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Original research

Evolution of clinical nature, treatment and survival of locally recurrent rectal cancer: Comparative analysis of two national cross-sectional cohorts☆

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ABSTRACT

Background: In the Netherlands, use of neoadjuvant radiotherapy for rectal cancer declined after guideline revision in 2014. This decline is thought to affect the clinical nature and treatability of locally recurrent rectal cancer (LRRC). Therefore, this study compared two national cross-sectional cohorts before and after the guideline revision with the aim to determine the changes in treatment and survival of LRRC patients over time. *Methods:* Patients who underwent resection of primary rectal cancer in 2011 (n = 2094) and 2016 (n = 2855) from two nationwide cohorts with a 4-year follow up were included. Main outcomes included time to LRRC, synchronous metastases at time of LRRC diagnosis, intention of treatment and 2-year overall survival after LRRC. *Results:* Use of neoadjuvant (chemo)radiotherapy for the primary tumour decreased from 88.5% to 60.0% from 2011 to 2016. The 3-year LRRC rate was not significantly different with 5.1% in 2011 (n = 114, median time to LRRC 16 months) and 6.3% in 2016 (n = 202, median time to LRRC 16 months). Synchronous metastasis rate did

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not significantly differ (27.2% vs 33.7%, p = 0.257). Treatment intent of the LRRC shifted towards more curative treatment (30.4% vs. 47.0%, p = 0.009). In the curatively treated group, two-year overall survival after LRRC diagnoses increased from 47.5% to 78.7% (p = 0.013).
Conclusion: Primary rectal cancer patients in 2016 were treated less often with neoadjuvant (chemo)radiotherapy, while LRRC rates remained similar. Those who developed LRRC were more often candidate for curative intent treatment compared to the 2011 cohort, and survival after curative intent treatment also improved substantially.

1. Introduction

In recent decades, developments in rectal cancer treatment have decreased local recurrence rates to 5–10% [1,2]. Nevertheless, the treatment of locally recurrent rectal cancer (LRRC) remains challenging; only 35–40% presents with a resectable tumour and without widespread metastases and are eligible for curative treatment [3,4]. Palliative care is indicated for remaining patients with widespread metastatic disease or with an unresectable recurrence [5,6]. In the Netherlands, and according to the ESMO guidelines, curative intent treatment of LRRC in radiotherapy (RT)-naive patients typically involves neoadjuvant full-course chemoradiotherapy (CRT) followed by surgical resection, with an adapted schedule of chemo-reirradiation for patients who have received prior RT [7,8]. Reported five-year survival rates after curative intent treatment range between 25% and 41%, which improves to 58% if resection with clear margins (R0) is achieved [3,4,9–12].

While R0 resection is the most important prognostic factor in LRRC patients, primary tumour treatment is also thought to affect the clinical behaviour and prognosis [13]. One study analysed LRRC patient outcomes from the Dutch TME-trial, in which total mesorectal excision (TME) only was compared to short-course RT (5×5Gy) followed by TME as primary rectal cancer treatment [14]. Fewer LRRC developed after RT, but these LRRCs were associated with an increased distant metastases (DM) rate (74% vs 40%) and a decrease in median survival time (6 vs 16 months) compared to LRRCs after TME alone [14].

In recent years LRRC treatment has changed towardsmore centralized care in tertiary referral centres. Furthermore, new intentional curative treatment options have become available for metastatic disease, such as surgery, (non-)thermal ablation and stereotactic RT, with or without systemic therapy. At the same time, therapeutic approaches have been de-escalated for early stages of primary rectal cancer following the 2014 Dutch colorectal cancer guideline revision. Afterwards, RT was not recommended for low-risk tumours, while shared decision-making was advised in intermediate-risk rectal cancer due to marginal oncological benefits and increased toxicity [15]. The impact of reduced neoadjuvant RT on LRRC's clinical nature, treatment and survival remains unknown.

Therefore, this study compared 2011 and 2016 national cross-sectional cohorts of rectal cancer patients, to determine the changes in clinical nature, treatment and survival of LRRC over time.

2. Methods

Two national retrospective cross-sectional cohorts by the Dutch Snapshot Research Group were combined. The first cohort comprises patients who underwent surgical resection for primary rectal cancer in 71/94 hospitals providing rectal cancer care in 2011, with data collection in 2015 [16]. For a second cohort, with identical study design, data was collected between 2020 and 2021 in 67/69 hospitals providing rectal cancer care in 2016. Patients who underwent local excision without a completion TME were excluded (appendix 1). Eligible patients were identified from the Dutch Colorectal Audit (DCRA), and data were enriched with disease and treatment characteristics as well as long-term outcomes by local collaborative teams, including surgeons, residents, and abdominal radiologists [17]. Since patients were often referred to tertiary expert centres, relevant information could sometimes not be retrieved. As a consequence of the study design with its focus on the primary tumour, information about the treatment of LRRC was sometimes not complete.

Both Snapshot projects were approved by Medical Ethical Committees and both were exempt from the Dutch Medical Research Involving Human Subjects Act. The 2011 LRRC cohort has previously been published [18].

2.1. Guideline recommendations

From 2008 to 2014, the Dutch rectal cancer guideline recommended neoadjuvant CRT (28×1.8 Gy or 25×2Gy in combination with Capecitabine) for patients with a threatened mesorectal fascia (MRF+, ≤1 mm), cT4 or cN2, while short course RT (5×5Gy) was recommended for cT2–3N0MRF- or cT1–3N1. Only cT1N0 or proximal cT2N0 were exempt from neoadjuvant RT. In 2014, the Dutch guideline was revised and neoadjuvant RT was no longer recommended for low-risk (cT1-cT3abN0) rectal cancer. Shared decision making with TME alone or short course RT for intermediate risk (cT3cdN0 or cT1–3N1(MRF-, >1 mm)) was advised. CRT was still recommended for more advanced tumours (cT4, MRF+, cN2, or pathological extramesorectal nodes).

The follow-up after primary resection according to the Dutch guideline consists of CEA measurements every 3–6 months, and a CT-scan and colonoscopy after 12 months. An additional CT- or PET-scan is performed in case of an abnormal CEA value.

2.2. Outcomes and definitions

The primary outcomes of this study were 2-year overall survival (OS) and cancer specific survival (CSS) after LRRC diagnosis. Secondary outcomes included characteristics of the LRRC, intention of treatment of LRRC, and 2-year metachronous DM after LRRC diagnosis. In 2011, only the first time a patient developed metachronous metastases after the primary tumour was registered, while in 2016 metachronous metastases could be registered at different time points during the disease course. As a result, the synchronous and metachronous metastases rates of the LRRC were incomplete for 2011 and are not reported.

Diagnosis of LRRC was based on documentation in the original patient files, and any LRRC after TME-surgery was included. Intention of treatment for LRRC was based on documentation of curative or palliative intent at the time of start of treatment for LRRC, as determined by the multidisciplinary team in each hospital.

2.3. Statistical analysis

Analyses were performed with SPSS (v28) and R (v4.2.1). Baseline characteristics were analysed according to cohort and development of LRRC. Continuous variables were presented as means with standard deviation (SD) or median with interquartile range (IQR), depending on distribution, and were compared with an independent t-test or a Mann-Whitney U test, respectively. Cumulative incidence function was calculated for LRRC development with death as competing. Competing risk univariable and multivariable hazard regressions were performed, with a backward selection for the multivariable regression. Survival analyses after LRRC development were performed with Kaplan Meier for patients who developed a LRRC within 3 years, and compared using a

log-rank test. This was done to correct for the longer follow-up time in 2016, which allows for more LRRC to develop and to ensure a minimum of one year follow-up after LRRC diagnosis. A two-sided p-value < 0.05 was considered statistically significant.

3. Results

In 2011 and 2016, 2094 and 2855 patients were included with a median follow-up time of 41 (IQR 25–47) and 49 (IQR 35–55) months, respectively. In total, 114 patients (5.1%) developed LRRC in 2011, compared to 202 patients (6.3%, p = 0.200, Fig. 1) in 2016.

3.1. Risk factors for LRRC in 2011 and 2016

In 2011, 88.5% of the patients received RT for their primary tumour, compared to 60.0% in 2016 ($p < 0.001$), with a most pronounced decrease for short course RT with short interval to surgery. Primary tumours were located more proximal in 2011 (Table 1), and proximal location was associated with a decreased LRRC risk in 2016 (>7 cm from the anorectal junction; HR 0.55, 95% CI 0.37–0.83, Table 2) but not in 2011. From 2011 to 2016, surgical resection shifted from Hartmann's procedures (HP) towards more restorative resections. In both cohorts, there was a strong association between positive resection margin and the development of LRRC in multivariate analysis (Table 2).

3.2. LRRC characteristics and treatment intent

The median time to LRRC was 16 months in both cohorts. In 2016, LRRCs occurred most often in the lateral compartment (n = 47, 28.0%, Table 3). In 2011, 27.2% of the patients were diagnosed with synchronous metastases at time of LRRC diagnosis, compared to 33.7% in 2016 (p = 0.257). While in 2011 the majority of the patients was treated with palliative intent (n = 78, 69.6%), this decreased to 53.0% (n = 107, p = 0.004) in 2016. For those treated with curative intent, more patients received some form of chemo(re)irradiation in 2016 (Table 3). The proportion of LRRC patients that received full-course CRT increased (13.3% vs 31.9%, p = 0.009), as there were more RT-naive LRRC in 2016. Results for RT naïve patients compared to those who received prior RT and according to intention of treatment can be found in appendix 2.

3.3. Oncological and survival outcomes after LRRC

For those who developed a LRRC within 3 years, the 2-year OS increased from 20.9% in 2011 to 47.0% in 2016 ($p < 0.001$) and the 2-year CSS from 30.3% to 49.2% (p = 0.004, Fig. 2A-D). When analyzed per intention of treatment, the 2-year OS in 2016 was significantly higher for both LRRC patients treated with curative intent (78.7% vs 47.5%, p = 0.013) as well as those treated with palliative intent (20.0% vs 10.5%, p = 0.013) as compared to 2011. The 2-year CSS for curatively treated LRRC patients was 53.6% in 2011 compared to 81.3% in 2016 (p = 0.110). In the palliative setting, the 2-year CSS was 20.2% and 21.1%, respectively (p = 0.271).

For 2011, survival analyses per treatment category of the LRRC could not be made due to low numbers of patients treated with curative intent. 2-year CSS in 2016 was similar for those who did not receive neo-adjuvant therapy (n = 24, 91.7%), re-irradiation (n = 33, 71.5%) and full-course CRT (n = 22, 81.3%).

3.4. Timing of distant metastases relative to LRRC in the 2016 cohort

The distribution of the development of metastases in LRRC patients of the 2016 cohort is shown in Fig. 3. Patients with synchronous metastases at the time of LRRC diagnosis were treated with palliative intent more often compared to those without synchronous metastases (78.3% vs 41.7%, $p < 0.001$). The 2-year OS and CSS for curatively treated LRRC patients with synchronous metastases (n = 13) compared to those without (n = 67) was 2-year OS of 58.3% (95%CI 30.5%–86.1%) vs 83.4% (95%CI 74.0%–92.8%) and 2-year CSS of 58.3% (95%CI 30.5%–86.1%) vs 86.7% (95%CI 78.1%–95.3%). The 2-year distant metachronous metastases rate in the LRRC patients without previous distant metastases and treated with curative intent (n = 60) was 27.1%.

4. Discussion

This study revealed differences in the management and outcomes of LRRC between two Dutch cross-sectional cohorts of patients treated for primary rectal cancer in 2011 and 2016. A noteworthy increase occurred in the proportion of LRRC patients receiving curative intent treatment, and significant improvements in OS and CSS rates for those diagnosed with LRRC in 2016 as compared to 2011 were found. Concurrently, the use of RT for the primary tumour decreased from 88.5% in 2011 to

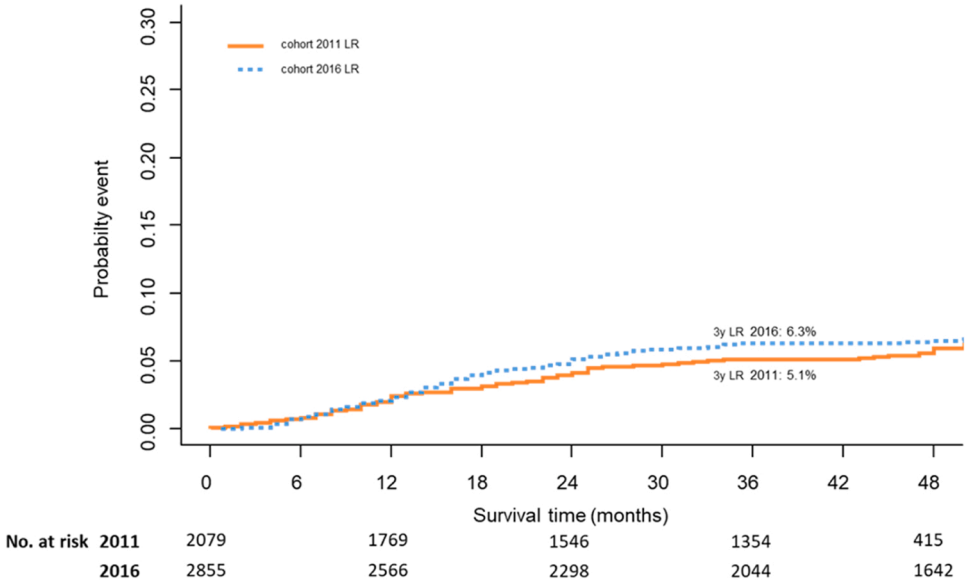

Fig. 1. Cumulative local recurrence per cohort 3-year cumulative rate of locally recurrent rectal cancer after primary rectal cancer diagnosis, corrected for all-cause mortality and compared between 2011 (5.1%) and 2016 (6.3%), p = 0.200.

Table 1
Baseline characteristics stratified per cohort and LRRC diagnosis.

	2011, n = 2094 (%)	2016, n = 2855 (%)	p-value	2011 LRRC, n = 114 (% of 2011)	2016 LRRC, n = 202 (% of 2016)	p-value LRRC 2011 vs 2016
Gender			0.268			0.215
Male	1316 (62.9)	1840 (64.4)		71 (5.3)	140 (7.6)	
Female	777 (37.1)	1015 (35.6)		43 (5.5)	62 (6.1)	
Missing	1	0		0	0	
Age (years), mean (SD)	66.8 (11.2)	66.9 (10.1)	0.344	66.4 (12.4)	65.4 (11.3)	0.480
ASA-score			0.397			0.424
ASA I/II	1693 (83.4)	2158 (82.1)		90 (5.3)	171 (7.9)	
ASA III/IV/V	339 (16.6)	469 (17.9)		21 (6.2)	30 (6.4)	
Missing	62	26		3	1	
Distance ARJ (cm), mean (SD)	5.9 (3.9)	5.2 (3.6)	**< 0.001**	5.6 (4.4)	4.2 (3.4)	**0.008**
Missing	483	205		27	9	
cT-stage			**< 0.001**			**< 0.001**
cT1	80 (4.1)	71 (2.6)		5 (6.3)	1 (1.4)	
cT2	473 (24.3)	753 (27.4)		19 (4.0)	43 (5.7)	
cT3	1067 (54.8)	1627 (59.2)		49 (4.6)	116 (7.1)	
cT4	180 (9.2)	271 (9.9)		25 (13.9)	33 (12.2)	
cTx	146 (7.5)	27 (1.0)		7 (4.8)	1 (3.7)	
Missing	148	106		9	8	
MRF*			0.413			1.000
Threatened	347 (38.9)	544 (37.0)		18 (5.2)	52 (9.6)	
Not threatened	544 (61.1)	998 (63.0)		22 (4.0)	61 (6.1)	
Missing	176	39		9	3	
cN-stage			**< 0.001**			**< 0.001**
cN0	752 (38.7)	1099 (42.7)		42 (5.6)	76 (6.9)	
cN1	683 (35.2)	825 (31.6)		36 (5.3)	42 (5.1)	
cN2	301 (15.5)	618 (25.2)		18 (6.0)	74 (12.0)	
cNx	206 (10.6)	13 (0.5)		9 (4.4)	0 (0.0)	
Missing	152	106		9	8	
Synchronous metastases* *	170 (8.1)	174 (6.1)	**0.007**	14 (8.2)	15 (8.6)	0.160
Preoperative radiotherapy			**< 0.001**			**< 0.001**
None	226 (11.5)	1142 (40.0)		21 (9.3)	72 (6.3)	
5×5 Gy short-interval	957 (48.8)	476 (16.7)		34 (3.6)	10 (2.1)	
5×5 Gy long-interval	67 (3.4)	298 (10.4)		5 (7.5)	36 (12.1)	
CRT	711 (36.3)	939 (32.9)		40 (5.6)	84 (8.9)	
Missing	133	0		14	0	
Surgical procedure			**< 0.001**			**0.016**
(L)AR	1012 (48.3)	1747 (61.2)		34 (3.4)	90 (5.2)	
APR	680 (32.5)	721 (25.3)		42 (6.2)	69 (9.6)	
HP	402 (19.2)	387 (13.6)		38 (9.5)	43 (11.1)	
(y)pT-stage			**< 0.001**			**0.009**
(y)pT0	133 (6.5)	208 (7.3)		5 (3.8)	2 (1.0)	
(y)pT1	156 (7.7)	343 (12.0)		1 (0.6)	11 (3.2)	
(y)pT2	658 (32.4)	902 (31.6)		14 (2.1)	37 (4.1)	
(y)pT3	938 (46.1)	1282 (44.9)		64 (6.8)	129 (10.1)	
(y)pT4	104 (5.1)	117 (4.1)		22 (21.2)	22 (18.8)	
(y)pTx	45 (2.2)	3 (0.1)		2 (4.4)	1 (33.3)	
Missing	60	0		3	0	
(y)pN-stage			0.086			0.841
(y)pN0	1227 (63.5)	1798 (67.8)		51 (4.2)	90 (5.0)	
(y)pN1	486 (25.2)	594 (22.4)		34 (7.0)	68 (11.4)	
(y)pN2	176 (9.1)	258 (9.7)		25 (14.2)	42 (16.3)	
(y)pNx	43 (2.2)	3 (0.1)		1 (2.3)	0 (0.0)	
Missing	48	0		3	0	
Incomplete resection	94 (4.7)	167 (5.9)	0.071	19 (20.2)	46 (27.5)	0.308
Missing	81	3		5	0	

*Only for T3 tumours
* *Within 3 months of resection of the primary tumour
Abbreviations: LRRC: locally recurrent rectal cancer, ASA: American Society of Anesthesiologist-Classification, ARJ: Anorectal Junction, cT stage: clinical tumour stage, cN-stage: clinical nodal stage, MRF: mesorectal fascia, RT: radiotherapy, CRT: chemo radiotherapy, (L)AR: Low Anterior Resection, APR: Abdominoperineal Resection, HP: Hartmann's Procedure, (y)pT-stage: pathological tumour stage, (y)pN-stage: pathological nodal stage.

60.0% in 2016, without compromising LRRC rates [19].

A tendency towards higher OS rates after treatment of LRRC over time was already observed in a systematic review of the literature published between 1990 and 2010 [3], and is also parallel to overall outcome improvements of cancer in general [20]. The higher rate of curatively treated patients (46.5% in 2016 vs 28.6% in 2011), may be indicative of ongoing advancements in treatment options. In the last two decades, treatment of LRRC has successfully been centralized in expert centres, with surgeon further specializing. The collaborative efforts of multidisciplinairy team, along the implementation of prehabilitiation and enhanced recovery after surgery (ERAS) programmes, are all potential contributing factors to the improvement of oncological outcomes [21,22]. Moreover, managing rectal cancer metastases has become more effective, with more local and systemic treatment options [23–25].

Table 2
Uni- and multi-variate analysis of LRRC diagnosis.

	2011 Univariate analysis				*2011 Multivariate analysis*			*2016 Univariate analysis*				*2016 Multivariate analysis*		
Variable	No.	HR	95% CI	P	HR	95% CI	P	No.	HR	95% CI	P	HR	95% CI	P
Age: ≤ 65	904	1.000						1225	1.000		0.300			
> 65	1175	1.243	0.847-1.825	0.270				1630	0.864	0.654-1.141				
Sex: Male	1307	1.000						1840	1.000		0.200			
Female	771	1.108	0.756-1.624	0.600				1015	0.822	0.609-1.109				
ASA-score: I/II	1694	1.000						2329	1.000		0.430			
III/IV/V	337	0.917	0.540-1.557	0.750				499	0.855	0.580-1.262				
Distance to the ARJ: ≤ 3 cm	480	1.000						815	1.000					
3.1-7 cm	905	0.737	0.468-1.160	0.190				1223	0.606	0.445-0.826	**0.002**	0.684	0.491-0.953	**0.025**
> 7 cm	694	0.734	0.454-1.187	0.210				817	0.441	0.300-0.646	**< 0.001**	0.554	0.370-0.827	**0.004**
cT stage: cT1	79	1.000						71	1.000					
cT2	467	0.595	0.221-1.600	0.300				753	3.725	0.511-27.158	0.190			
cT3	1062	0.701	0.279-1.761	0.450				1627	4.680	0.651-33.648	0.130			
cT4	179	2.383	0.914-6.211	0.076				271	8.375	1.140-61.530	**0.037**			
cTx	144	0.657	0.201-2.152	0.490				27	2.743	0.167-44.974	0.480			
cN stage: cN0	747	1.000						1175	1.000					
cN1	679	0.962	0.612-1.511	0.870				868	0.725	0.498-1.055	0.093	0.649	0.441-0.956	**0.029**
cN2	300	1.119	0.640-1.956	0.690				693	1.617	1.172-2.231	**0.003**	1.390	1.001-1.931	**0.049**
cNx	205	0.715	0.335-1.523	0.380				13	0.000	NA	NA			
Synchronous metastases: No	1909	1.000						2681	1.000					
Yes	170	1.532	0.850-2.729	0.160				174	1.265	0.749-2.137	0.380			
Neoadjuvant radiotherapy: None	221	1.000						1142	1.000					
5×5 short interval	952	0.395	0.225-0.693	**0.001**				476	0.284	0.142-0.566	**< 0.001**			
5×5 long interval	66	0.898	0.335-2.404	0.830				298	1.927	0.286-2.887	**0.002**			
CRT	707	0.624	0.361-1.077	0.090				939	1.378	1.004-1.891	**0.047**			
Type of surgery: (L) AR	1007	1.000						1747	1.000					
APR	673	2.053	1.306-3.226	**0.006**				721	1.860	1.356-2.551	**< 0.001**			
HP	399	3.571	2.247-5.675	**< 0.001**	1.971	1.228-3.163	**0.005**	387	2.386	1.656-3.438	**< 0.001**	1.679	1.166-2.418	**0.005**
Margin status: R0	1906	1.000						2685	1.000					
R1/R2	94	4.843	2.947-7.956	**< 0.001**	3.745	2.028-6.919	**< 0.001**	167	6.945	4.992-9.661	**< 0.001**	5.102	3.560-7.313	**< 0.001**

*Synchronous metastases to the primary tumour
Abbreviations: LRRC: locally recurrent rectal cancer, ASA: American Society of Anesthesiologist-Classification, ARJ: Anorectal Junction, RT: radiotherapy, CRT: chemo radiotherapy, (LAR): (Low) Anterior Resection, APR: Abdominoperineal Resection, HP: Hartmann's Procedure, cT-stage: pathological tumour stage, cN-stage: pathological nodal stage

In addition to treatment advances, the imaging guideline adapted towards risk adapted MR staging, resulting in less overstaging and stricter application of RT on the primary tumour [26,27]. This decrease in application of RT might have also contributed to the higher curative intent rate in 2016, as challenges associated with re-irradiating LRRC patients might have led to a low curative intent treatment rate in 2011. The vast majority of the 2011 patients received prior RT, which makes the ability to administer a full dose of RT for LRRC limited due to toxicity [14,28,29]. The 20% more patients with LRRC who received full-course CRT in 2016, together with an absolute 11% increase in re-irradiation, increased utilization of RT to 70% in 2016, which likely contributed to better tumour downsizing and more curative surgery. To further downstage and improve LRRC outcomes, induction chemotherapy as addition to CRT is currently being investigated in the Pelvex-II study in the Netherlands [30,31] and induction chemotherapy in combination with CRT is compared to chemotherapy only in the GRECCAR 15 study in France [32]. While information regarding induction chemotherapy was not collected for these cohorts, this was not standard therapy in the Netherlands in 2011 and 2016.

The percentage of curatively treated patients in 2011 is similar as compared to previous cohort studies, with rates between 29%– 35% from before or during implementation of TME-surgery [4,33], but lower than the 47% in the 2016 cohort. During implementation of the TME-technique in Sweden, a decrease in curative intent treatment of

Table 3
Tumour characteristics of LRRC.

	2011 LRRC n = 114 (%)	2016 LRRC n = 202 (%)	p-value
Time until LRRC *(median, IQR)*	16 [9–25]	16[10–26]	0.278
Location	NA		NA
Lateral		47 (28.0)	
Presacral		23 (13.7)	
Anastomosis		33 (19.6)	
Rectal stump		24 (14.3)	
Anterior		14 (8.3)	
Perineal		7 (4.2)	
Multifocal		19 (11.3)	
Peritoneal		1 (0.6)	
Missing		34	
Metastases at time of LRRC* *	31 (27.2)	68 (33.7)	0.257
Intention of Treatment			**0.004**
Curative	34 (30.4)	95 (47.0)	
Palliative	78 (69.6)	107 (53.0)	
Missing	2		
Neo-adjuvant (chemo) radiotherapy*			**0.009**
None	18 (60.0)	28 (29.5)	
Chemo-re-irradiation	8 (26.7)	36 (38.3)	
Full-course chemoradiotherapy	4 (13.3)	30 (31.9)	
Missing	4	1	
Type of surgical treatment*			0.256
(L)AR	2 (8.7)	4 (5.8)	
APR	6 (26.1)	24 (34.8)	
Posterior exenteration	5 (21.7)	7 (10.1)	
Total exenteration	5 (21.7)	9 (13.0)	
Resection pelvic side wall (lateral)	5 (21.7)	12 (17.4)	
CRS+HIPEC	0 (0.0)	8 (11.6)	
Debulking	0 (0.0)	5 (7.4)	
Missing	11	26	
Complete resection*	NA		NA
R0		45 (68.2)	
R1		18 (27.3)	
R2		3 (4.5)	
Missing		28	

*Only for curatively treated LRRC patients
* *Metastases < 30 days before LRRC until > 30 days after LRRC
Abbreviations: LRRC: locally recurrent rectal cancer; IQR: inter-quartile range, NA: not available; (L)AR: (Low) Anterior Resection, APR: Abdominoperineal Resection, CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy

LRRC from 38% to 29% was found [4]. Although part of this observation could have been a learning curve effect, reversed stage migration also played a role. More extensive or better treatment for the primairy tumour results in fewer recurrences, resulting in an on average less favourable prognostic group. When only the worse prognostic cases remain, this leads to skewed overall outcomes. Nevertheless, ten years after TME-surgery was implemented in the Netherlands, in the period 2009–2013, a remarkable improvement in radicality of TME-surgery was observed, with a decrease in CRM positivity from 14.2% to 5.6% [34], which may also have influenced the treatability of LRRC (e.g. less multifocal recurrence).

While previous studies found more synchronous metastases after neoadjuvant RT [14], our study reports a similar percentage in 2011 and 2016 (27.2% vs. 33.7%, respectively), despite the decrease of RT usage for the primary tumour. This difference might be explained by the previously explained reverse stage migration, leaving aggressive types of LLRCs after RT. Interestingly, our synchronous metastases rates are much lower than the 74% and 40% rates reported by van den Brink et al., which may be explained by further quality improvement of TME-surgery; positive margins or tumour spillage were found in 23% in the TME-trial [35], while in this cohort the R1 resection rate was 4.7% in 2011 and 5.9% in 2016. Imaging modalities have also improved significantly since the TME-trial, affecting not only the detection of metastases, but also the selection of LRRC patients. In addition, even though not readily apparent from clinical TN staging (which remains inaccurate and has limited prognostic relevance [36–39]), it is highly likely that an effect of the implementation of population screening in 2014 in the 2016 dataset led to a higher proportion of less advanced tumours.

Centralization of LRRC care might have improved survival outcomes, as centralization of care has led to better oncological outcomes in other oncological settings, such as genitourinary and oesophageal malignancies [40, 41,42]. However, despite guideline recommendation, numerous patients still seem not to undergo RT for their recurrence. While the number of radiotherapy naïve patients who received full-course CRT decreased to 17% in 2016, further centralization to specialized centres might contribute to more neoadjuvant RT of LRRC to achieve tumour downsizing, and consequently a R0 resection and an improved disease-free survival.

Although this study shows improved outcomes after LRRC treatment over the years, the retrospective character of this study limits the ability to analyse contributing factors. The retrospective set up may have also missed systematic detection of all LRRC. While the Dutch guideline recommends CT of the thorax and abdomen in case of elevated CEA levels, some palliative cases might not have undergone additional imaging, leading to an overrepresentation of the proportion of curatively treated patients. Nevertheless, this is applicable to both cohorts and therefore unlikely to impact the observed increase in curative treatment. Another limitation of this study is the limited data registration, caused by the fact that both studies were primarily designed to examine the outcomes of primary rectal cancer over a 4-year follow-up period, which also limits the follow-up time after LRRC diagnosis. Moreover, variables on LRRC were kept to a minimum to reduce registration burden for the local investigators. For both cohorts, only data from the hospital where the primary tumour was treated were accessible and investigators were dependent on available letters about the LRRC treatment elsewhere.

5. Conclusion

LRRC was more often curatively treated in 2016 compared to 2011 in the Netherlands, and LRRC patients treated with curatively intent had a better OS and CSS in 2016 compared to 2011. More restricted indications for neoadjuvant RT and introduction of risk adapted staging for the primary tumour might have contributed to this, as full dose CRT could be administered more often in LRRC RT-naive patients. Nevertheless, improvements of care, including centralization of LRRC care with optimized multimodality treatment and more treatment options for metastases might have also contributed to this observation.

Declarations

The twenty five main authors, and all collaborative authors, contributed substantially in the acquisition of data. All authors read the manuscript critically and granted approval for publication.

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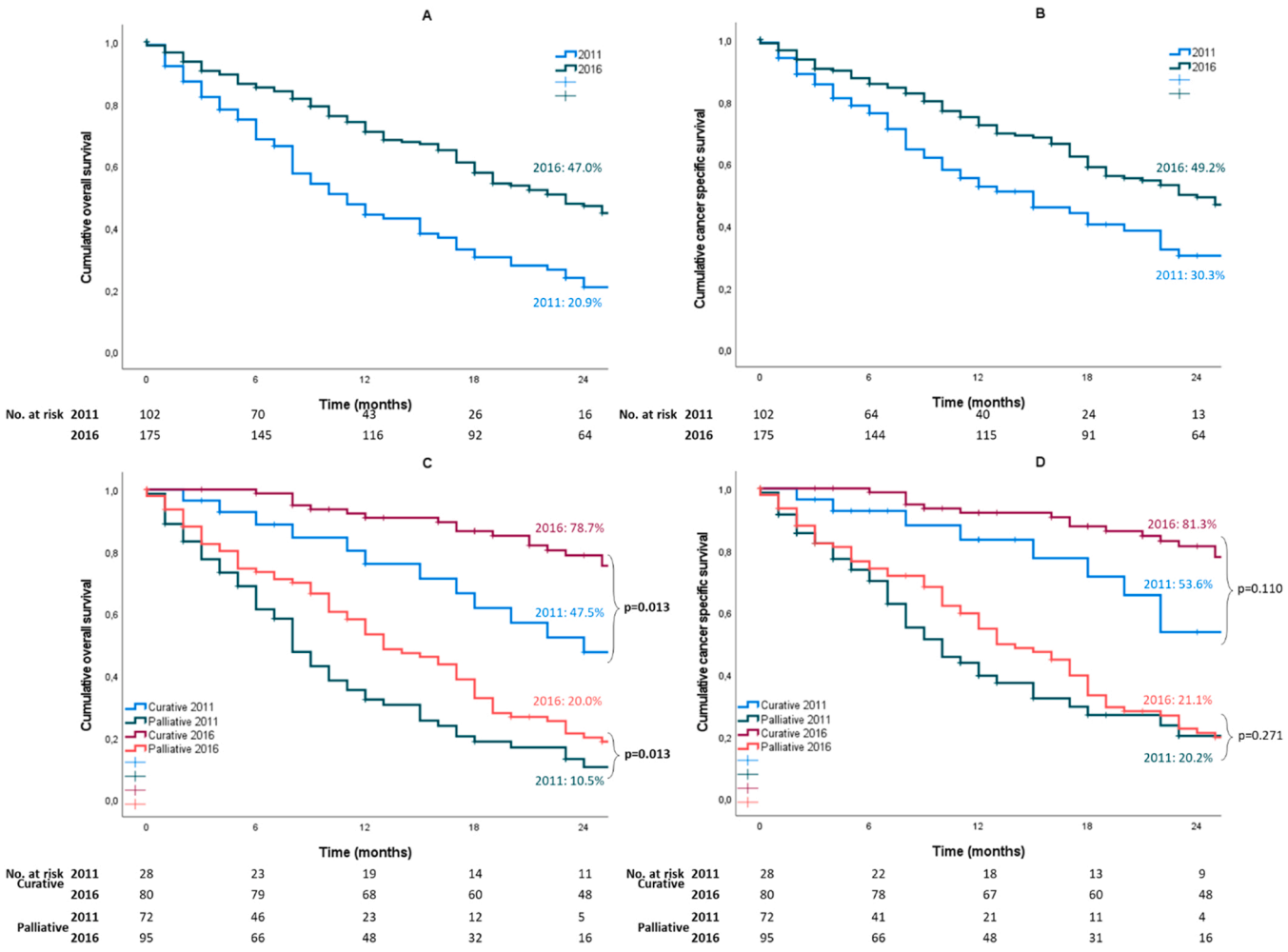

Fig. 2. Survival outcomes after LRRC diagnosis Overall (A and C) and cancer-specific (B and D) survival outcomes stratified per cohort (2011 and 2016) and per intention of treatment (curative vs palliative, C and D). (A) 2-year overall survival after LRRC diagnosis in 2011 (20.9%) and 2016 (47.0%, $p < 0.001$). (B) 2-year cancer specific survival after LRRC diagnosis in 2011 (30.3%) and 2016 (49.2%, $p = 0.004$). (C) 2-year overall survival after LRRC diagnosis in curatively treated patients in 2011 (51.2%) and 2016 (79.8%, $p = 0.041$), and palliative patients in 2011 (10.2%) and in 2016 (19.8%, $p = 0.010$). (D) 2-year overall survival after LRRC diagnosis in curatively treated patients in 2011 (82.4%) and 2016 (57.9%, $p = 0.287$), and palliative patients in 2011 (19.5%) and in 2016 (20.9%, $p = 0.271$).

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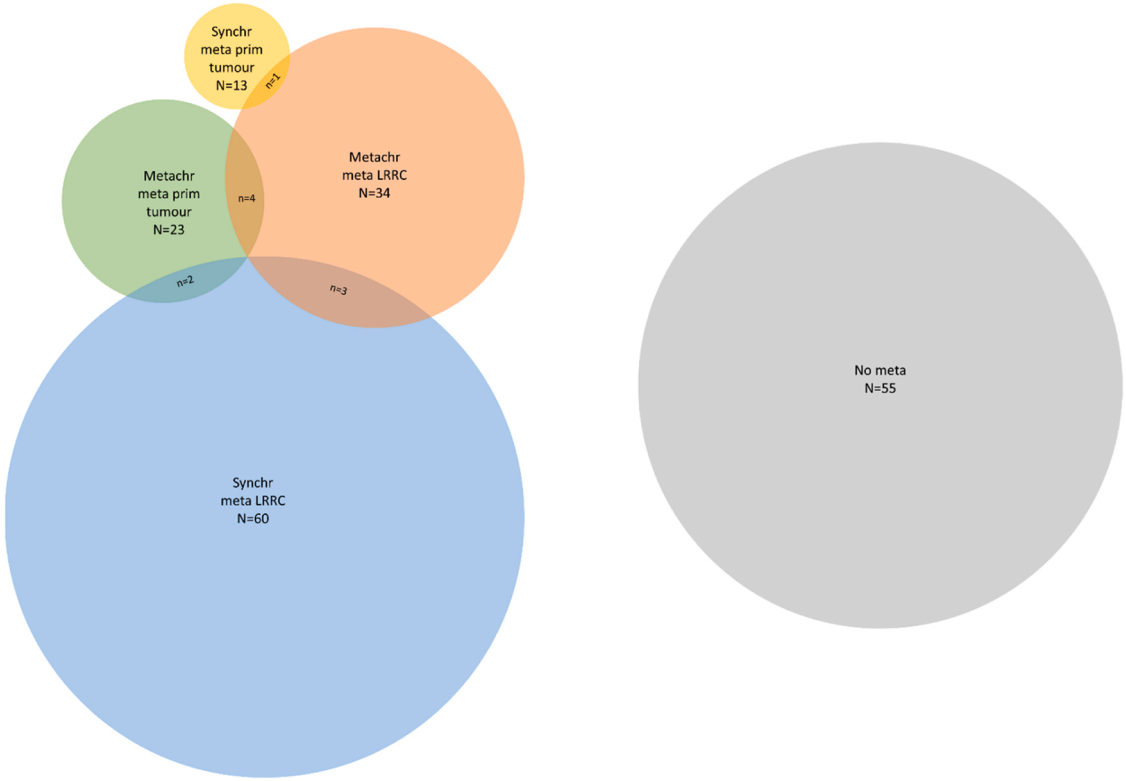

Fig. 3. Distribution of metastases for the 2016 cohort Distribution and overlap of the 175 patients with a LRRC < 3 years of primary surgery divided into five categories; no metastases (grey), synchronous metastases to the primary tumour (yellow), metachronous metastases to the primary tumour (green), synchronous metastases to the LRRC (blue), metachronous metastases to the LRRC (orange).

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114021.

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