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Locally recurrent rectal cancer and distant metastases: is there still a chance ofcure?

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ABSTRACT

Introduction: Patients with locally recurrent rectal cancer (LRRC) generally have poor prognosis, especially those who have (a history of) distant metastases. The aim of this study was to investigate the impact of distant metastases on oncological outcomes in LRRC patients undergoing curative treatment.
Methods: Consecutive patients with surgically treated LRRC between 2005 and 2019 in two tertiary referral hospitals were retrospectively analysed. Oncological survival of patients without distant metastases were compared with outcomes of patients with synchronous distant metastases with the primary tumour, patients with distant metastases in the primary-recurrence interval, and patients with synchronous LRRC distant metastases.
Results: A total of 535 LRRC patients were analysed, of whom 398 (74%) had no (history of) metastases, 22 (4%) had synchronous metastases with the primary tumour, 44 (8%) had metachronous metastases, and 71 (13%) had synchronous LRRC metastases. Patients with synchronous LRRC metastases had worse survival compared to patients without metastases (adjusted hazard ratio: 1.56 [1.15–2.12]), whilst survival of patients with synchronous primary metastases and metachronous metastases of the primary tumour was similar as those patients who had no metastases. In LRRC patients who had metastases in primary-recurrence interval, patients with early metachronous metastases had better disease-free survival as patients with late metachronous metastases (3-year disease-free survival: 48% vs 22%, $p = 0.039$).
Conclusion: LRRC patients with synchronous distant metastases undergoing curative surgery have relatively poor prognosis. However, LRRC patients with a history of distant metastases diagnosed nearby the primary tumour have comparable (oncological) survival as LRRC patients without distant metastases.

1. Introduction

Locally recurrent rectal cancer (LRRC) occurs in 6–10% of patients who are curatively treated for primary rectal cancer [1–3]. LRRC significantly impacts quality of life and has poor prognosis, but can be cured in selected cases [4–6]. Curative treatment for LRRC, consisting of neoadjuvant treatment and surgery, is associated with considerable morbidity [7–9]. Due to previous radiation and surgery, resection of LRRC is technically challenging and unlike primary rectal cancer, local recurrences frequently present with ingrowth in adjacent organs such as the bladder and reproductive organs, making multivisceral resections necessary. Generally, treatment with curative intent is only considered when a radical resection of the pelvic recurrence, along with possible resectable metastatic disease, can be obtained [10,11].

Over the last decades, novel treatment approaches such as preoperative (chemo-)radiotherapy and total mesorectal excision (TME) for primary rectal cancer have reduced local recurrence rates, but that also means that the biological behaviour of the tumours that do recur is different [12–14]. Nowadays, patients tend to have more synchronous distant metastases with LRRC, with a reported incidence of 36%–74% [12,15,16]. Due to the poor prognosis of these patients, treatment for patients with synchronous metastases is usually with palliative intent, aiming at delaying

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progression of disease and prolonging survival. Uncertainty remains whether long-term disease-free survival with curative intended treatment can be achieved in at least some of these patients, and how these patients should be selected. For example, it has been suggested that the presence of indeterminate lung nodules in LRRC does not influence outcomes, and that these patients should not be excluded from surgery based on the presence of these lesions alone [17].

Evidence that local treatment of distant metastases can improve outcomes for LRRC with synchronous metastases is limited, but some small retrospective series have demonstrated good outcomes in selected LRRC patients [18,19]. A recent retrospective cohort study demonstrated that LRRC patients with a history of curatively treated distant metastases have similar oncological outcomes compared to patients without metastases, implying that curative treatment should not be excluded solely based on formerly diagnosed metastases [20]. Conversely, patients who present with synchronous distant metastases along with the pelvic recurrence have a poor prognosis. These findings suggest that the moment of metastases could impact LRRC patients' prognosis, and it might be of interest to further explore the metastatic history of curatively treated LRRC patients.

The primary aim of this study is to investigate the impact of distant metastases on oncological outcomes in patients with locally recurrent rectal cancer undergoing curative treatment. The primary aim of this study is to investigate the impact of distant metastases on oncological outcomes in patients with locally recurrent rectal cancer undergoing curative treatment. The hypothesis of this research is that patients presenting with LRRC and synchronous metastases, as well as patients with late metachronous metastases after primary tumour treatment, have poor prognosis.

2. Methods

2.1. Patients

All consecutive patients with surgically treated LRRC between 2005 and 2019 in two tertiary referral hospitals, Catharina Hospital (CHE) and Erasmus MC Cancer Institute (EMC), were retrospectively analysed. Patients treated for local re-recurrence were excluded. LRRC was defined as local recurrence in the pelvic area after curative treatment of rectal or rectosigmoidal adenocarcinoma. Diagnosis of LRRC had to be confirmed by either a biopsy or a combination of imaging and raised serum carcinoembryonic antigen (CEA) levels. All patients were discussed in a dedicated LRRC multidisciplinary team (MDT), including expert surgeons, radiologists, radiation oncologists and medical oncologists. Patient demographics, clinicopathological disease characteristics and outcome measures were obtained by review of hospital medical records, from referral hospitals and from general practitioners.

Patients were categorised in four groups: 1) LRRC patients without a history of distant metastases; 2) LRRC patients after curatively treated primary rectal cancer with synchronous distant metastases; 3) LRRC patients with a history of metachronous distant metastases, diagnosed between the primary rectal cancer and the local recurrence; and 4) LRRC patients with synchronous distant metastases diagnosed simultaneous with the local recurrence. Patients with both a history of metastases and synchronous metastases at the moment of LRRC were categorised as having "synchronous LRRC metastases". Patients with both synchronous metastases with the primary rectal cancer and metachronous metastases between primary and LRRC were categorised as having "metachronous metastases". This study was approved by the medical ethics committee of EMC (MEC-2020-0104) and CHE (AW21.067/W21.178).

2.2. Treatment strategy

At the discretion of the MDT, the most preferable treatment strategy was discussed for each individual patient. In general, curative treatment was considered, when a radical resection of the LRRC and local treatment for all distant metastases was considered feasible, taking anticipated downstaging by neoadjuvant therapy into account. Patients with clinical deterioration or progression during neoadjuvant treatment, either local or distant, were usually not considered for LRRC surgery. Palliative treatment (either chemotherapy, radiation therapy, a combination of both, or best supportive of care) was advised in patients with extensive or incurable metastases and/or expected irresectable pelvic recurrences. For example, patients with tumours with extensive ingrowth in adjacent structures (i.e. pelvic bones, neuroforamina, encasement of the ischiadic nerve) without response to treatment were not considered surgical candidates.

Curative treatment in radiotherapy naïve patients included neoadjuvant radiotherapy (44.6–52Gy), usually with the addition of capecitabine as radiosensitiser [21]. Treatment of choice of previously irradiated LRRC patients was (chemo)re-irradiation up to 30Gy [22]. In CHE, induction chemotherapy was administrated before radiation therapy in a part of the patients since 2012. Restaging with thoracic- and abdominal (PET-)CT and pelvic MRI was performed 6-8 weeks after the last fraction of chemoradiation treatment. Patients who were treated with induction chemotherapy were restaged after 3-4 cycles of chemotherapy. In LRRC patients with synchronous metastases, local treatment of distant metastases was usually performed after induction chemotherapy, and before chemoradiation treatment. Patients were then re-discussed in the MDT to assess the treatment response and development of de novo metastases. Depending on the findings patients either continued with curatively intended surgical resection, or in case of progressive disease, treatment was with palliative intent, which did not include palliative resection.

Surgery consisted of low anterior resection (LAR) or abdominoperineal resection (APR), usually combined with an additional resection, extra-anatomical resection of the local recurrence, or multivisceral resection. Multivisceral resection was defined as tumour resection with addition of any other pelvic organ such as the bladder, uterus, vagina, ovaries, prostate, or vesicles. Intraoperative radiotherapy (IORT) was administered in case of clinically suspected or frozen section proven positive margins.

Treatment strategies for patients with synchronous metastases were determined based on the location and extent of the distant metastases. Surgery, radiofrequency ablation, stereotactic radiation, chemotherapy, or a combination were used to treat liver metastases. Lung metastases were treated with metastasectomy or stereotactic radiotherapy, with or without the use of chemotherapy. Metastases were treated before LRRC treatment, between neoadjuvant therapy and surgery, or after the surgical resection of the LRRC. Peritoneal metastases were treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) concurrently with LRRC resection. Usually, inguinal or para-aortic lymph node metastases were resected during LRRC surgery. Follow-up was conducted according to the Dutch colorectal cancer guidelines, and consisted of CEA measurements and thoracic- and abdominal CT imaging. Depending on patient preference, follow-up was done at the referral centre or the referring hospital. The same follow-up schedule, which is according to the Dutch Colorectal Cancer guidelines, was conducted after primary tumour- and LRRC treatment.

2.3. Outcomes

Oncological outcomes were compared between patients with

LRRC in combination with different metastatic patterns, according to the groups described before. Overall survival (OS) was defined as the time between the date of LRRC surgery and the date of death or last follow up. Disease-free survival (DFS) was defined as the time from LRRC surgery to the date of disease recurrence or death, whichever came first. Local recurrence-free survival (LRFS) and metastases-free survival (MFS) were defined as the time between the date of LRRC surgery and the date of local re-recurrence or last follow-up, and the date of diagnosis of distant metastases or last follow-up, respectively.

2.4. Statistics

Continuous data were reported as median (interquartile range or 95% confidence interval) and categorical data were reported as count (percentage). Group and individual comparisons were made using the Chi-square or Mann-Whitney-U-test as appropriate. Survival rates were calculated by the method of Kaplan-Meier and compared with the log-rank test. The Cox regression method was used for univariable and multivariable survival analyses. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 28.0.0.0 and R version 4.2.1 (http://www.r-project.org).

3. Results

Of the 616 curatively treated cases of LRRC in the two referral centres, 535 individual patients who were diagnosed with a first local recurrence were analysed (71 patients with a local re-recurrence were excluded). The majority (n = 398, 74%) of patients had no (history of) distant metastases. A total of 22 patients (4%) had synchronous distant metastases with the primary tumour, 44 patients (8%) had metachronous distant metastases and 71 patients (13%) had synchronous LRRC distant metastases. Eight patients with synchronous LRRC metastases also had metachronous metastases (and were analysed in the synchronous LRRC group). Five patients with metachronous metastases also had primary synchronous metastases (and were analysed in the metachronous metastases group). One patient had metastases at all three time points. Baseline characteristics were shown in Table 1 and details about the LRRC and the subsequent treatment in Table 2. An overview of distant metastases and corresponding treatment details is provided in Table 3.

3.1. Oncological outcomes

Median survival in the cohort was 40 months (95% confidence interval (CI): 36.1–45.0 months). Survival outcomes are shown in Fig. 1. The 3-year OS rate was 57% (95% CI: 53%–62%) in patients without metastases, 55% (95% CI: 37%–80%) in patients with primary synchronous metastases, 61% (95% CI: 48%–77%) in patients with primary metachronous metastases, and 34% (95% CI: 24%–47%) in patients synchronous metastases LRRC (long rank p = 0.021). Disease-free survival, local recurrence-free survival and

Table 1
Baseline characteristics.

		No metastases (n = 398)	Synchronous metastases primary (n = 22)	Metachronous metastases (n = 44)	Synchronous metastases LRRC (n = 71)	p-value
Age (median [IQR])		65.9 [59.0, 72.6]	61.6 [55.2, 69.5]	64.3 [58.5, 69.4]	63.8 [58.5, 70.1]	0.074
Sex (%)	Male	260 (65.3%)	14 (63.6%)	28 (63.6%)	44 (62.0%)	0.954
	Female	138 (34.7%)	8 (36.4%)	16 (36.4%)	27 (38.0%)	
ASA score (%)	1	47 (12.8%)	1 (5.6%)	2 (5.0%)	4 (6.1%)	0.556
	2	267 (72.6%)	13 (72.2%)	29 (72.5%)	48 (72.7%)	
	3	53 (14.4%)	4 (22.2%)	9 (22.5%)	14 (21.2%)	
	4	1 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Induction chemotherapy primary (%)	Yes	8 (2.0%)	5 (22.7%)	3 (6.8%)	4 (5.6%)	<0.001
	No	388 (98.0%)	17 (77.3%)	41 (93.2%)	67 (94.4%)	
(y)pT stage primary (%)	0	2 (0.9%)	1 (5.3%)	0 (0.0%)	1 (1.4%)	0.030
	1	15 (6.4%)	0 (0.0%)	1 (2.3%)	2 (2.8%)	
	2	48 (20.5%)	1 (5.3%)	6 (14.0%)	5 (7.0%)	
	3	131 (56.0%)	11 (57.9%)	32 (74.4%)	46 (64.8%)	
	4	38 (16.2%)	6 (31.6%)	4 (9.3%)	17 (23.9%)	
(y)pN stage primary (%)	0	126 (53.6%)	7 (36.8%)	11 (25.6%)	35 (49.3%)	0.008
	1	70 (29.8%)	9 (47.4%)	16 (37.2%)	19 (26.8%)	
	2	39 (16.6%)	3 (15.8%)	16 (37.2%)	17 (23.9%)	
M stage primary (%)	0	393 (100.0%)	0 (0.0%)	39 (88.6%)	69 (97.2%)	<0.001
	1	0 (0.0%)	22 (100.0%)	5 (11.4%)	2 (2.8%)	
Neoadjuvant radiation scheme primary (%)	None	190 (47.9%)	10 (45.5%)	10 (22.7%)	33 (46.5%)	0.001
	Chemoradiation	100 (25.2%)	9 (40.9%)	17 (38.6%)	25 (35.2%)	
	Short-course (25Gy)	100 (25.2%)	1 (4.5%)	13 (29.5%)	12 (16.9%)	
	Long-course (44–60Gy)	7 (1.8%)	2 (9.1%)	4 (9.1%)	1 (1.4%)	
Type of surgery primary (%)	APR	99 (27.2%)	5 (22.7%)	18 (41.9%)	22 (31.9%)	0.306
	LAR	200 (54.9%)	14 (63.6%)	20 (46.5%)	34 (49.3%)	
	Sigmoid	59 (16.2%)	2 (9.1%)	5 (11.6%)	13 (18.8%)	
	Exenteration	4 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
	W&W	2 (0.5%)	1 (4.5%)	0 (0.0%)	0 (0.0%)	
Resection margin primary (%)	R0	156 (78.4%)	9 (90.0%)	18 (78.3%)	29 (65.9%)	0.588
	R1	41 (20.6%)	1 (10.0%)	5 (21.7%)	14 (31.8%)	
	R2	2 (1.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	
Adjuvant chemotherapy primary (%)	Yes	65 (16.6%)	6 (28.6%)	15 (34.1%)	9 (12.7%)	0.011
	No	326 (83.4%)	15 (71.4%)	29 (65.9%)	62 (87.3%)	
Interval primary - LRRC (median [IQR])		23.3 [12.3, 41.7]	18.6 [10.7, 34.6]	36.0 [22.5, 57.7]	20.7 [12.0, 40.5]	0.002

Abbreviations: APR - abdominoperineal resection. ASA - American Society of Anesthesiologists. IQR - interquartile range. LAR - low anterior resection. LRRC – locally recurrent rectal cancer. W&W – watch and wait.

metastasis-free survival was poorest in patients with synchronous metastases with the local recurrence (resp. 3-year survival rates: 24%, 28% and 24%), and best in patients synchronous metastases only with the primary tumour (resp. 3-year survival rates: 48%, 55% and 66%) (see Fig. 2).

3.2. Univariable and multivariable survival analyses

Results of the Cox (proportional hazards) regression analyses is shown in Table 4. In univariable and multivariable analyses, age, neoadjuvant chemoradiation for the primary tumour, synchronous metastases with the LRRC, IORT, multifocality, multivisceral resection of LRRC, and R1-and R2 resections were all associated with poor survival. The most important factor for impaired survival was a R0 resection (OR: 2.00 (95% CI: 1.58−2.55) and OR: 3.43 (95% CI: 1.39−8.51) for R1-and R2 resection respectively). Patients with LRRC and synchronous metastases had impaired survival compared to patients without metastases. Primary synchronous metastases and metachronous metastases did not influence survival.

3.3. Subgroup analyses

A hypothesis-driven subgroup survival analysis was performed to determine the impact of the moment of metastases in the primary-recurrence interval in 52 patients with metachronous metastases. Herein, patients who were diagnosed with metastases within one year after primary rectal cancer surgery (n = 21) were compared with those who had metastases within one year before diagnosis of LRRC (n = 17) (early metachronous versus late metachronous). Patients who were categorised in both groups were excluded (n = 6). Another six patients with metachronous metastases but who did not have any metastases within one year after primary rectal cancer and within one year before diagnosis of LRRC were also not included in this analysis. In two patients the time of metastases diagnosis was missing.

In the subgroup analysis, overall survival between patients with early and late metachronous distant metastases did not differ, but an improved disease-free survival was observed in patients with early metachronous metastases (3-year disease-free survival rate 48%, 95% CI: 29%−79%) versus those with late metachronous metastases (3-year disease-free survival rate 22%, 95% CI: 8%−58%)(log rank p = 0.039).

4. Discussion

The aim of this retrospective cohort study was to investigate the oncological outcomes of surgically treated LRRC patients with a history or present metastases. Results demonstrate that the moment of diagnosis of distant metastases has significant impact on prognosis, wherein patients with distant metastases diagnosed nearby the primary tumour have better oncological outcomes as compared to those who have metastases shortly prior to, or synchronous with, LRRC. In multivariable analysis, synchronous distant metastases diagnosed with LRRC was an independent risk factor for poor survival.

In this study, 14% of patients who were eligible for surgery for their local recurrence also had distant metastases. Obviously, this is much lower than the approximate 40% synchronous distant metastases rate in the entire LRRC population encountered in daily practice [12,16,23−25]. Most LRRC patients diagnosed with concomitant metastases will not undergo curative intended treatment, and previously published data from one of the participating institutes demonstrate that the reason not to initiate curative treatment is mainly due to metastatic disease (58%) [15]. Unfortunately, the occurrence of LRRC is associated with (extensive) distant metastases and poor prognosis [12]. For example, it was shown from data from the Dutch TME trial that 74% of the twenty-three LRRC patients in the preoperative radiotherapy plus TME group developed distant metastases, most of them with a short interval between local recurrence to metastatic disease (median 0.9

Table 2
LRRC and treatment details.

		No metastases (n = 398)	Synchronous metastases primary (n = 22)	Metachronous metastases (n = 44)	Synchronous metastases LRRC (n = 71)	p-value
Multifocality (%)	Yes	36 (9.7%)	2 (9.1%)	11 (25.0%)	19 (27.1%)	<0.001
	No	334 (90.3%)	20 (90.9%)	33 (75.0%)	51 (72.9%)	
Induction chemotherapy LRRC (%)	Yes	98 (24.6%)	5 (22.7%)	19 (43.2%)	40 (56.3%)	<0.001
	No	300 (75.4%)	17 (77.3%)	25 (56.8%)	31 (43.7%)	
Differentiation (%)	Adenocarcinoma	305 (87.4%)	19 (90.5%)	33 (86.8%)	67 (98.5%)	0.218
	Mucinous carcinoma	34 (9.7%)	1 (4.8%)	4 (10.5%)	1 (1.5%)	
	Complete response	10 (2.9%)	1 (4.8%)	1 (2.6%)	0 (0.0%)	
Radiation scheme LRRC (%)	None	5 (3.3%)	1 (4.8%)	1 (2.4%)	4 (6.1%)	0.036
	(Chemo)radiation (50Gy)	82 (54.7%)	11 (52.4%)	11 (26.8%)	24 (36.4%)	
	(Chemo)irradiation (30Gy)	62 (41.3%)	9 (42.9%)	29 (70.7%)	36 (54.5%)	
	Short-course radiation (25Gy)	1 (0.7%)	0 (0.0%)	0 (0.0%)	2 (3.0%)	
Type of surgery LRRC (%)	APR[a]	140 (35.6%)	9 (40.9%)	22 (50.0%)	22 (31.0%)	0.510
	LAR[a]	91 (23.2%)	5 (22.7%)	5 (11.4%)	18 (25.4%)	
	Extra-anatomical resection of the local recurrence	18 (4.6%)	1 (4.5%)	1 (2.3%)	3 (4.2%)	
	Posterior exenteration	14 (3.6%)	2 (9.1%)	2 (4.5%)	6 (8.5%)	
	Total exenteration	130 (33.1%)	5 (22.7%)	14 (31.8%)	22 (31.0%)	
IORT (%)	Yes	288 (72.4%)	15 (68.2%)	32 (72.7%)	52 (73.2%)	0.974
	No	110 (27.6%)	7 (31.8%)	12 (27.3%)	19 (26.8%)	
Complications (%)	Clavien-Dindo 0-2	290 (72.9%)	16 (72.7%)	27 (61.4%)	48 (67.6%)	0.378
	Clavien-Dindo 3-5	108 (27.1%)	6 (27.3%)	17 (38.6%)	23 (32.4%)	
Resection margin LRRC (%)	R0	269 (67.6%)	18 (81.8%)	28 (65.1%)	42 (60.0%)	0.386
	R1	126 (31.7%)	4 (18.2%)	14 (32.6%)	26 (37.1%)	
	R2	3 (0.8%)	0 (0.0%)	1 (2.3%)	2 (2.9%)	

Abbreviations: APR - abdominoperineal resection. IORT − intraoperative radiotherapy. IQR - interquartile range. LAR - low anterior resection. LRRC − locally recurrent rectal cancer.

[a] Usually combined with an additional resection.

Table 3
Metastases details. *The numbers do not correspond with groups because some patients had both primary synchronous metastases, metachronous metastases and/or synchronous metastases with LRRC.

		Synchronous primary (n = 29)	Metachronous (n = 52)	Synchronous LRRC (n = 71)
Location	Liver	20 (69%)	32 (62%)	22 (31%)
	Lung	3 (10%)	14 (27%)	20 (28%)
	Peritoneal	3 (10%)	2 (4%)	10 (14%)
	Lymph nodes	2 (7%)	0 (0%)	14 (20%)
	Other	0 (0%)	4 (8%)	3 (4%)
	More than one location	1 (3%)	0 (0%)	2 (3%)
Solitary/multiple	Solitary	13 (45%)	28 (54%)	28 (39%)
	Multiple	16 (55%)	24 (56%)	43 (61%)
Treatment	Chemotherapy (CTx)	3 (10%)	2 (4%)	9 (13%)
	Radiotherapy	0 (0%)	2 (4%)	8 (12%)
	RFA	2 (7%)	1 (2%)	0 (0%)
	Metastectomy	14 (48%)	34 (65%)	31 (44%)
	CTx + metastectomy	7 (24%)	7 (14%)	17 (24%)
	No treatment (W&W)	0 (0%)	0 (0%)	2 (3%)
	Combination	3 (10%)	6 (15%)	4 (6%)
Timing metastases treatment	Before primary/LRRC treatment	13 (45%)	NA	37 (52%)
	During primary/LRRC treatment	5 (17%)	NA	29 (40%)
	After primary/LRRC treatment	11 (38%)	NA	3 (4%)
	Untreated	0 (0%)	NA	2 (3%)

Abbreviations: CTx – chemotherapy. LRRC – locally recurrent rectal cancer. W&W – watch and wait.

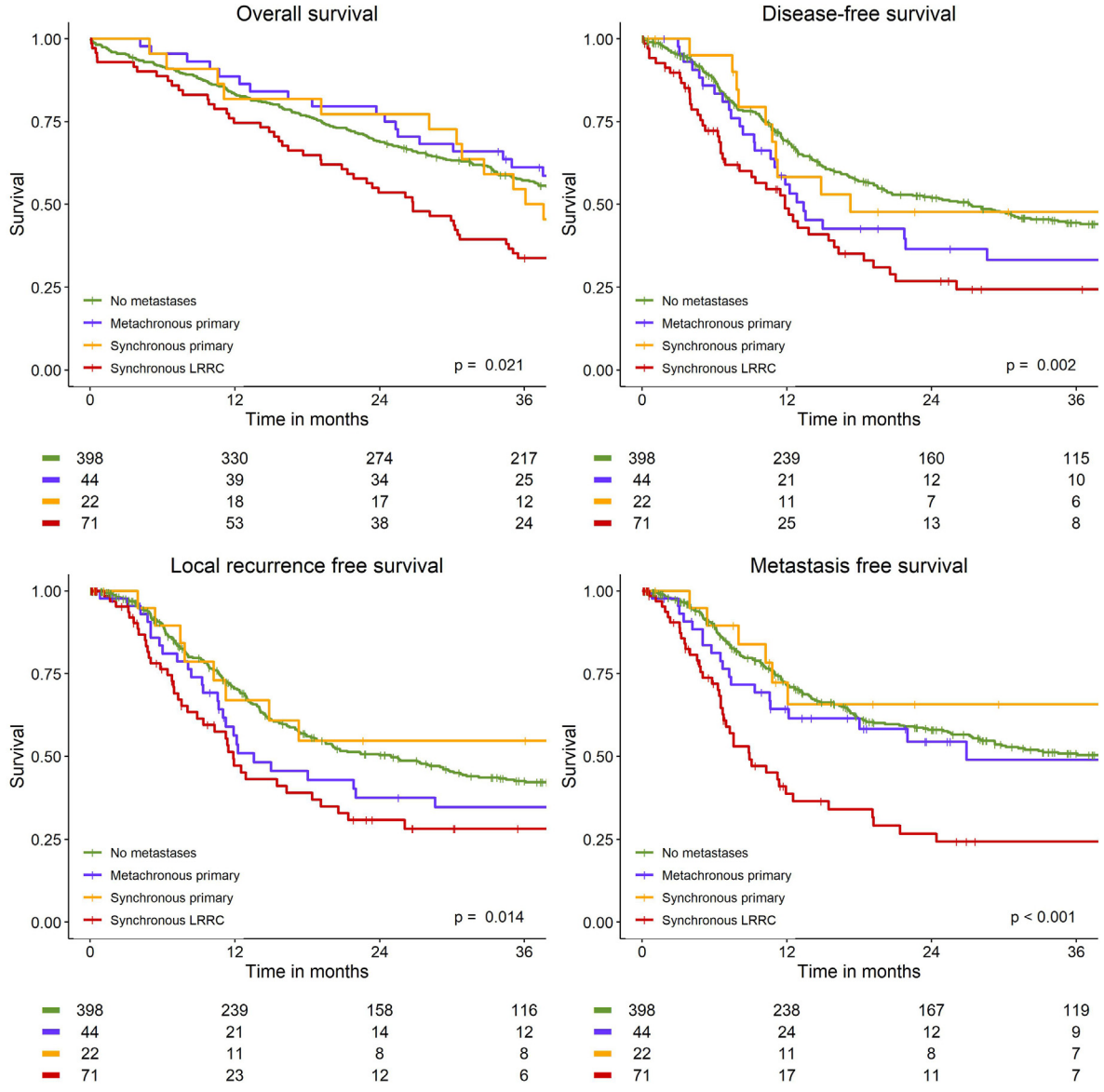

Fig. 1. Oncological outcomes in surgically treated LRRC patients with or without a history of or present metastases.

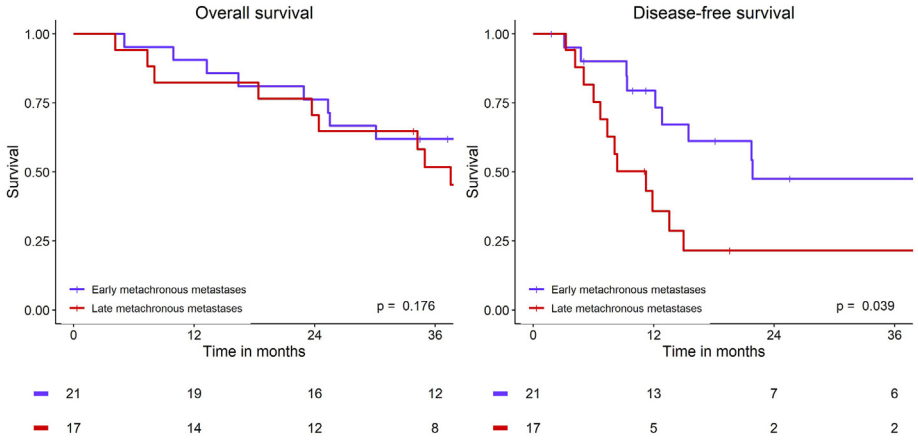

Fig. 2. Overall- and disease-free survival of LRRC patients with early and late metachronous metastases in primary-recurrence interval.

Table 4
Cox (proportional hazards) regression analyses.

	Univariate HR (95% CI)	*P*-value	Multivariable HR (95% CI)	*P*-value
Age	1.02 (1.01–1.04)	<0.001	1.03 (1.02–1.05)	<0.001
Female sex	1.07 (0.86–1.31)	0.559	1.07 (0.84–1.35)	0.594
T-stage (T3-4)	1.02 (0.76–1.38)	0.889		
N-stage (N1-2)	1.09 (0.85–1.40)	0.476		
Radiation primary tumour				
Preoperative chemoradiation primary (vs. no radiation)	**1.45 (1.14–1.85)**	**0.003**	**1.34 (1.01–1.76)**	**0.040**
Long-course radiation primary (vs. no preoperative radiation)	1.53 (0.85–2.76)	0.154	1.65 (0.85–3.22)	0.140
Short-course radiation primary (vs. no preoperative radiation)	1.28 (0.99–1.64)	0.058	1.05 (0.78–1.42)	0.732
Metastases				
Synchronous metastases primary (vs. no metastases)	1.07 (0.73–1.56)	0.731	0.93 (0.62–1.41)	0.746
Metachronous metastases (vs. no metastases)	0.91 (0.54–1.53)	0.725	1.16 (0.67–2.02)	0.603
Synchronous metastases LRRC (vs. no metastases)	**1.56 (1.17–2.07)**	**0.002**	**1.56 (1.15–2.12)**	**0.005**
Induction chemotherapy LRRC	1.09 (0.87–1.36)	0.449		
IORT	**1.28 (1.01–1.62)**	**0.039**	**1.24 (0.95–1.62)**	**0.118**
Multifocality	**1.47 (1.09–1.98)**	**0.012**	**1.46 (1.05–2.02)**	**0.024**
Multivisceral resection	**1.41 (1.14–1.73)**	**0.001**	**1.34 (1.06–1.69)**	**0.014**
R1 resection (vs R0)	**1.98 (1.61–2.44)**	**<0.001**	**2.00 (1.58–2.55)**	**<0.001**
R2 resection (vs R0)	**3.63 (1.61–8.18)**	**0.002**	**3.43 (1.39–8.51)**	**0.008**

Abbreviations: HR – hazard ratio. IORT – intraoperative radiotherapy. LRRC – locally recurrent rectal cancer.

months, 95% CI: 0.3–1.5 months) [12]. Thus, the 14% of LRRC patients with synchronous metastases included in this study, should be considered as selection of patients in whom the biological behaviour is considered to be relatively good by treating physicians.

Disease-free survival of patients with metastases synchronous to the primary tumour and patients with metachronous metastases was similar to patients without metastases, which may be explained by the selection process. It is reasonable to suggest that patients with a history of metastases and unfavourable disease characteristics will have developed extensive (untreatable) metastases before presenting with LRRC. Contrarily, a long disease-free interval before the diagnosis of LRRC might be suggestive for disease with less metastatic potential. This also explains that patients with early metachronous metastases of the primary tumour have better outcomes in terms of recurrences compared to patients with late metachronous metastases of the primary tumour (3-year DFS: 48% vs 22%, p = 0.039).

In previously reported results of a single centre study by Voogt et al. patients with metastases synchronous to the primary tumour and patients with metachronous metastases were analysed as a single group [20]. In this current study, we found that these patients have comparable oncological outcomes, but that in patients with metachronous metastases, the timing of diagnosis in the primary-recurrence interval is associated with disease-free survival after LRRC treatment. As demonstrated by Voogt et al. patients with synchronous metastases with LRRC have worse prognosis compared to patients without metastases or only a history of metastases. Presumably, patients in this group have tumours with poor biology. This is shown by the relatively high proportion of irradical resections, which suggest uglier, more invading recurrent tumours in which the achievement of clear margins was not possible.

In order to improve patient selection for curative treatment in patients with synchronous metastases and LRRC, administration of induction chemotherapy may be of added value in discriminating patients into risk groups based on disease behaviour. Patients who achieve sufficient response whilst on treatment are likely to be better candidates for curative treatment. On the other hand, patients with disease progression during systemic treatment most likely have an extremely poor prognosis, and palliative treatment that focusses on comfort and quality of death is usually superior to surgery [15]. Therefore, initiating treatment with systemic chemotherapy may provide an opportunity to further observe disease behaviour and select those patient who are likely to benefit from curative treatment.

Limitations of this study are mainly associated with the retrospective design, and the relatively small sample sizes of patients included in the compared groups. Generally, both hospitals share

the same case-mix and adhere to the same guidelines and follow-up schedules, but some differences in LRRC management, such as the use of induction chemotherapy in CHE, should be acknowledged. Also, only patients who underwent curative intended surgery for LRRC were included in this study, so patients in whom palliative treatment was started (often because of metastatic disease), or those who started curative treatment but did not get surgery (usually because of progressive disease) were excluded. Therefore, it is important to mention that the analysed patients were highly selected, and that LRRC patients encountered in daily practice on an intention-to-treat basis, have much higher chances of having unfavourable disease characteristics (e.g. extensive metastatic disease) compared to those in this study. Despite these limitations, we consider the study population, derived from a prospectively maintained database, an accurate reflection of the *surgically* treated LRRC population.

In conclusion, there is a chance of cure in patients with locally recurrent rectal cancer, who have or have had distant metastases. Especially patients with distant metastases diagnosed synchronously of shortly after the primary tumour have outcomes similar to patients without metastases. In these patients, treatment with curative intent should not be withheld on the basis of the history of metastatic disease. In patients with metastases diagnosed shortly prior to, or synchronous with LRRC, curative treatment should be carefully considered, as these patients tend to have a relatively poor oncological outcome. In patients with LRRC and synchronous metastases, initiating treatment with systemic chemotherapy may provide an opportunity to further observe disease behaviour and select those patient who are likely to benefit from curative treatment.

CRediT authorship contribution statement

J.M. van Rees: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **S. Nordkamp:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Project administration. **P.W. Harmsen:** Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **H. Rutten:** Conceptualization, Methodology, Writing – review & editing, Supervision. **J.W.A. Burger:** Conceptualization, Methodology, Writing – review & editing, Supervision. **C. Verhoef:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of competing interest

None.

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