients with LRRC after treatment with induction chemotherapy and chemo(re)irradiation, translating into exceptional outcomes in these patients. In addition, response to neoadjuvant treatment is a powerful predictor of improved oncological outcome, underlining the importance of achieving a good response. To determine whether the addition of induction chemotherapy to chemo(re)irradiation in the treatment of LRRC improves outcomes for curative treatment of LRRC in general, a randomized controlled trial is warranted.

ACKNOWLEDGEMENT The authors declare no competing interests and received no funding/support for this study or in the preparation of the manuscript.

FUNDING None.

DISCLOSURE The authors declare that they have no conflict of interest.

REFERENCES

1. Bosman SJ, Holman FA, Nieuwenhuijzen GAP, Martijn H, Creemers GJ, Rutten HJT. Feasibility of reirradiation in the treatment of locally recurrent rectal cancer. *Br J Surg*. 2014;101(10):1280–9. <https://doi.org/10.1002/bjs.9569>.
2. Van Der Meij W, Rombouts AJM, Rutten H, Bremers AJA, De Wilt JHW. Treatment of locally recurrent rectal carcinoma in previously (chemo)irradiated patients: a review. *Dis Colon Rectum*. 2016;59(2):148–56. <https://doi.org/10.1097/DCR.0000000000000547>.
3. Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345(9):638–46.
4. Nielsen MB, Laurberg S, Holm T. Current management of locally recurrent rectal cancer. *Color Dis*. 2011;13(7):732–42. <https://doi.org/10.1111/j.1463-1318.2009.02167.x>.
5. Kusters M, Dresen RC, Martijn H, et al. Radicality of resection and survival after multimodality treatment is influenced by sub-site of locally recurrent rectal cancer. *Int J Radiat Oncol Biol Phys*. 2009;75(5):1444–9. <https://doi.org/10.1016/j.ijrobp.2009.01.015>.
6. Westberg K, Palmer G, Hjern F, Johansson H, Holm T, Martling A. Management and prognosis of locally recurrent rectal cancer: a national population-based study. *Eur J Surg Oncol*. 2018;44(1):100–7. <https://doi.org/10.1016/j.ejso.2017.11.013>.
7. Nielsen M, Rasmussen P, Pedersen B, Hagemann-Madsen R, Lindegaard J, Laurberg S. Early and late outcomes of surgery for locally recurrent rectal cancer: a prospective 10-year study in the total mesorectal excision era. *Ann Surg Oncol*. 2015;22(8):2677–84. <https://doi.org/10.1245/s10434-014-4317-y>.
8. Valentini V, Morganti AG, Gambacorta MA, et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: a multicentric phase II study. *Int J Radiat Oncol Biol Phys*. 2006. <https://doi.org/10.1016/j.ijrobp.2005.09.017>.
9. Dresen RC, Gosens MJ, Martijn H, et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. *Ann Surg Oncol*. 2008. <https://doi.org/10.1245/s10434-008-9896-z>.
10. Alberda WJ, Verhoef C, Schipper MEI, et al. The importance of a minimal tumor-free resection margin in locally recurrent rectal cancer. *Dis Colon Rectum*. 2015. <https://doi.org/10.1097/DCR.0000000000000388>.
11. Westberg K, Palmer G, Hjern F, et al. Population-based study of factors predicting treatment intention in patients with locally recurrent rectal cancer. *Br J Surg*. 2017;104(13):1866–1873. <https://doi.org/10.1002/bjs.10645>.
12. Tekkis P, Road F. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. *Br J Surg*. 2013;100(8):1009–14. <https://doi.org/10.1002/bjs.9192>.
13. Vermaas M, Ferenschild FTJ, Nuytens JJME, et al. Preoperative radiotherapy improves outcome in recurrent rectal cancer. *Dis Colon Rectum*. 2005;48(5):918–28. <https://doi.org/10.1007/s10350-004-0891-6>.
14. Wiig JN, Larsen SG, Dueland S, Giercksky KE. Clinical outcome in patients with complete pathologic response (pT0) to preoperative irradiation/chemo-irradiation operated for locally advanced or locally recurrent rectal cancer. *J Surg Oncol*. 2005;92:70–5. <https://doi.org/10.1002/jso.20340>.
15. Yu SKT, Bhangu A, Tait DM, Tekkis P, Wotherspoon A, Brown G. Chemoradiotherapy response in recurrent rectal cancer. *Cancer Med*. 2014;3(1):111–7. <https://doi.org/10.1002/cam4.169>.
16. van Zoggel DMGI, Bosman SJ, Kusters M, et al. Preliminary results of a cohort study of induction chemotherapy-based treatment for locally recurrent rectal cancer. *Br J Surg*. 2018;105:447–52. <https://doi.org/10.1002/bjs.10694>.
17. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer*. 1994;73(11):2680–6.
18. Common Terminology Criteria for Adverse Events (CTCAE) v.5.0. National Cancer Institute. 2009. https://ctep.cancer.gov/prTOCOLDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. Accessed 9 Dec 2019.
19. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205–13.
20. Fernández-Martos C, Pericay C, Aparicio J, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, I. *J Clin Oncol*. 2010;28(5):859–65. <https://doi.org/10.1200/JCO.2009.25.8541>.
21. Chau I, Brown G, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. *J Clin Oncol*. 2006;24(4):668–74. <https://doi.org/10.1200/JCO.2005.04.4875>.
22. Chua YJ, Barbachano Y, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a

- phase 2 trial. *Lancet Oncol.* 2010;11(3):241–8. [https://doi.org/10.1016/S1470-2045\(09\)70381-X](https://doi.org/10.1016/S1470-2045(09)70381-X).
23. Yu X, Wang QX, Xiao WW, et al. Neoadjuvant oxaliplatin and capecitabine combined with bevacizumab plus radiotherapy for locally advanced rectal cancer: results of a single-institute phase II study. *Cancer Commun (London, England)*. 2018;38(1):24. <https://doi.org/10.1186/s40880-018-0294-z>.
 24. Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. *J Natl Compr Canc Netw.* 2014;12(4):513–9.
 25. Garcia-Aguilar J, Chow OS, Smith DD, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. *Lancet Oncol.* 2015;16(8):957–66. [https://doi.org/10.1016/S1470-2045\(15\)00004-2](https://doi.org/10.1016/S1470-2045(15)00004-2).
 26. Perez K, Safran H, Sikov W, et al. Complete neoadjuvant treatment for rectal cancer: The Brown University Oncology Group CONTRE study. *Am J Clin Oncol Cancer Clin Trials.* 2017;40(3):283–7. <https://doi.org/10.1097/COC.000000000000149>.
 27. Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. *JAMA Oncol.* 2018;4(6). <https://doi.org/10.1001/jamaoncol.2018.0071>.
 28. Kusters M, Bosman SJ, Van Zoggel DMGI, et al. Local recurrence in the lateral lymph node compartment: improved outcomes with induction chemotherapy combined with multimodality treatment. *Ann Surg Oncol.* 2016;23(6):1883–9. <https://doi.org/10.1245/s10434-016-5098-2>.
 29. PelvEx Collaborative. Factors affecting outcomes following pelvic exenteration for locally recurrent rectal cancer. *Br J Surg.* 2018;105:650–7. <https://doi.org/10.1002/bjs.10734>.
 30. Tanis PJ, Doeksen A, Van Lanschot JJB. Intentionally curative treatment of locally recurrent rectal cancer: a systematic review. *Can J Surg.* 2013;56(2):135–44. <https://doi.org/10.1503/cjs.025911>.
 31. Vecchio FM, Valentini V, Minsky BD, et al. The relationship of pathologic tumor regression grade (TRG) and outcomes after preoperative therapy in rectal cancer. *Int J Radiat Oncol Biol Phys.* 2005;62(3):752–60. <https://doi.org/10.1016/j.ijrobp.2004.11.017>.
 32. Peng YF, Yu WD, Pan H Da, et al. Tumor regression grades: Potential outcome predictor of locally advanced rectal adenocarcinoma after preoperative radiotherapy. *World J Gastroenterol.* 2015;21(6):1851–6. <https://doi.org/10.3748/wjg.v21.i6.1851>.
 33. Mace AG, Pai RK, Stocchi L, Kalady MF. American joint committee on cancer and college of American pathologists regression grade: a new prognostic factor in rectal cancer. *Dis Colon Rectum.* 2015;58(1):32–44. <https://doi.org/10.1097/DCR.0000000000000266>.
 34. Mancini R, Pattaro G, Diodoro MG, et al. Tumor regression grade after neoadjuvant chemoradiation and surgery for low rectal cancer evaluated by multiple correspondence analysis: 10 years as minimum follow-up. *Clin Colorectal Cancer.* 2018;17(1):e13–9. <https://doi.org/10.1016/j.clcc.2017.06.004>.
 35. Rödel C, Martus P, Papadopoulos T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J Clin Oncol.* 2005;23(34):8688–96. <https://doi.org/10.1200/JCO.2005.02.1329>.
 36. PelvEx Collaborative. Surgical and survival outcomes following pelvic exenteration for locally advanced primary rectal cancer. *Ann Surg.* 2017. <https://doi.org/10.1097/SLA.0000000000002528>.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.