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Comparison of three-year oncological results after restorative low anterior resection, non-restorative low anterior resection and abdominoperineal resection for rectal cancer

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ABSTRACT

Introduction: Oncological outcome might be influenced by the type of resection in total mesorectal excision (TME) for rectal cancer. The aim was to see if non-restorative LAR would have worse oncological outcome. A comparison was made between non-restorative low anterior resection (NRLAR), restorative low anterior resection (RLAR) and abdominoperineal resection (APR).
Materials and methods: This retrospective cohort included data from patients undergoing TME for rectal cancer between 2015 and 2017 in eleven Dutch hospitals. A comparison was made for each different type of procedure (APR, NRLAR or RLAR). Primary outcome was 3-year overall survival (OS). Secondary outcomes included 3-year disease-free survival (DFS) and 3-year local recurrence (LR) rate.
Results: Of 998 patients 363 underwent APR, 132 NRLAR and 503 RLAR. Three-year OS was worse after NRLAR (78.2%) compared to APR (86.3%) and RLAR (92.2%, $p < 0.001$). This was confirmed in a multivariable Cox regression analysis (HR 1.85 (1.07, 3.19), $p = 0.03$). The 3-year DFS was also worse after NRLAR (60.3%), compared to APR (70.5%) and RLAR (80.1%, $p < 0.001$), HR 2.05 (1.42, 2.97), $p < 0.001$. The LR rate was 14.6% after NRLAR, 5.2% after APR and 4.8% after RLAR ($p = 0.005$), HR 3.22 (1.61, 6.47), $p < 0.001$.
Conclusion: NRLAR might be associated with worse 3-year OS, DFS and LR rate compared to RLAR and APR.

1. Introduction

The type of resection in total mesorectal excision (TME) for rectal cancer is thought to be of influence on oncological outcome [1–3]. In case of sphincter preserving surgery different types of resection can be performed. A restorative low anterior resection

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(RLAR) might be performed or a non restorative low anterior resection (NRLAR) with creation of an end colostomy, often referred to as Hartmann procedure. If sphincter preservation is not an option an abdominoperineal resection (APR) should be performed. Although there is a trend towards more restorative procedures, the rate of end colostomy construction can still be as high as 50% [17,18]. End colostomy construction is a valid option in case of expected poor functional outcome or high risk of mortality in case of an anastomotic leakage. Either an APR or NRLAR can be performed in such cases, but the rationale for NRLAR is often unclear and NRLAR might have an impact on oncological outcomes.

Oncological outcome seems to be independent of what surgical technique is used [4]. Introduction of laparoscopic surgery in the past decades reduced morbidity rates after surgery [5–8]. Robot-assisted TME and transanal TME (TaTME) aimed to further reduce morbidity rates [9–15]. One of the potential benefits of robot-assisted TME and TaTME is that they enable surgeons to safely perform sphincter preserving surgery more frequently [16].

Although inconclusive, data from several studies suggest that NRLAR is associated with worse oncological outcome compared to APR and restorative surgery [1–3]. One of the most important factors for survival is achieving a circumferential margin (CRM) of more than 1 mm. Positive CRM rates as high as 31.7% have been reported after NRLAR [19]. Most of this evidence originates from the time before laparoscopic TME, robot-assisted TME and TaTME were introduced. Therefore, this retrospective cohort study including laparoscopic TME, robot-assisted TME and TaTME aims to compare NRLAR, RLAR and APR with regard to 3-year oncological results.

2. Method

2.1. Study design

A retrospective cohort study was performed in eleven dedicated rectal cancer centres in the Netherlands with extensive experience in laparoscopic TME, robot-assisted TME or transanal TME (TaTME). Each centre was considered high-volume, performing at least 40 TME procedures each year, of which at least 30 procedures were performed using the dedicated technique the centre had most experience with (laparoscopic in 5 centres, robot-assisted in 3, TaTME in 3). Three year oncological outcomes were compared between the different type of procedure (APR, NRLAR or RLAR).

All patients undergoing rectal resection for primary rectal adenocarcinoma between January 1st 2015 and December 31, 2017 were identified from the prospective obligatory national Dutch ColoRectal Audit (DCRA) database. Patients were eligible for inclusion if they were older than 18 years and had MRI defined rectal cancer according to the sigmoid take-off definition by d'Souza et al. [20]. Patients were excluded if they underwent local excision only, if they had metastatic disease (cM1) or non-curative disease, if they underwent hyperthermic intraperitoneal chemotherapy (HIPEC) or intra-operative radiotherapy (IORT) or if they underwent acute surgery. For one robot-assisted and one TaTME centre that began to use the expert technique as late as 2014 procedures from 2015 were excluded. This was done because less than 30 procedures were performed with the expert technique in these centres in 2014 and the learning curve had not yet fully run its course. Each patient was discussed by a local multidisciplinary cancer board and indications for neoadjuvant treatment was according to the Dutch National guidelines for colorectal cancer [21]. No adjuvant therapy was administered, according to the Dutch guidelines.

Missing data was complemented using patients electronic medical records and all preoperative MRI were reviewed by instructed researchers with extensive training by a radiologist. This study received approval from the Medical research Ethics Committees United (MEC-U) medical ethics committee (AW 19.023/W18.100) and was approved by the local ethic boards of all participating centres.

2.2. Outcomes and definitions

The primary outcome was overall survival (OS) at three years of follow-up. Overall survival was defined as the proportion of patients alive at three years of follow-up. Secondary outcomes were 3-year disease-free survival (DFS), 3-year systemic recurrence (SR) rate, 3-year local recurrence (LR) rate and rate of multifocal recurrence. Disease -free survival was defined as the proportion of patients alive at 3 years postoperative without recurrent disease. Systemic recurrence was defined as any distant metastasis, pathologically proven or a lesion suspect for metastasis on radiological imaging that showed growth on consecutive imaging. Local recurrence was defined as any tumour deposit in the pelvic cavity that was pathologically proven adenocarcinoma, or a lesion suspect for recurrence on radiological imaging that showed growth on consecutive imaging. Location of LR was reported according to the classification by Georgiou et al. [22]. Multifocal recurrence was defined as presence of more than one pelvic lesion.

Baseline characteristics included age in years, body mass index (BMI), American Society of Anesthesiologsts (ASA) classification, history of abdominal surgery, distance to the anorectal junction (ARJ) on MRI in centimetres, mesorectal fascia (MRF) involvement on pre-treatment MRI, clinical TNM stage and administration of neoadjuvant therapy. A low rectal tumour was defined according to the definition of the English National low rectal cancer development program (LOREC): "a tumour with its lower border at or below the origin of the levators on the pelvic sidewall" based on sagittal MRI images [23].

The type of procedure was defined according to the type of procedure performed during primary TME surgery. RLAR was defined as a TME dissection with the formation of a stapled or hand-sewn colorectal or coloanal anastomosis, with or without diverting ileostomy creation. NRLAR was defined as low anterior resection with the formation of an end colostomy, thus leaving a rectal stump in situ. APR was defined as a complete rectal resection with intersphincteric or complete proctectomy and the formation of and end colostomy. An intersphincteric resection with mucosectomy was scored as an APR. Conversion was defined as conversion to laparotomy to complete the mesorectal dissection. Intraoperative complications were scored. Surgical complications were categorized according to the Clavien-Dindo classification [24]. Clavien-Dindo grade III or higher was defined as major morbidity. Anastomotic leakage was defined as radiological or clinical evidence of anastomotic dehiscence [25]. A pelvic abscess was defined as collection visible on radiologic evaluation. Pelvic sepsis was defined as the occurrence of either a pelvic abscess or anastomotic leakage. Quality of the TME specimens was defined according to Quirke et al. [26]. Positive circumferential margin (CRM) was defined as a margin of 1 mm or less.

2.3. Statistical analysis

All categorical data are presented as number of cases and percentages and continuous data are shown as mean (standard deviation) or median [range]. Categorical variables were compared using the Chi-square test, and continuous variables using the independent sample T-test or the Mann-Whitney test, depending on the distribution. Kaplan-Meier survival analysis was used for uncorrected OS, DFS, SR and LR per type of surgery. Multivariable Cox regression analyses using backward selection were performed to evaluate the association between type of surgery (APR, NRLAR or RLAR) and OS, DFS and LR. Variables used in the Cox-regression were supposed risk factors based on literature. Variables used in the Cox-regression were: surgical technique(laparoscopic, robot-assisted or TaTME), age category(<70, 70–80 or >80 years old), BMI category (<18.5, 18.5–25, 25–30 or >30), sex (male or female), ASA(I/II versus III/IV), low rectal tumour according to the LOREC definition, MRF involvement, cT4, cN+, administration of neoadjuvant therapy (none, radiotherapy or chemoradiation) and type of procedure (APR, NRLAR or RLAR). Missing data was imputed using multiple imputations if the type of missing data was missing at random or completely at random. The variance inflation factor (VIF) was calculated for each variable for each outcome to identify any multicollinearity. If the VIF was below 1, the severity of multicollinearity was considered low. If the VIF was above 4, it was assumed that multicollinearity was present. Multivariate analysis were only performed if no signs of multicollinearity were present. A p-value <0.05 was considered statistically different. The statistical software R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) was used for the analysis with the packages “survival” and “survminer”.

3. Results

A total of 998 patients were included of which 363 underwent APR, 132 underwent NRLAR and 503 underwent RLAR. A flowchart can be seen in Fig. 1.

3.1. Baseline characteristics

Table 1 gives a baseline comparison per type of procedure. Patients in the NRLAR group were significantly older (mean age 74 years (9.3), compared to 68(10.4) in APR and 64(9.7) in RLAR, $p < 0.001$), more frequently presented with a ASA III classification (34.1%, compared to 22.9% in APR and 14.1% in RLA, $p < 0.001$) and more frequently had history of abdominal surgery (39.4%, compared to 30.0% in APR and 24.1% in RLAR, $p < 0.001$). NRLAR was most frequently performed laparoscopically (70.5%, versus 53.4% in APR and 34.8% in RLAR, $p < 0.001$).

Patients in the APR group had lower distance to ARJ on MRI (2 cm [0,4], versus 6 cm [4,8] and 7 cm [5,9] in NRLAR an RLAR respectively, $p < 0.001$), higher rate of LOREC tumours (90.9%, versus 51.5% and 39.4% in NRLAR and RLAR respectively, $p < 0.001$), higher rate of MRF involvement (43.7%, versus 30.2% and 24.0% in NRLAR and RLAR respectively, $p < 0.001$) and more administration of neoadjuvant chemo radiation (37.5%, versus 21.9% and 29.0% in NRLAR and RLAR respectively, $p < 0.001$).

Conversion rates, rate of intra-operative complications, rate of surgical complications or major morbidity did not differ between groups. Pelvic sepsis was most common in patients undergoing RLAR (18.3% compared to 8.8% after APR and 12.1% after NRLAR, $p < 0.001$). The rate of incomplete TME specimen was highest in APR (10.0%, compared to 3.1% in NRLAR and 3.7% in RLAR, $p < 0.001$) and the rate of positive CRM was highest in APR (8.0%, compared to 6.4% in NRLAR and 2.8% in RLAR, $p = 0.005$).

3.2. Three-year oncological outcome

Table 2 gives a comparison of oncological outcomes. NRLAR was associated with significantly worse rates of 3-year OS, 3-year DFS, 3-year SR and 3-year LR.

Fig. 2 gives an overview of 3-year OS and DFS. Three-year OS rate was 78.2% in NRLAR, 92.2% in RLAR and 86.3% in APR ($p < 0.001$). Multivariable analysis showed that NRLAR was independently associated with worse 3-year OS (HR 1.85 (95%CI: 1.07–3.19, $p = 0.03$). Other independent variables associated with worse 3-year OS were age 70–80 years old and >80 years old, male sex, ASA II/IV and cT4. Three-year DFS was 60.3% in NRLAR, 80.1% in RLAR and 70.5% in APR ($p < 0.001$). NRLAR was also independently associated with worse 3-year DFS (HR 2.05 (95%CI:1.42–2.97), $p < 0.001$). Other independent variables associated with worse 3-year DFS were ASA III/IV and cT4. The univariable and multivariable Cox regression analysis for factors associated with 3-year OS and 3-year DFS are shown in Table 3.

Three-year SR rate was 23.2% in NRLAR, 12.7% in RLAR and 21.9% in APR ($p = 0.002$). Both APR (HR 1.62 (95%CI: 1.13–2.32), $p = 0.009$) and NRLAR (HR 2.12 (95%CI: 1.31–3.42), $p = 0.002$) were independently associated with worse 3-year SR. Another independent variable was cT4. Three-year LR rate was 14.6% in NRLAR, 4.8% in RLAR and 5.2% in APR ($p = 0.005$). Multivariable analysis

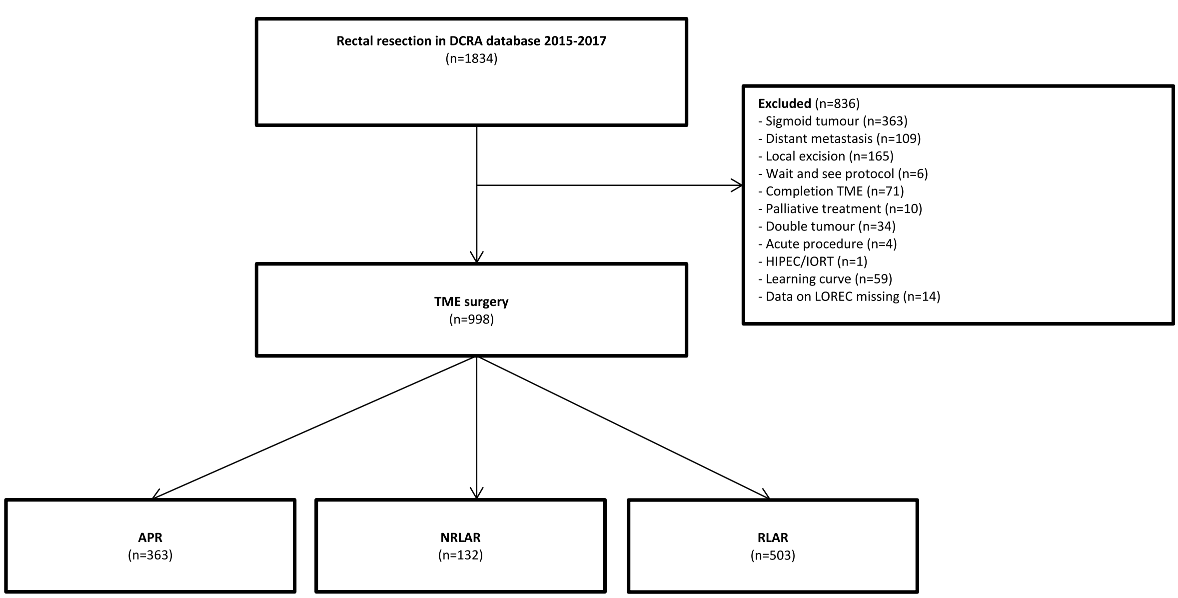

Fig. 1. Flowchart
Abbreviations: DCRA = Dutch ColoRectal Audit, HIPEC/IORT = hyperthermic intraperitoneal chemotherapy/intra-operative radiotherapy, LOREC = MRI-defined low rectal tumour, APR = abdominoperineal resection, NRLAR = non restorative low anterior resection, RLAR = restorative low anterior resection.

Table 1
Baseline comparison per type of procedure.

		Total	APR	NRLAR	RLAR	p-value
N		998	363	132	503	
Age in years (mean(SD))		67 (10.5)	68 (10.4)	74 (9.3)	64 (9.7)	<0.001
BMI (mean(SD))		26.2 (4.3)	26.5 (4.2)	26.5 (5.0)	25.8 (4.1)	0.05
Sex (%)	Male	641 (64.2)	239 (65.8)	81 (61.4)	321 (63.8)	0.63
	Female	357 (35.8)	124 (34.2)	51 (38.6)	182 (36.2)	
ASA (%)	I	199 (19.9)	63 (17.4)	12 (9.1)	124 (24.7)	<0.001
	II	592 (59.3)	214 (59.0)	73 (55.3)	305 (60.6)	
	III	199 (19.9)	83 (22.9)	45 (34.1)	71 (14.1)	
	IV	8 (0.8)	3 (0.8)	2 (1.5)	3 (0.6)	
History of abdominal surgery (%)		282 (28.3)	109 (30.0)	52 (39.4)	121 (24.1)	0.001
Distance to ARJ on MRI in cm (median[IQR])		5 [2, 8]	2 [0, 4]	6 [4, 8]	7 [5, 9]	<0.001
LOREC (%)		596 (59.7)	330 (90.9)	68 (51.5)	198 (39.4)	<0.001
MRF involvement on MRI (%)	MRF involved	316 (32.0)	157 (43.7)	39 (30.2)	120 (24.0)	<0.001
	Missing	10 (1.0)	4 (1.1)	3 (2.3)	3 (0.6)	
cT (%)	1	9 (0.9)	0 (0.0)	0 (0.0)	9 (1.8)	<0.001
	2	285 (28.6)	110 (30.4)	30 (23.1)	145 (28.8)	
	3	609 (61.2)	200 (55.2)	91 (70.0)	318 (63.2)	
	4	92 (9.2)	52 (14.4)	9 (6.9)	31 (6.2)	
	Missing	3 (0.3)	1 (0.3)	2 (1.5)	0 (0.0)	
cN (%)	0	436 (43.8)	159 (43.8)	54 (41.2)	223 (44.4)	0.62
	1	338 (33.9)	120 (33.1)	42 (32.1)	176 (35.1)	
	2	222 (22.3)	84 (23.1)	35 (26.7)	103 (20.5)	
	Missing	2 (0.2)	0 (0.0)	1 (0.8)	1 (0.2)	
Neoadjuvant therapy (%)	None	365 (37.1)	111 (31.3)	53 (41.4)	201 (40.2)	0.004
	Radiotherapy	312 (31.7)	111 (31.3)	47 (36.7)	154 (30.8)	
	Chemoradiation	306 (31.1)	133 (37.5)	28 (21.9)	145 (29.0)	
	Missing	15 (1.5)	8 (2.2)	4 (3.0)	3 (0.6)	
Surgical technique (%)	Laparoscopic	462 (46.3)	194 (53.4)	93 (70.5)	175 (34.8)	<0.001
	Robot-assisted	312 (31.3)	100 (27.5)	23 (17.4)	189 (37.6)	
	TaTME	224 (22.4)	69 (19.0)	16 (12.1)	139 (27.6)	
Conversion (%)		37 (3.7)	15 (4.1)	9 (6.8)	13 (2.6)	0.06
Intraoperative complication (%)		62 (6.2)	31 (8.5)	8 (6.1)	23 (4.6)	0.06
Surgical complication (%)		342 (34.3)	114 (31.4)	41 (31.1)	187 (37.2)	0.15
Major complication (CD $\geq$ 3) (%)		208 (20.8)	66 (18.2)	27 (20.5)	115 (22.9)	0.25
Pelvic sepsis (%)		149 (14.9)	32 (8.8)	16 (12.1)	92 (18.3)	<0.001
CRM+ (%)		47 (5.1)	26 (8.0)	8 (6.4)	13 (2.8)	0.005
Incomplete TME		58 (5.9)	36 (10.0)	4 (3.1)	18 (3.7)	<0.001
pT	0	80 (8.1)	35 (9.7)	5 (3.8)	40 (8.0)	0.07
	1	94 (9.5)	28 (7.7)	9 (6.9)	57 (11.4)	
	2	355 (35.8)	134 (37.0)	48 (36.9)	173 (34.5)	
	3	440 (44.3)	154 (42.5)	64 (47.7)	224 (44.7)	
	4	24 (2.4)	11 (3.0)	6 (4.6)	7 (1.4)	
pN	0	677 (67.9)	256 (70.5)	82 (62.1)	339 (67.5)	0.06
	1	229 (23.0)	84 (23.1)	38 (28.8)	107 (21.3)	
	2	91 (9.1)	23 (6.3)	12 (9.1)	56 (11.2)	

Abbreviations: BMI=Body Mass Index (kg/m2); ASA = American Society of Anesthesiologists; ARJ = anorectal junction; MRF = mesorectal fascia; APR = abdominoperineal resection; NRLAR = non restorative low anterior resection; RLAR = restorative low anterior resection; TaTME = transanal total mesorectal excision; CD=Clavien Dindo; CRM+ = circumferential margin 1 mm or less.

Table 2
Oncological outcome per type of procedure.

		Total	APR	NRLAR	RLAR	p-value
N		998	363	132	503	
Follow-up in months (median[IQR])		36 [25, 46]	35 [24, 48]	30 [18, 42]	37 [26, 46]	0.003
3-year overall survival (%)		894 (89.6)	319 (86.3)	107 (78.2)	468 (92.2)	<0.001
3-year disease-free survival (%)		768 (77.0)	267 (70.5)	89 (60.3)	413 (80.1)	<0.001
3-year local recurrence (%)		49 (4.9)	15 (5.2)	13 (14.6)	21 (4.8)	0.005
Location of local recurrence	Anterior	5 (0.5)	2 (0.6)	1 (0.8)	2 (0.4)	
	Lateral	12 (1.2)	6 (1.7)	1 (0.8)	5 (1.0)	
	Inferior	13 (1.3)	4 (1.1)	5 (3.8)	4 (0.8)	
	Central, anastomotic	10 (1.0)	2 (0.6)	0 (0.0)	8 (1.6)	
	Central, non-anastomotic	22 (2.2)	6 (1.7)	11 (8.5)	5 (1.0)	
	Peritoneal reflection	1 (0.1)	0 (0.0)	1 (0.8)	0 (0.0)	
	Multifocal local recurrence	7 (11.7)	2 (11.1)	2 (12.5)	3 (11.5)	
3-year systemic recurrence (%)		149 (15.0)	69 (21.9)	24 (23.2)	56 (12.7)	<0.001
	Liver	74 (7.4)	32 (8.8)	14 (10.8)	28 (5.6)	
	Lung	90 (9.0)	46 (12.7)	15 (11.5)	29 (5.8)	
	Peritoneal	25 (2.5)	11 (3.0)	6 (4.6)	8 (1.6)	
	Bone	6 (0.6)	2 (0.6)	1 (0.8)	3 (0.6)	
	Ovary	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	
	Brain	4 (0.4)	3 (0.8)	0 (0.0)	1 (0.2)	
	Other	18 (1.8)	6 (1.7)	4 (3.1)	8 (1.6)	

Abbreviations: APR = abdominoperineal resection; NRLAR = non restorative low anterior resection; RLAR = restorative low anterior resection; IQR = interquartile range.

showed that NRLAR was independently associated with worse LR rate (HR 3.22 (1.61–6.47), p < 0.001). Other independent variables associated with worse LR were cT4 and administration of neo-adjuvant radiotherapy. Supplementary Fig. 1 gives an overview of SR and LR free survival. The univariable and multivariable Cox regression analysis for factors associated with 3-year LR and 3-year systemic recurrence are shown in Table 4.

4. Discussion

In this retrospective multicentre cohort study from 11 Dutch hospitals, 998 patients undergoing elective primary rectal cancer resections were included. Non-restorative LAR (NRLAR) was associated with worse 3-year oncological results, compared to restorative LAR (RLAR) and APR. Before and after correction for confounding variables 3-year DFS, OS, SR rate and LR rate were significantly worse after NRLAR.

Most of the observed 3-year OS, DFS and LR rates are consistent with large randomized trials comparing laparoscopic with open

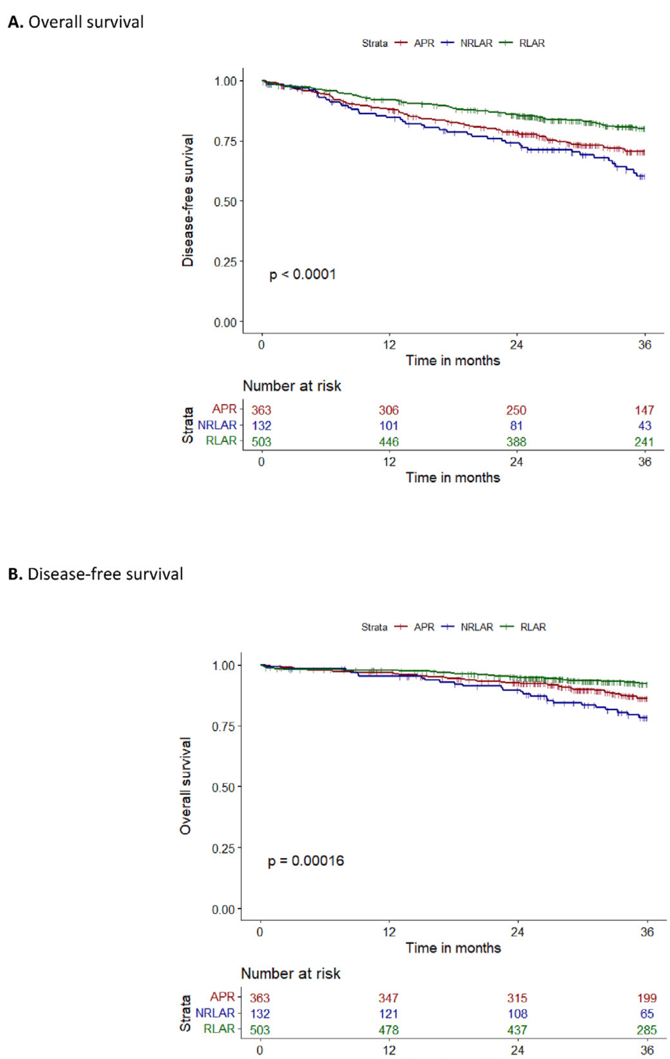

Fig. 2. Overall survival and disease-free survival until 3-years postoperative. Comparison between APR, NRLAR and RLAR.
APR = Abdominoperineal resection; NRLAR = non-restorative low anterior resection; RLAR = restorative low anterior resection.
A. Overall survival
B. Disease-free survival.

TME, such as COLOR II, ALaCART and ACOSOG Z6051 trial [6–8]. In randomized trials, the proportion of non-restorative procedures is relatively small compared to daily practice. Although there is a trend toward more restorative procedures, end colostomy rates can be as high as 50% [17,18]. The objective of this study was to determine the effect of NRLAR on oncological outcome. Uncorrected 3-year oncological results were significantly worse after NRLAR, compared to RLAR and APR. Although the relationship might be non-causal, inferior oncological outcome after NRLAR was still seen after correction for confounding variables. This finding is consistent with that of Roodbeen et al. who also found that NRLAR is associated with worse OS and a higher risk of LR [3].There are several possible explanations for the observed poorer oncological outcome after NRLAR. In the literature, various factors have been examined as possible causes of cancer recurrence after surgery.

One of the most crucial factors for survival is whether a radical resection can be achieved [27]. The number of positive CRM in this study was highest in the APR group (8.0%), but a relatively high CRM rate (6.4%) was seen in the NRLAR group as well, leading to a LR rate of 14.6% in the NRLAR group. These results reflect those of Andarin et al. who also found higher positive CRM rates in a study comparing RLAR and NRLAR [1]. Margins of 5% in RLAR and 14% in NRLAR led to 5% and 10% 5-year LR rates respectively. These results reflect those of Ortiz et al. who also found higher positive CRM rates and higher LR rates after NRLAR compared to RLAR [2]. However, Roodbeen et al. also found higher LR rates after NRLAR, but found comparable positive CRM rates.

Another important factor linked to higher LR rates is pelvic sepsis. Especially anastomotic leakage could comprise oncological outcome [28,29]. Leaving a rectal stump after NRLAR may lead to formation of pelvic abscess by leakage or blow-out of the rectal stump [30]. Jonker et al. showed fewer 30-day infective complications after low-Hartmann compared to LAR with anastomosis [31]. However, this difference seems to diminish over time because the median time to diagnosis of a pelvic abscess after NRLAR seems to be 21 days and over time, equal risk of abscess formation and similar need for reintervention were seen [30]. In the present study, higher pelvic sepsis rates were seen in the RLAR group. This might be a reflection of the 30-day time period. Pelvic sepsis in case of an anastomosis would probably lead to early detection of sepsis combined with proactive management. Pelvic sepsis is probably detected later and treated later in NRLAR and therefore underreported. Moreover, late detection of anastomotic leakage seems to have a negative impact on DFS and LR rates [29]. Late detection of pelvic sepsis after NRLAR might have a similar impact on DFS and LR rates.

Tumour distance might also be an important factor that influences survival. Poorer oncological outcome after NRLAR might be a reflection of technical difficulties during low pelvic dissection in a subset of patients with distal tumours. Future research should confirm what proportion of NRLAR was performed because of intra-operative change of management. A long and difficult dissection might lead to the choice of construction of and end colostomy. The mesorectum tapers towards the distal rectum. Therefore, a distal rectal tumour might lead to a more difficult dissection and some studies suggested that positive CRM rates increases as the distance to the anal verge decreases [32]. However, in the COLOR II trial laparoscopy was associated with lower positive CRM rates and lower LR rates compared to open surgery in patients with distal rectal cancer [6]. A better magnified an illuminated image of the operative field was thought to be a possible explanation. Robot-assisted and TaTME were supposed to add further technical benefits [33]. A previous study showed no difference in oncological outcome between the techniques [4]. The present study did not show any difference in oncological outcome for distal tumours. MRI

Table 3
Multivariable Cox-regression analysis for Overall Survival and Disease-free survival at 3-years follow-up.

		Overall survival				Disease free survival			
		Univariable		Multivariable		Univariable		Multivariable	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Procedure	RLAR	Reference		Reference		Reference		Reference	
	APR	1.74 (1.18, 2.71)	0.01	1.33 (0.84, 2.10)	0.22	1.58 (1.19, 2.11)	0.002	1.33 (0.99, 1.78)	0.06
	NRLAR	2.87 (1.72, 4.80)	<0.001	1.85 (1.07, 3.19)	0.03	2.15 (1.49, 3.09)	<0.001	2.05 (1.42, 2.97)	<0.001
Age	<70	Reference				Reference			
	70–80	2.61 (1.69, 4.04)	<0.001	1.78 (1.12, 2.83)	0.02	1.99 (1.34, 2.95)	<0.001		
	>80	3.64 (2.14, 6.18)	<0.001	2.05 (1.15, 3.67)	0.02	1.96 (1.20, 2.12)	0.001		
BMI	18.5–25	Reference				Reference			
	<18.5	1.02 (0.25, 4.22)	0.97			1.52 (0.67, 3.46)	0.32		
	25–30	0.77 (0.50, 1.19)	0.24			0.79 (0.59, 1.05)	0.11		
	>30	1.02 (0.60, 1.74)	0.95			0.84 (0.57, 1.23)	0.36		
Sex	Female	Reference				Reference			
	Male	1.59 (1.03, 2.47)	0.04	1.70 (1.10, 2.66)	0.02	1.15 (0.87, 1.51)	0.33	1.24 (0.94, 1.65)	0.12
ASA	I/II	Reference				Reference			
	III/IV	3.70 (2.51, 5.45)	<0.001	2.69 (1.78, 4.08)	<0.001	1.99 (1.50, 2.65)	<0.001	1.82 (1.37, 2.43)	<0.001
cT	T0-T3	Reference				Reference			
	T4	2.70 (1.46, 5.01)	0.002	2.99 (1.52, 5.90)	0.002	3.37 (2.22, 5.10)	<0.001	2.76 (1.94, 3.92)	<0.001
cN	cN0	Reference				Reference			
	cN1-2	1.01 (0.67, 1.46)	0.97			1.20 (0.92, 1.57)	0.17		
Mesorectal fascia	Not involved	Reference				Reference			
	Involved	1.02 (0.68, 1.54)	0.91	0.77 (0.40, 1.18)	0.17	1.33 (1.02, 1.74)	0.04		
LOREC	High rectal tumor	Reference				Reference			
	Low rectal tumor	1.04 (0.65, 1.42)	0.83			1.10 (0.84, 1.43)	0.50		
Neoadjuvant therapy	None	Reference				Reference			
	Radiotherapy	1.22 (0.77, 1.94)	0.40			1.19 (.85, 1.65)	0.31		
	Chemoradiation	1.05 (0.65, 1.70)	0.84			1.46 (1.07, 1.99)	0.02		
Technique	Laparoscopic	Reference				Reference			
	Robot-assisted	1.21 (0.78, 1.89)	0.40			1.18 (0.87, 1.58)	0.29		
	TaTME	1.25 (0.76, 2.03)	0.38			1.05 (0.75, 1.47)	0.78		

Abbreviations: OR = odds ratio; ASA = American Society of Anesthesiologists; RLAR = restorative low anterior resectionAPR = abdominoperineal resection; NRLAR = non-restorative low anterior resection; LOREC = MRI defined low rectal cancer; L-TME = laparoscopic total mesorectal excision; R-TME = robot-assisted total mesorectal excision; TaTME = transanal total mesorectal excision.

Table 4
Multivariable Cox-regression analysis for Local recurrence and Systemic recurrence at 3-years follow-up.

		Local recurrence				Systemic recurrence			
		Univariable		Multivariable		Univariable		Multivariable	
		HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Procedure	RLAR	Reference		Reference		Reference		Reference	
	APR	1.05 (0.54, 2.03)	0.89	0.88 (0.45, 1.72)	0.70	1.85 (1.30, 2.63)	<0.001	1.62 (1.13, 2.32)	0.009
	NRLAR	2.85 (1.43, 5.69)	0.003	3.22 (1.61, 6.47)	<0.001	2.02 (1.25, 3.25)	0.004	2.12 (1.31, 3.42)	0.002
Age	<70	Reference				Reference			
	70–80	1.29 (0.70, 2.35)	0.41			1.21 (0.85, 1.72)	0.29		
	>80	1.09 (0.38, 3.10)	0.88			1.28 (0.74, 2.21)	0.39		
BMI	18.5–25	Reference				Reference			
	<18.5	0.0 (0.0, 99.9)	0.99			1.63 (0.59, 4.49)	0.34		
	25–30	0.64 (0.34, 1.12)	0.16			0.83 (1.21, 0.58)	0.31		
	>30	0.93 (0.43, 2.00)	0.85			1.05 (0.67, 1.66)	0.82		
Sex	Female	Reference				Reference			
	Male	1.54 (0.81, 2.89)	0.19	1.76 (0.93, 3.33)	0.08	0.88 (0.63, 1.23)	0.46		
ASA	I/II	Reference				Reference			
	III/IV	1.41 (0.72, 2.75)	0.32			1.35 (0.92, 2.00)	0.13		
cT	T0-T3	Reference				Reference			
	T4	4.94 (2.08, 11.73)	<0.001	4.63 (2.13, 10.09)	<0.001	4.57 (2.75, 7.59)	<0.001	2.89 (1.91, 4.38)	<0.001
cN	cN0	Reference				Reference			
	cN1-2	0.78 (0.45, 1.37)	0.39			1.47 (1.17, 2.32)	0.004	1.42 (0.99, 2.02)	0.052
Mesorectal fascia	Not involved	Reference				Reference			
	Involved	1.92 (1.10, 3.37)	0.02			1.57 (1.13, 2.17)	0.007		
LOREC	High rectal tumor	Reference				Reference			
	Low rectal tumor	0.99 (0.57, 1.77)	0.99			1.26 (0.90, 1.76)	0.18		
Neoadjuvant therapy	None	Reference				Reference			
	Radiotherapy	0.46 (0.20, 1.05)	0.06	0.38 (0.17, 0.88)	0.02	0.46 (0.20, 1.05)	0.06		
	Chemoradiation	1.18 (0.64, 2.18)	0.59	0.76 (0.37, 1.57)	0.47	1.18 (0.64, 2.18)	0.59		
Technique	Laparoscopic	Reference				Reference			
	Robot-assisted	1.16 (0.61, 2.18)	0.65			0.99 (0.69, 1.42)	0.96		
	TaTME	0.94 (0.44, 1.98)	0.87			0.74 (0.48, 1.15)	0.18		

Abbreviations: OR = odds ratio; ASA = American Society of Anesthesiologists; RLAR = restorative low anterior resection; APR = abdominoperineal resection; NRLAR = non-restorative low anterior resection; LOREC = MRI defined low rectal cancer; L-TME = laparoscopic total mesorectal excision; R-TME = robot-assisted total mesorectal excision; TaTME = transanal total mesorectal excision.

defined low rectal tumour according to an international definition, who are thought to be more at risk, did not seemed to be more at risk of recurrence [33,34]. This finding suggests robot-assisted and TaTME can be performed safely for distal tumours [4].

Several other factors may have influenced survival. Radiotherapy is an important factor, but radiotherapy was administered equally to 30% in APR, RLAR and NRLAR and therefore does not seem to explain the observed difference in oncological outcome. Another factor was the reason to perform NRLAR. Patients undergoing NRLAR tended to have a higher age, more ASA III or more history of abdominal surgery compared to RLAR or APR, and there was more cT3 stage in NRLAR. In this study, we tried to correct for such potential confounders using a multivariable analysis. However, selection bias might be apparent because of the retrospective collection of the data, but might be less applicable because a large series of patients was used from 11 comparable centres with extensive experience [4].

This study has several other limitations that should be mentioned. There was insufficient data on restaging MRI after neoadjuvant therapy. A particular subgroup of patients of interest would be those with threatened margin to the mesorectal fascia or external sphincter on restaging MRI. Margin involvement may lead to another treatment strategy, including the choice to perform an APR. Because restaging MRI was missing, no correction was performed for poor responders or non-responders on neoadjuvant treatment who have a persistent threatened margin. Restaging MRI has become standard of practice. Response to neoadjuvant treatment influences the operative strategy or approach and might have resulted in bias. Another important limitation is some relevant confounders could not be accounted for. This included preoperative and intra-operative details on decision making. There was no correction for EMVI or anterior location of the tumour, which are prognostic unfavourable factors [35]. On the other hand, dedicated techniques were analysed, performed in expert centres beyond the learning curve after introduction of laparoscopic, robot-assisted or TaTME. Clinical staging was used in the multivariable analysis to correct for preoperative differences in staging that could have influenced decision making for a specific type of procedure. Also, this study compared MRI defined low rectal tumours based on strict anatomical definition with other MRI-defined rectal tumours. Thereby distal sigmoid tumours, which are associated with less morbidity and a more favourable prognosis, were excluded.

Notwithstanding these limitations, this study suggests worse oncological outcomes after NRLAR compared to APR and RLAR. We suggest an intersphincteric APR should be considered in case of poor function or expected technical difficulty. Removal of the rectal stump by intersphincteric APR or mucosectomy might lead to better oncological results. The reader should bear in mind that this study was based on retrospective data. There is a currently ongoing randomized trial comparing APR with NRLAR with regard to postoperative surgical morbidity [36]. Moreover, in the multivariable analysis robot-assisted TME and TaTME were associated with equal oncological outcome, as was seen in a previous analysis [4]. Previous research showed that robot-assisted TME and TaTME facilitate the safe creation of an anastomosis [16]. Within laparoscopic TME the highest percentage of NRLAR was present. Since both robot-assisted and TaTME were associated with low NRLAR rates, this finding might favour robot-assisted and TaTME in term of oncological outcomes.

5. Conclusion

This study identified that NRLAR for primary rectal cancer might be associated with worse 3-year OS, DFS and higher SR and LR rates compared to RLAR or APR.

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Ethics approval

A protocol regarding the study design, methods and statistical analysis was composed prior to initiation of the study. This study was approved by the Medical research Ethics Committees United (MEC-U) medical ethics committee (AW 19.023/W18.100) and was approved by the local ethic boards of all participating centres.

CRediT authorship contribution statement

Jeroen C. Hol: contributed in study design, acquisition of data, Formal analysis, interpretation of the data and participated, Writing – original draft. **Thijs A. Burghgraef:** contributed in study design, acquisition of data, Formal analysis, interpretation of the data and participated, Writing – original draft. **Marieke L.W. Rutgers:** contributed in study design, acquisition of data, Formal analysis, interpretation of the data and participated, Writing – original draft. **Rogier M.P.H. Crolla:** contributed in study design, acquisition of data and revised the article critically. **Nanette A.W. van Geloven:** contributed in study design, acquisition of data and revised the article critically. **Jeroen W.A. Leijtens:** contributed in study design, acquisition of data and revised the article critically. **Fatih Polat:** contributed in study design, acquisition of data and revised the article critically. **Apollo Pronk:** contributed in study design, acquisition of data and revised the article critically. **Anke B. Smits:** contributed in study design, acquisition of data and revised the article critically. **Jurriaan B. Tuynman:** contributed in study design, acquisition of data and revised the article critically. **Emiel G.G. Verdaasdonk:** contributed in study design, acquisition of data and revised the article critically. **Esther C.J. Consten:** study design, acquisition of data, Formal analysis, interpretation of the data and participated, Writing – original draft. **Roel Hompes:** contributed in study design, acquisition of data and revised the article critically. **Colin Sietses:** study design, acquisition of data, Formal analysis, interpretation of the data and participated, Writing – original draft, All authors made substantial contribution to the study and the manuscript. All authors gave final approval of the version of the manuscript to be published.

Declaration of competing interest

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Appendix A. Supplementary data

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