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Treatment and survival of locally recurrent rectal cancer: A cross-sectional population study 15 years after the Dutch TME trial

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ABSTRACT

Introduction: Optimized treatment of primary rectal cancer might have influenced treatment characteristics and outcome of locally recurrent rectal cancer (LRRC). Subgroup analysis of the Dutch TME trial showed that preoperative radiotherapy (PRT) for the primary tumour was an independent poor prognostic factor after diagnosis of LRRC. This cross-sectional population study aimed to evaluate treatment and overall survival (OS) of LRRC patients, stratified for prior preoperative radiotherapy (PRT) and intention of treatment of LRRC.

Methods: All patients developing LRRC were selected from a collaborative Snapshot study on 2095 surgically treated rectal cancer patients from 71 Dutch hospitals in the year 2011. Cox proportional hazard analysis was performed to determine predictors for OS.

Results: A total of 107 LRRC patients (5.1%) were included, of whom 88 (82%) underwent PRT for their primary tumour. LRRC was treated with initial curative intent in 31 patients (29%), with eventual resection in 20 patients (19%). Median OS was 22 and 8 months after curative and palliative intent treatment, respectively ($p < 0.001$). Initial CRM positivity and palliative intent treatment were associated with worse OS after LRRC, while prior PRT was not.

Conclusions: This cross-sectional study revealed that rectal cancer patients, who underwent curative resection in the Netherlands in 2011 and subsequently developed local recurrence, were amenable for again curative intent treatment in 29%, with a corresponding median survival of 22 months. Prior PRT was not significantly associated with survival after diagnosis of LRRC.

Introduction

In recent years, the treatment of primary rectal cancer has significantly improved. With the introduction of preoperative radiotherapy (PRT) and Total Mesorectal Excision (TME), the incidence of locally recurrent rectal cancer (LRRC) has decreased to 5–11% [1,2]. Although only a small group of patients will be diagnosed with LRRC nowadays, this still constitutes an important clinical problem. LRRC is often a sign of aggressive biological behaviour, considering the high percentage of distant metastases occurring simultaneously or within one year from diagnosis of LRRC [3]. Curative intent treatment of isolated LRRC is difficult after previous TME surgery with or without PRT, due to an often close relationship to pelvic organs, vessels, nerves and bony structures [4]. Prognosis of LRRC is generally poor, but reported 5-year overall

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Table 1
Characteristics and outcomes of patients with local recurrence of rectal cancer, stratified by intention of treatment.

		Intention of treatment		P-value
		Curative (n = 31)	Palliative (n = 76)	
Gender	Male	21/31 (68%)*	47/76 (62%)	0.565
	Female	10/31 (32%	29/76 (38%)	
Age (years)	<75	26/31 (84%)	49/76 (64%)	0.108
	≥75	4/31 (13%)	25/76 (34%)	
	Unknown/missing	1/31 (3%)	2/76 (3%)	
ASA	I-II	27/31 (87%)	59/76 (78%)	0.513
	III+	3/31 (10%)	14/76 (18%)	
	Unknown/missing	1/31 (3%)	3/76 (4%)	
Tumour characteristics of primary rectal cancer				
Distance to the ARJ	<3 cm	13/31 (42%)	19/76 (25%)	0.587
	3.1–7.0 cm	5/31 (16%)	17/76 (22%)	
	>7 cm	9/31 (29%)	20/76 (26%)	
	Unknown	4/31 (13%)	20/76 (26%)	
cT score	cT1-3	18/31 (58%)	51/76 (67%)	0.488
	cT4	9/31 (29%)	15/76 (20%)	
	Unknown/missing	4/31 (13%)	10/76 (13%	
cN score	cN0	12/31 (39%)	28/76 (37%)	0.738
	cN1	8/31 (26%)	27/76 (15%)	
	cN2	6/31 (19%)	10/76 (13%)	
	Unknown/missing	5/31 (16%)	11/76 (15%)	
Treatment of primary rectal cancer				
Type of preoperative radiotherapy	None	4/31 (13%)	15/76 (20%)	0.257
	SCRT-IS	6/31 (19%)	9/76 (12%)	
	SCRT-DS	0/31 (0%)	6/76 (8%)	
	(L)CRT	15/31 (48%)	28/76 (37%)	
	Other	6/31 (19%)	18/76 (24%)	
Type of operative procedure	Low Anterior Resection	8/31 (26%)	23/76 (30%)	0.815
	Abdomino-perineal resection	13/31 (42%)	26/76 (34%)	
	Hartmann's procedure	10/31 (32%)	26/76 (34%)	
	Proctocolectomy	0/31 (0.0%)	1/76 (1%)	
CRM*	Positive	6/28 (21%)	17/60 (28%)	0.492
	Negative	22/28 (79%)	43/60 (72%)	
Distant metastasis at time of primary tumour resection (synchronous)**		5/31 (16%)	13/76 (17%)	0.903
Distant metachronous metastasis diagnosed between primary tumour resection and local recurrence***		1/31 (3%)	15/76 (20%)	0.030
Distant metachronous metastasis diagnosed simultaneous with local recurrence and thereafter****		3/31 (10%)	25/76 (33%)	**0.013**
Time to LRRC (median, IQR) (months)		18 [11–25]	16 [9–25]	
Curative treatment of recurrent rectal cancer				
Preoperative therapy for local recurrence	None	10/31 (32%)	NA	NA
	Systemic therapy	3/31 (10%)	NA	
	CRT without prior irradiation	1/31 (3%)	NA	
	CRT with prior irradiation	6/31 (19%)		
	Systemic therapy & CRT without prior irradiation	1/31 (3%)	NA	
	Systemic therapy & CRT with prior irradiation	4/31 (13%)		
	Unknown/missing	6/31 (19%)	NA	
Surgical treatment for local recurrence	Yes	20/31 (65%)		
Intra-operative Radiotherapy*****	Yes	11/20 (55%)	NA	NA
Adjuvant Chemotherapy	Yes	5/20 (25%)	NA	NA
Palliative treatment of recurrent rectal cancer				
Palliative treatment	None	NA	46/76 (61%)	NA
	Palliative radiotherapy	NA	9/76 (12%)	
	Palliative chemotherapy	NA	6/76 (8%)	
	Palliative surgery	NA	1/76 (1%)	
	Other	NA	10/76 (13%)	
	Unknown	NA	4/76 (5%)	
Survival after recurrent rectal cancer				

Table 1 (*continued*)

	Intention of treatment		P-value
	Curative (n = 31)	Palliative (n = 76)	
Follow-up time (median, IQR) (months)	11 [4–23]	6 [2.25–11.75]	
Patients alive at end of follow-up	19/31 (61%)	15/76 (20%)	
Overall Survival (median, 95% CI) (months)	22 [9.2–34.7]	8 [6.4–9.5]	

ASA = American Society of Anaesthesiologists-Classification, BMI = Body Mass Index, ARJ = Anorectal junction, cT stage = clinical tumour stage, cN stage = clinical nodal stage, SCRT-IS = Short Course (5 × 5 Gy) Radiotherapy-Immediate Surgery (≤3 weeks interval), SCRT-DS = Short Course (5 × 5 Gy) Radiotherapy-Delayed Surgery (>3 weeks interval), (L)CRT = Long Course Radiotherapy/Chemoradiotherapy, CRM = Circumferential Resection Margin, NA=Not Applicable, CI=Confidence Interval.
*All percentages are rounded to the nearest full point; therefore, they may not add to 100%.
*CRM (≤1 mm) is calculated after exclusion of complete responders (y)pT0 and unknown CRM status.
**Synchronous metastasis at time of primary rectal cancer diagnosis.
***Metachronous metastasis diagnosed after primary tumour resection and until 30 days before diagnosis of locally recurrent rectal cancer.
****Metachronous metastasis diagnosed simultaneously with or following diagnosis of recurrent rectal cancer (30 days before until end of FU).
*****Calculated in patients undergoing surgical resection of recurrent rectal cancer.

survival (OS) varies between 35 and 43% if an R0-resection can be achieved [5,6]. Whereas the treatment of primary rectal cancer is set out in guidelines, the treatment of LRRC is less standardized and requires a more individualized approach. Curative treatment options consist of full PRT in radiotherapy naive patients or re-irradiation after previous PRT, followed by surgical resection with optional intraoperative radiotherapy (IORT) [7]. Recently, induction systemic therapy has been suggested as a valid treatment option [8]. However, the role of adjuvant chemotherapy after resection of LRRC is unclear [9]. Initial treatment for the primary tumour has an important influence on the therapeutic strategy of LRRC, besides anatomical location and extensiveness. Previous PRT also had prognostic implications in subgroup analysis of the Dutch TME-trial, with significantly shorter OS after diagnosis of LRRC in the short course radiotherapy arm [3]. Most published literature on LRRC originates from expert centres with tertiary referral patterns and selected patient populations, while there is a lack of real life population based data [10,11].

Therefore, the aim of this nationwide, retrospective, cross-sectional study was to evaluate recent treatment and outcomes of LRRC in the Netherlands, stratified for PRT of the primary tumour and intention of treatment for LRRC.

Materials and methods

All patients undergoing surgical treatment for primary rectal cancer in the Netherlands are registered in the Dutch ColoRectal Audit (DCRA) [12]. The dataset used for this study was retrieved from a multi-centre, retrospective cross-sectional Snapshot study, which was carried out by the Dutch Snapshot Research Group (DSRG) in 2015. A total of 71 hospitals collected additional data on long-term surgical- and oncological outcomes of patients registered in the DCRA in 2011. Details of the methodology of this Snapshot study have been published previously [13].

Patient selection

All patients who were diagnosed with LRRC during follow-up were included. Patients were considered eligible for analysis when date of birth, date of primary resection and the intention of LRRC treatment was available. Patients with a date of LRRC diagnosis within three months after primary resection were considered as residual tumour instead of LRRC, and were therefore excluded. This study was conducted in accordance with the STROBE guidelines [14]. No ethical approval or informed consent was required from the included patients in the Snapshot study as decided by the Medical Ethical Committee of the Amsterdam UMC, University of Amsterdam, the Netherlands.

Outcome parameters and definitions

The primary outcome of this study was overall survival (OS) after diagnosis of LRRC. Secondary outcomes were treatment characteristics and oncological outcomes for LRRC. The cohort of LRRC patients was stratified in two ways: by intention of LRRC treatment (curative versus palliative) and by initial treatment of the primary tumour (PRT + TME-surgery versus TME-surgery alone). LRRC was defined as recurrent disease at the anastomotic site, in the pelvis or in the perineal wound based on chart review by the collaborators in the various hospitals. No specified data on location of LRRC was available. No specific definitions for intention of LRRC treatment were included when the study was designed, and classification of curative or palliative intent was left to the assessment of the collaborators. Diagnosis of distant metastasis was divided in three categories: synchronous metastasis at time of diagnosis of primary rectal cancer, metachronous metastasis until 30 days before LRRC diagnosis, and metachronous metastasis simultaneously with or following LRRC diagnosis (until 30 days before and end of follow-up). Time to LRRC was defined as the time from primary resection until diagnosis of LRRC. The time from LRRC diagnosis until last follow-up or death was considered as the follow-up period. As a consequence of the cross-sectional study design, all included patients had a similar follow-up duration (from primary resection in 2011 until chart review in 2015). For this reason, a patient might have been diagnosed with LRRC just before the time of cross-sectional follow-up assessment in 2015, and subsequently received treatment beyond the scope of this study, resulting in missing values.

Guideline recommendations

The Dutch guideline for rectal cancer published in 2008 (valid until 2014) recommended PRT for all stages of rectal cancer except for cT1N0 and proximal cT2N0 tumours. At that time, the guideline recommended chemoradiotherapy (CRT), consisting of 28 fractions of 1.8 Gy or 25 fractions of 2 Gy with concomitant Capecitabine, in patients with a suspected positive CRM or in whom four or more clinically positive lymph nodes were diagnosed. Short course radiotherapy (5 × 5 Gy) was recommended for all other patients with an indication for PRT.

Table 2
Baseline characteristics of the primary resection in patients who developed locally recurrent rectal cancer, stratified by pre-operative radiotherapy.

		Preoperative radiotherapy + surgery	Surgery alone	
		No. of patients (n = 88)	No. of patients (n = 19)	*P*-value
Gender	Male	53/88 (60%)[a]	15/19 (79%)	0.124
	Female	35/88 (40%)	4/19 (21%)	
Age (years)	<75	63/86 (72%)	12/19 (63%)	0.661
	≥75	23/86 (26%)	6/19 (32%)	
	Unknown/missing	2/88 (2%)	1/19 (5%)	
ASA-score	I-II	73/88 (83%)	13/19 (68%)	0.344
	III+	12/88 (14%)	5/19 (26%)	
	Unknown/missing	3/88 (3%)	1/19 (5%)	
BMI (kg/m^2)	<30	71/88 (81%)	12/19 (63%)	**0.018**
	≥30	14/88 (16%)	3/19 (16%)	
	Unknown/missing	3/88 (3%)	4/19 (21%)	
Preoperative MRI	Yes	82/88 (93%)	13/19 (68%)	**0.001**
	No	4/88 (5%)	6/19 (32%)	
	Unknown/missing	2/88 (2%)	0/19 (0%)	
Distance to the ARJ	<3 cm	30/88 (34%)	2/19 (11%)	0.107
	3.1–7.0 cm	19/88 (22%)	3/19 (16%)	
	>7 cm	22/88 (25%)	7/19 (37%)	
	Unknown/missing	17/88 (19%)	7/19 (37%)	
cT score	cT1	4/88 (5%)	1/19 (5.3%)	0.332
	cT2	12/88 (14%)	6/19 (32%)	
	cT3	38/88 (43%)	8/19 (42%)	
	cT4	22/88 (25%)	2/19 (11%)	
	cTX/unknown	12/88 (14%)	2/19 (11%)	
cN score	cN0	31/88 (35%)	9/19 (47%)	0.555
	cN1	29/88 (33%)	6/19 (32%)	
	cN2	15/88 (17%)	1/19 (5%)	
	cNX/unknown	13/88 (15%)	3/19 (16%)	
cM score	cM0	67/88 (76%)	15/19 (79%)	0.910
	cM1	8/88 (9%)	2/19 (11%)	
	cMX/unknown	13/88 (15%)	2/19 (11%)	
Type of preoperative radiotherapy	SCRT-IS	15/88 (17%)	NA	NA
	SCRT-DS	6/88 (7%)	NA	
	(L)CRT	43/88 (49%)	NA	
	Other	24/88 (27%)	NA	
Setting	Elective	85/88 (97%)	13/19 (68%)	**<0.001**
	Emergency	1/88 (1%)	5/19 (26%)	
	Unknown/missing	2/88 (2%)	1/19 (5%)	
Approach	Open	50/88 (57%)	11/19 (58%)	0.856
	Laparoscopic	28/88 (32%)	6/19 (32%)	
	Laparoscopic conversion	8/88 (9%)	1/19 (5%)	
	Unknown/missing	2/88 (2%)	1/19 (5%)	
Type of operative procedure	Low Anterior Resection	22/88 (25%)	9/19 (47%)	**0.016**
	Abdomino-perineal resection	38/88 (43%)	1/19 (5%)	
	Hartmann's procedure	27/88 (31%)	9/19 (47%	
	Proctocolectomy	1/88 (1%)	0/19 (0%)	
Multi-visceral resection	Yes	22/88 (25%)	0/19 (0%)	**0.044**
	Unknown/missing	2/88 (2%)	1/19 (5%)	

ASA = American Society of Anaesthesiologists-Classification, BMI = Body Mass Index, MDT = multidisciplinary meeting, MRI = Magnetic Resonance Imaging, Multidisciplinary Team, ARJ = Anorectal junction, cT stage = clinical tumour stage, cN stage = clinical nodal stage, cM stage = clinical metastasis stage, SCRT-IS=Short Course (5×5 Gy) Radiotherapy-Immediate Surgery (≤3 weeks interval), SCRT-DS = Short Course (5 × 5 Gy) Radiotherapy-Delayed Surgery (>3 weeks interval), (L)CRT = Long Course Radiotherapy/Chemoradiotherapy, NA=Not Applicable.

[a] All percentages are rounded to the nearest full point; therefore, they may not add to 100%.

Statistical analysis

Patient and treatment characteristics as well as outcomes were described for the total cohort and subgroups based on intention of treatment and prior PRT. Pearson Chi-square test was used to compare categorical variables between groups. T-test or Mann-Whitney U tests were used to compare continuous variables. Survival analyses were performed using a Kaplan Meier analysis. Patient and tumour characteristics associated with OS were estimated with univariable cox proportional hazards analyses. Due to small sample size, multivariable regression analysis could not be performed. All statistical analyses were performed with SPSS statistical software (version 24; IBM Corp, Armonk, NY).

Results

Baseline characteristics

Of 2095 patients surgically treated for primary rectal cancer in 2011 and registered in the Snapshot study, 117 (5.6%) were reported

Table 3
Pathological and postoperative outcomes of the primary resection in patients with locally recurrent rectal cancer, stratified by pre-operative radiotherapy.

		Preoperative radiotherapy + surgery	Surgery alone	
		No. of patients (n = 88)	No. of patients (n = 19)	*P*-value
Pathological tumour stage	(y)pT0 (y)pT1 (y)pT2 (y)pT3 (y)pT4 (y)pTX/ unknown	5/88 (6%)[a] 0/88 (0%) 12/88 (14%) 48/88 (55%) 19/88 (22%) 4/88 (5%)	0/19 (0%) 1/19 (5%) 2/19 (11%) 15/19 (79%) 0/19 (0%) 1/19 (5%)	**0.033**
Pathological nodal stage	(y)pN0 (y)pN1 (y)pN2 (y)pNX/ unknown	43/88 (49%) 25/88 (28%) 17/88 (19%) 3/88 (3%)	5/19 (26%) 7/19 (37%) 6/19 (32%) 1/19 (5%)	0.320
CRM[b]	Positive Negative	19/74 (26%) 55/74 (74%)	4/14 (29%) 10/14 (71%)	0.821
30-day postoperative overall complication rate	Yes Unknown/ missing	37/88 (42%) 3/88 (3%)	8/19 (42%) 1/19 (5%)	0.897
Postoperative transfusion needed	Yes Unknown/ missing	26/88 (30%) 5/88 (6%)	3/19 (16%) 2/19 (11%)	0.257
Length of stay (median, IQR)		9 [7–19]	12 [6–16]	0.098
Re-admission rate (>30 days)	Yes	0/88 (0%)	1/19 (5%)	0.526
Re-intervention (>30 days)	Yes	35/88 (40%)	2/19 (11%)	0.058
Follow-up months (median, IQR)		28 [15–39]	35 [19–40]	0.454
Time interval (months) between primary resection and local recurrence (median, IQR)		16 [10–24]	21 [11–38]	0.414
Distant metastasis at time of primary tumour resection (synchronous)[c]		15/88 (17%)	3/19 (16%)	0.894
Distant metachronous metastasis diagnosed between primary tumour resection and local recurrence[d]		14/88 (16%)	2/19 (11%)	0.551
Distant metachronous metastasis diagnosed simultaneous with local recurrence and thereafter[e]		21/88 (24%)	7/19 (37%)	0.243
Curative/palliative intent treatment for local recurrence	Curative Palliative	27/88 (31%) 61/88 (69%)	4/19 (21%) 15/19 (79%)	0.401

pT = pathological tumour stage, pN = pathological nodal stage, CRM = Circumferential Resection Margin, IQR = Interquartile range.
[a] All percentages are rounded to the nearest full point; therefore, they may not add to 100%.
[b] CRM (≤1 mm) is calculated after exclusion of complete responders (y)pT0 resections and unknown CRM status.
[c] Synchronous metastasis at moment of primary rectal cancer.
[d] Metachronous metastasis diagnosed after primary tumour resection and until 30 days before diagnosis locally recurrence rectal cancer.
[e] Metachronous metastasis diagnosed simultaneously with or following diagnosis of recurrent rectal cancer (30 days before until end of FU).

to have LRRC during follow-up. After exclusion of patients with diagnosis of LRRC within three months after the primary resection, 107 patients (5.1%) were included for analysis. The median time to diagnosis of LRRC was 17 months (IQR 10–25 months), and 95 patients (89%) were diagnosed within 36 months. The median follow-up time of the LRRC patients was 29 months [IQR 16–40 months]. The total cohort consisted predominantly of males (n = 68, 64%) and the mean age was 66 years (SD 12,7 years) at time of primary resection. Forty-one percent of patients had developed distant metachronous metastases until or simultaneous with diagnosis of LRRC. Out of all 107 patients, 31 (29%) received treatment with curative intention.

Curative versus palliative intention of treatment for LRRC

Patient, tumour and treatment characteristics at the time of primary resection are shown in Table 1 and were comparable between the two groups. Curative patients had significantly less distant metastasis being diagnosed before or following LRRC (10% vs 33%, p = 0.013). Time to LRRC was comparable between curative and palliative patients (18 months vs 16 months, p = 0.158). More detailed data are provided in Appendix Table 1a–b.

Curative intent therapy started with induction therapy (chemoradiotherapy or systemic therapy) in 16 of 31 patients (52%). Three of those 16 patients died before surgery and two patients reached end of follow-up before scheduled surgery. Intentionally curative surgery for LRRC was eventually performed in 20 patients, consisting of total pelvic exenterations (n = 5), abdominoperineal resections (n = 4), posterior pelvic exenterations (n = 2) and other procedures (n = 9). Out of the 20 patients undergoing surgical resection, 11 (55%) received IORT. Adjuvant chemotherapy was administered in 4 of 20 patients (20%) who underwent resection. Of the 11 other patients who started curative intent treatment, no resection was (still) performed in 8 patients and treatment strategy was unknown due to referral without further documentation in 3 patients. (Appendix Tables 1 and 2).

The majority of palliative treated LRRC patients (n = 50, 66%) did not receive any further treatment based on available data in the

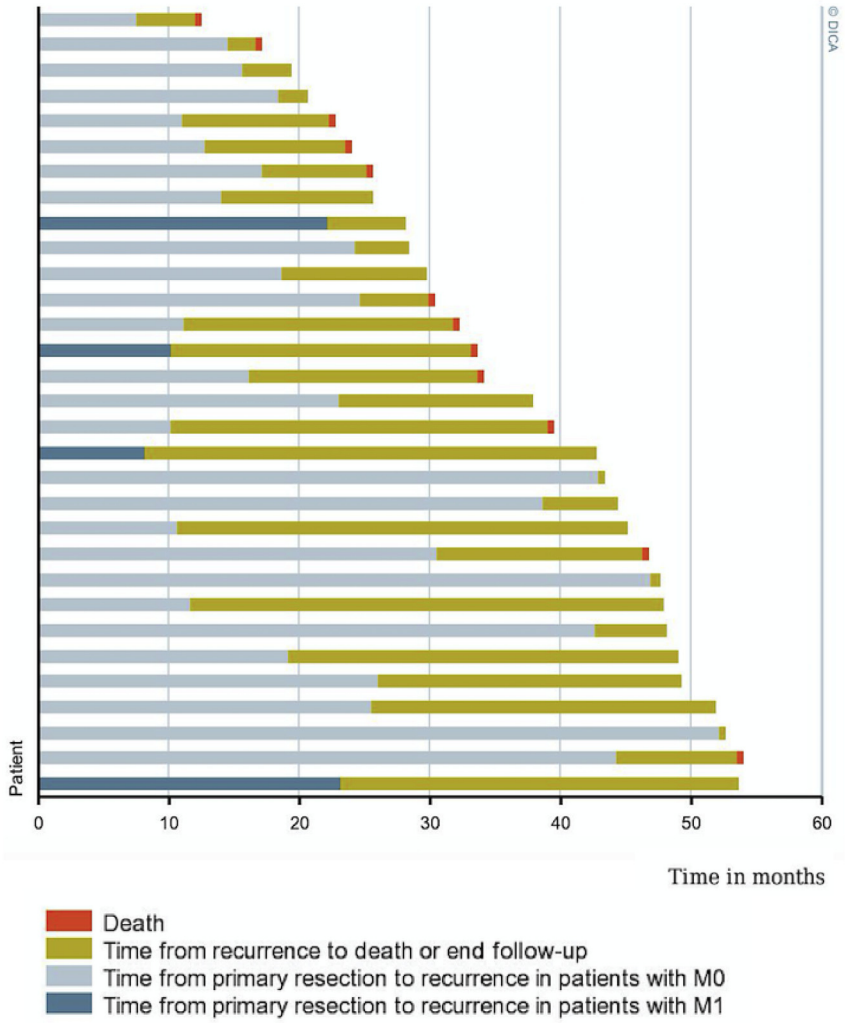

Fig. 1a. Timelines in patients with LRRC and a curative intention of treatment.

patient files. Nine patients were treated with radiotherapy (12%) and six patients (8%) with chemotherapy. Additionally, one patient underwent palliative surgical resection, and seven patients underwent palliative interventions for symptom control, such as an ileostomy, colostomy, stenting or enteral bypass.

LRRC treatment and outcome stratified for prior PRT

Patient, tumour and treatment characteristics compared between patients initially treated with PRT + TME-surgery and TME-surgery alone are shown in Tables 2 and 3**.** Out of all 107 LRRC patients, 88 (82%) patients were preoperatively treated with PRT for primary rectal cancer. When compared to prior PRT-TME-surgery, patients who initially underwent TME-surgery alone were less often staged by pre-operative MRI (68% vs. 93%, $p = 0.001$) and were more often operated in an emergency setting (26% vs 1%, $p < 0.001$). TME-surgery alone consisted more often of low anterior resections (47% vs. 25%) and Hartmann's procedures (47% vs 31%). Time to LRRC and the intention of LRRC treatment were comparable between the groups with or without prior PRT.

Survival analysis

The timelines from primary rectal cancer to LRRC and from LRRC to death or the end of follow-up in curative and palliative patients are depicted in Fig. 1a and Fig. 1b. Fig. 2 shows the Kaplan Meier curves for OS, stratified by intention at the start of treatment for LRRC. One-year OS for patients with a curative and palliative intention of treatment was 42% versus 24%, respectively. Corresponding 2-year OS was 23% and 5%, and median survival was 22 and 8 months, respectively. For the 20 patients who underwent resection, 1-year OS was 50%, 2-year OS 30%, and median OS 11 months. Fig. 3 shows the Kaplan Meier curves for OS in LRRC patients, stratified by prior PRT or surgery alone. One-year OS for patients initially treated with TME-surgery alone was 42%, compared to 26% in patients who initially underwent PRT followed by TME surgery. Corresponding 2-year OS rates were 16% and 9%, and median survival 15 and 7 months, respectively. Univariable analyses for OS after LRRC are displayed in Table 4a and Table 4b. Prior PRT was not associated with OS after diagnosis of LRRC. CRM involvement after resection of primary rectal cancer was negatively associated with OS. Curative intent treatment, curative resection and curative intent radiotherapy were all positively associated with OS. No multivariable regression analysis was performed because of the small sample size.

Discussion

This cross-sectional study of primary rectal cancer surgery in the Netherlands in 2011 was able to consecutively determine the

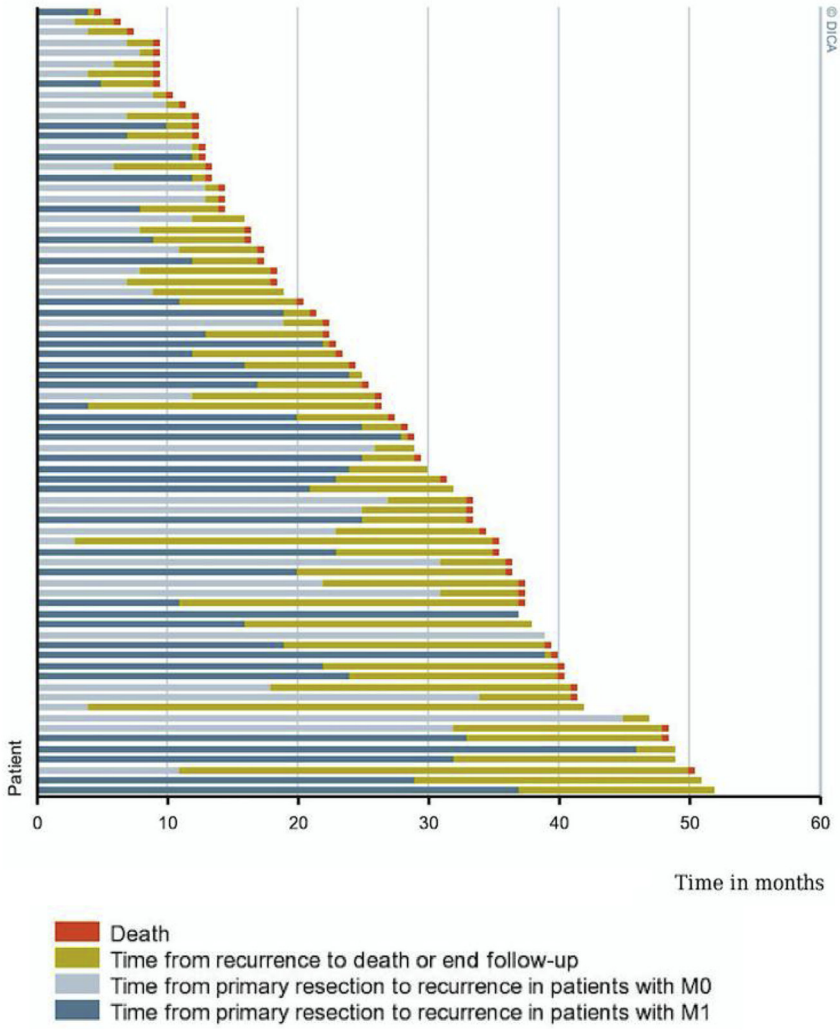

Fig. 1b. Timelines in patients with LRRC and a palliative intention of treatment.

incidence of LRRC, subsequent treatment and survival. Out of 2095 patients, 107 (5.1%) patients were diagnosed with LRRC, of whom 29% started treatment with a curative intention and eventually 19% underwent resection. Two-year OS after treatment with curative and palliative intent was 23% and 5% and median survival was 22 and 8 months, respectively. Prior PRT for primary rectal cancer was not significantly associated with OS after diagnosis of LRRC but CRM positivity of the primary resection appeared to be a risk factor in univariable analysis, in contrast to similar analyses in LRRC patients from the Dutch TME-trial [3].

There are no similar cross-sectional population studies as far as we are aware of, with only limited longitudinal population based studies available on treatment characteristics and subsequent outcome of LRRC. Palmer et al. published in 2007 results from 2381 patients treated for primary rectal cancer between 1995 and 2003 in the Stockholm region in Sweden [15]. The proportion of PRT was 55% and 141 patients developed local recurrence (6%). Surgical resection was attempted in 57 of those 141 patients (40%), but this was intentionally curative (R0-1) in only 25 (18%). Palliative radio- or chemotherapy was given in 34%, and symptom palliation in 26%. With median 12 months' follow-up, reported 5-year OS was 9% for the whole group with LRRC was 9%, and 57% after resection with curative intent. These results were better compared to those of patients treated between 1980 and 1991 in the Stockholm region [15]. The resection rate in our current study was 19%, and similar to a recent Swedish study by Westberg et al. who reported results of patients diagnosed with LRRC between 1995 and 2007 in Sweden. The results showed that 149 of 426 LRRC patients (35%) underwent surgery, 22.3% (95/426) of the patients had potentially curative surgery, and reported 3-year OS was 56% [16]. However, survival in our study was lower with a median survival of only 22 months.

Surgical resection rates of LRRC in the Dutch TME trial were 17% in the PRT arm, and 35% in the surgery alone arm [2]. In a recent Korean study, 147 local recurrences (6%) developed in 2485 curatively treated rectal cancer patients, of which 33 were resected (22%) [17]. This suggests that the proportion of LRRC patients who undergo resection has not changed over time, and that still most patients get palliative care with restricted life expectancy. In this study, the median time to LRRC was 18 and 16 months in curative and palliative patients respectively, which differs from literature, in which the median time to LRRC was found to be 23 months [18]. This difference is likely explained by the "real world" data compared to studies originating from expert centres, the latter comprising selected populations with potential publication bias.

A systematic review of intentionally curative treatment of LRRC by Tanis et al. included 55 cohort studies published between 1993 and 2010, comprising 3767 patients [19]. This review suggested some historical changes in the curative management and outcome

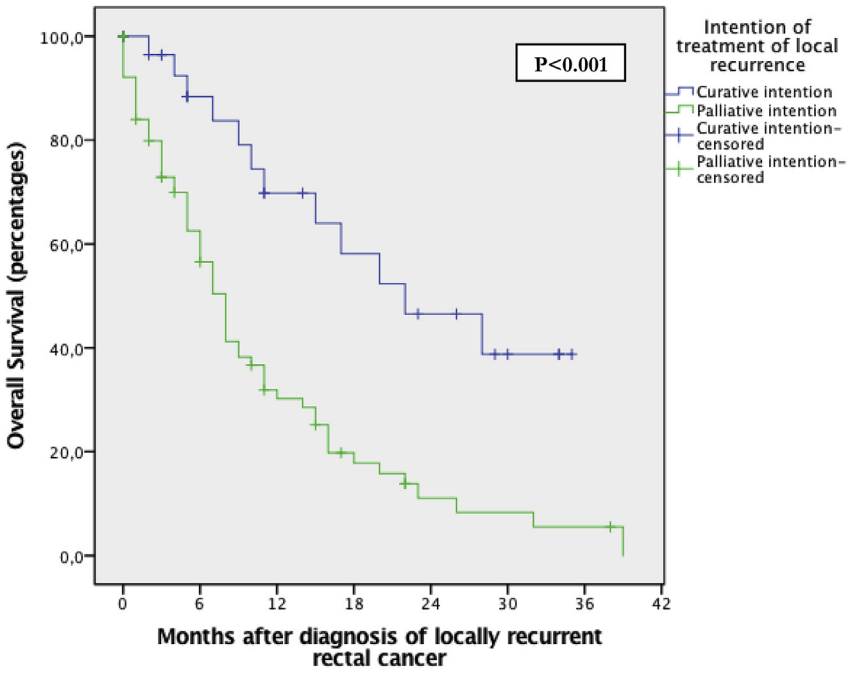

Fig. 2. Overall Survival using Kaplan Meier analysis of patients with locally recurrent rectal cancer, stratified for intention of treatment of local recurrence.

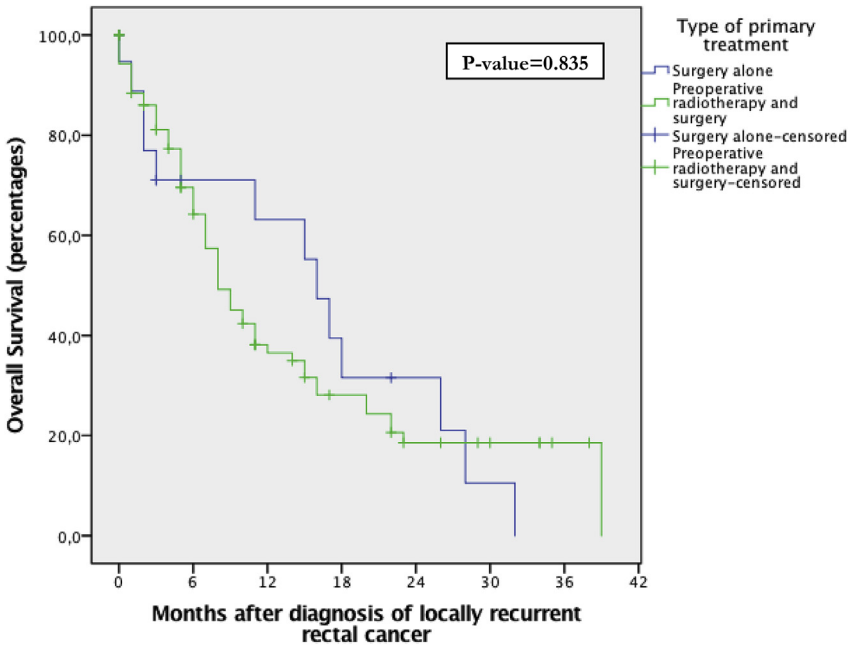

Fig. 3. Kaplan Meier analysis of Overall Survival after diagnosis of locally recurrent rectal cancer, stratified by type of primary treatment (pre-operative radiotherapy followed by surgery or surgery alone).

of LRRC. Reported 5-year OS rates were plotted versus year of publication, which revealed increasing OS rates over time. There seemed to be an increasing consensus on the use of pre-operative radiotherapy for LRRC, of which the schedule depends on prior PRT. Still 10 of 31 patients in the present study who started curative intent treatment did not receive any type of induction therapy. The large referral centres in the Netherlands routinely apply induction therapy nowadays, with significant improvements in outcome, that are not dependent on prior PRT anymore [20–22]. Also, a recent review on treatment of LRRC in previously irradiated patients revealed that re-irradiation schedules were applied in 2 of 9 included studies [23]. This illustrates the value of real life data, demonstrating that published results from expert centres do not reflect daily practice within that country. Interestingly, the PelvEx collaborative group did not found improved survival after induction therapy in 614 patients out of a total cohort of 1184 patients who underwent pelvic exenteration for LRRC [24].

Stratification for PRT revealed a remarkable high emergency resection rate (26%) in the TME-surgery alone group at baseline (Table 2), while this was only 2% in the whole cohort. Like

Table 4a
Univariable analyses of Overall Survival after local recurrence of rectal cancer: patient- and disease-related variables of primary rectal cancer.

		Hazard ratio for death (95% CI)	P-value
Gender (%)	Female	1.00 (ref)	
	Male	1.31 (0.81–2.11)	0.273
Age (years)	<75	1.00 (ref)	
	≥75	1.12 (0.95–1.32)	0.186
Treatment primary rectal cancer	Surgery alone	1.00 (ref)	
	Preoperative radiotherapy + surgery	1.07 (0.58–1.95)	0.839
Distance to the ARJ	>3 cm	1.00 (ref)	
	≤3 cm	1.07 (0.62–1.87)	0.801
Setting	Elective	1.00 (ref)	
	Emergency	1.21 (0.38–3.88)	0.744
Approach	Open	1.00 (ref)	
	Laparoscopic	0.67 (0.33–1.39)	0.283
	Laparoscopic conversion	0.62 (0.28–1.39)	0.246
Type of operative procedure (%)	Low Anterior Resection	1.00 (ref)	
	Abdomino-perineal resection*	1.16 (0.66–2.04)	0.606
	Hartmann's procedure	0.82 (0.47–1.43)	0.483
Multi-visceral resection	Yes	1.58 (0.90–2.79)	0.114
pT score	pT1-3	1.00 (ref)	
	pT4	1.43 (0.82–2.51)	0.208
pN score	pN0	1.00 (ref)	
	pN1-2	1.05 (0.65–1.69)	0.841
CRM**	Negative	1.00 (ref)	
	Positive	**2.25 (0.74–6.83)**	**0.017**
Distant metastasis until diagnosis of local recurrence	No	1.00 (ref)	
	Yes	1.09 (0.54–2.18)	0.817
Median time interval between primary resection and local recurrence	>18 months	1.00 (ref)	
	≤18 months	1.31 (0.80–2.13)	0.286

CI=Confidence Interval, ARJ = Anorectal junction, pT = pathological tumour stage, pN = pathological nodal stage, CRM = Circumferential Resection Margin, IQR = Interquartile range.
**CRM positivity defined as ≤1 mm.
* Included proctocolectomy patient with definitive ileostomy (n = 1).

Table 4b
Univariable analyses of Overall Survival after local recurrence of rectal cancer: treatment-related variables of local recurrence.

		Hazard ratio for death (95% CI)	P-value
Intention of treatment	Curative	1.00 (ref)	
	Palliative	**3.08 (1.65–5.77)**	**<0.001**
Induction chemotherapy, intentionally followed by resection	No	1.00 (ref)	
	Yes	0.47 (0.11–1.91)	0.288
Radiotherapy for LRRC*	No or palliative	1.00 (ref)	
	Curative	**0.27 (0.14–0.52)**	**<0.001**
Resection of LRRC**	No or palliative	1.00 (ref)	
	Curative	**0.26 (0.12–0.55)**	**<0.001**

CI = Confidence Interval, LRRC = Locally recurrent rectal cancer.
*n = 21 curative intent radiotherapy, of which 16 eventually underwent resection and n = 9 palliative radiotherapy.
*n = 20 curative and n = 1 palliative resection.

previously demonstrated, emergency surgery for colorectal cancer is positively associated with high overall recurrence rates [25]. Therefore, one should refrain from emergency resection whenever possible. Obstruction can be managed by a decompressing stoma, which enables adequate staging and multidisciplinary treatment planning. Regarding margin status after primary tumour resection, CRM was negative in more than 70% of all LRRC patients, regardless of prior PRT. In the LRRC patients of the TME trial, CRM at primary surgery was negative in 66% after surgery alone and 46% after prior 5 × 5 Gy [3]. Initial CRM status lost its significance in multivariable analysis of predictors for OS after diagnosis of LRRC in the TME trial, while positive CRM of the primary resection was associated with poor OS after LRRC in the present study. This suggests that changes in primary treatment since the TME trial have influenced patterns and predictors of LRRC as well as subsequent oncological outcome. This is also illustrated by the percentage of simultaneous distant metastases after prior PRT: 74% in the TME trial versus 24% in the present study. Due to several changes in rectal cancer management, the TME surgery alone group of the present study constitutes a completely different patient population when compared to the TME trial, likely explaining the observation that prior PRT is no longer associated with OS after diagnosis of LRRC. With tailored down staging radiotherapy and improved quality of TME surgery, the risk of LRRC has been significantly reduced [15]. Nowadays,

LRRC after adequate neo-adjuvant and surgical treatment likely reflects an inherent aggressive biological behaviour, explaining the high proportion of palliative intent treatment (71%), as found in this study.

Some limitations of this cross-sectional study need to be addressed. The retrospective collection of data resulted in missing data, therefore some factors of the complex clinical decision making in LRRC patients were not available. Additionally, not all hospitals in the Netherlands participated in this Snapshot study, which may have biased the results. Also, due to the design of this cross-sectional study, no information was available on LRRC patients referred to specialized centres after being treated in a local hospital for primary rectal cancer. Furthermore, at the time of the Snapshot study, the DCRA did not discriminate between partial mesorectal excision (PME) and TME for resection of the primary tumour. This would have been interesting to analyse, because the presence of residual mesorectum after PME could have been a source of LRRC.

Conclusion

This study provided real life data on characteristics and treatment of LRRC in the Netherlands reflecting current daily practice. Patterns of LRRC and predictors of subsequent oncological outcome have changed since the TME trial. However, the proportion of patients eventually undergoing curative resection is still small and survival poor. Optimized multimodality treatment in expert centres might improve outcome in the future.

Ethics approval and consent to participate

No ethical approval or informed consent was required from the included patients in the Snapshot study as decided by the Medical Ethical Committee of the Amsterdam UMC, University of Amsterdam, the Netherlands. The study was performed in accordance with the Declaration of Helsinki.

Consent for publication

No consent for publication was required from the included patients in the Snapshot study, the manuscript doesn't contain any individual person's data in any form.

Availability of data and material

The Snapshot data used for this study are available from the Dutch Snapshot Research Group (DSRG) but are not publicly available. The Snapshot data can be made accessible for other clinical researchers upon reasonable request and with permission of the Dutch Snapshot Research Group.

Author agreement/declaration

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Authors' contributions

'RD and EGK' made substantial contributions to conception and design and acquisition of data and analysis and interpretation of data. 'RD, EGK, and WAAB' participated in drafting the article. 'RD, EGK, WAAB, CAMM, CJHV, WAB, GLB, PJT, and AGJ' participated in revising the article critically for important intellectual content and give final approval of the version to be published.

Disclaimers

None.

Declarations of interest

None.

Conflict of interest statement

Robin Detering, Eleonora G. Karthaus, Wernard A.A. Borstlap, Corrie A.M. Marijnen, Cornelis J.H. van de Velde, Willem A. Bemelman, Geerard L. Beets, Pieter J. Tanis, and Arend G. J. Aalbers, have no conflicts of interest or financial ties to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.06.016.

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