Minimally Invasive Approaches for Total Mesorectal Excision

Hol, Jeroen Clemens

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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Rectal resections are fundamental in the curative treatment for rectal cancer. Although surgical techniques used for rectal resection have evolved over time, it remains a challenging operation due to the narrow pelvic anatomy. The first rectal resection for rectal cancer was performed in 1739 by Faget (1). Due to poor understanding of the anatomy and the biology of the underlying disease oncological results were poor, with early recurrence rates as high as 95%.

Nineteenth century anatomists helped to develop the basis of modern surgical dissection by defining the anatomical planes surrounding the rectum. It was realised that cancer spread via the lymph nodes surrounding the rectum. Therefore, the rectum should be excised with its surrounding fatty tissue, incorporating the draining potential malignant lymph nodes. Meanwhile, antisepsis and anesthesiological techniques with deep muscle relaxation improved, enabling the opening of the abdomen by laparotomy. In 1908 Miles introduced the first modern rectal resection. He used an abdominal approach in combination with an abdominoperineal resection (APR) with 'en bloc' lymphadenectomy (2). Knowledge of lymphatic spread of cancer cells and removing all primary lymph nodes was a big step forward: local recurrence rates dropped to 29.5%. However, it was definitely a morbid operation, associated with severe urogenital dysfunction and mortality rates of 31%, mostly due to sepsis.

A major disadvantage of the aforementioned techniques was that it involved the creation of a permanent colostomy. The first confirmation of safety of sphincter preserving resection was done by Dixon in 1948 (3). His anterior resection technique with creation of an anastomosis had an acceptable mortality rate of 2.6% (3). Subsequently, the development of circular stapler devices enabled the creation of an anastomosis in the lower part of the rectum (4).

TOTAL MESORECTAL EXCISION

The next milestone was the popularisation of the total mesorectal excision principle (TME) by RJ Heald in the 1980's. TME comprises resection of the rectum and the mesorectum: the fatty envelope surrounding the rectum, which is the base for the arterial supply and venous and lymphatic drainage of the rectum. In TME, dissection under direct vision is performed between the mesorectum and the surrounding tissues up to the level of the levator muscles. Because of the lateral tumour spread, there is a strong positive correlation between the circumferential margin involvement and local recurrence with subsequent worse overall survival (5). Previous techniques used blunt dissection, whereas total mesorectal excision uses sharp dissection along the embryologic plane

("Healds holy plane"). Therefore, TME led to a decrease of positive lateral margins. By sharp dissection along the avascular plane surrounding the mesorectum local recurrence rates could be reduced. Local recurrence rates dropped from 12-20% to 3.7% in five-years follow-up (6). Similar local recurrence rates were seen in different subsequent trials (7, 8).

Because the surrounding mesorectum is the area of spread, TME also confirmed that an APR (resection of the rectum and anus) is not always necessary, without comprising oncological outcome. This led to more sphincter preserving surgery, with APR only reserved to those cases with levator muscle involvement or pre-existent faecal incontinence (9). By sharp dissection of the avascular plane, excessive perioperative blood loss was reduced (10). Furthermore, the autonomic nerves could be preserved and postoperative functional disorders were reduced (11). Since its introduction TME has become the current gold standard for surgical resection of rectal cancer.

Despite improved oncological and functional results, TME has several limitations. Firstly, performing dissection under direct vision can be challenging in the confined area of the pelvis. Even when direct vision is possible, working within the narrow area within the bony constraints of the deep distal pelvis can be demanding, leading to circumferential margin (CRM) involvement, incomplete specimen, distal margin rates and local recurrences. This is reflected in clinical outcomes in patients operated on for low rectal tumours in particular. In the lower part of the rectum the mesorectum has a funnelling shape, becomes tapered towards the anorectal junction and there is limited room to mobilise the rectum. In low rectal tumours, CRM involvement rates of 22 % are seen (12). Secondly, TME surgery is associated with significant morbidity, including anastomotic leakage and unintended end colostomies. A laparotomy size incision is necessary with the associated pain and risk of infection. Until recently, all rectal resections were performed via laparotomy (e.g. open surgery). To overcome the limitations of TME, several minimally invasive approaches have been introduced in the past decades.

LAPAROSCOPY

Oncological results after laparoscopy are comparable to open surgery. However, short-term outcomes improved, as shown in several randomized controlled trials (8, 13, 14). Such improvements include: decreased length of hospital stay, decreased morbidity rates, reduced infection rates and reduction of blood-loss during surgery (15). Laparoscopy offers patients the benefits of minimally invasive surgery and therefore has gradually replaced open surgery in most western countries. Despite improvements over open surgery, laparoscopic TME has important limitations. Short-term morbidity

rates are still relatively high: 30-40%, including anastomotic leakage rates of 8% to 20% (16, 17). Because laparoscopy uses rigid instruments, working in the small and confined area of the deep pelvis is considered to be difficult and conversion to open surgery is inevitable in 10% of all cases as reported in large clinical trials (12, 18). Conversion is associated with increased morbidity and can compromise long-term survival (19). The limitations of laparoscopy led to the development of two new techniques: robot-assisted and transanal TME.

ROBOT-ASSISTED TOTAL MESORECTAL EXCISION

In robot-assisted surgery a robotic system with robotic arms is used. The system is controlled using a tele manipulator managed by a surgeon. Robotic surgery was originally intended for remote surgery, but surgeons became interested not in the remote surgery aspect, but in other features of robotic systems (20). Such features include: 3D vision with up to 30 times magnification, tremor filter, superior ergonomics and instruments with 7 degrees of freedom that mimic movements by a surgeon's hand (21, 22). Although robotic surgery was planned to use in cardiac surgery, surgeons soon realized the stable platform with superior vision might be useful in resection of pelvic organs. In 2001 the first robot-assisted radical prostatectomy was introduced (23). The first robot-assisted right hemicolectomy in 2002 paved the way for widespread implementation of robotics in colorectal surgery (24). Most studies have focussed since then on TME (25, 26).

Because the high quality vision and superior instrument handling, it was proposed robot-assisted TME would lead to lower conversion rates and more precise dissection. In initial series lower conversion rates were seen (27, 28). Shorter length of hospital stay was reported in several studies (29). Other advantages of robotic surgery over laparoscopy are improved ergonomics and reduced surgeon fatigue (30). However, laparoscopy and robot-assisted surgery share much in common, and definite advantage of robot-assisted TME has not been demonstrated for rectal cancer surgery (21, 22, 31). The largest randomized trial comparing robot-assisted and laparoscopic TME failed to show any significant difference in short-term and long-term outcomes (21, 32). These results need to be interpreted with caution, as this might have been the results of a methodological flaw. Sample size did not allow detecting smaller differences and robot surgeons in that trial were not as experienced as their laparoscopic counterparts (33).

TRANSANAL TOTAL MESORECTAL EXCISION

Transanal TME (TaTME) is without a doubt the most disruptive technique because it uses a completely different concept compared to open, laparoscopic and robot-assisted TME. Unlike the abdominal techniques, it approaches the rectum from below. Performing the most difficult part of the dissection transanal makes the distal TME dissection possible under direct vision. Endoscopic visualisation enables direct control of the distal margin. Therefore, it was thought to be best suited for the most challenging patients (34). Especially in male or obese patients with a narrow pelvis, mobilisation of the rectum becomes more difficult and TaTME enables mobilisation of the rectum with intact mesorectum.

TaTME was introduced in 2009 by Sylla and de Lacy and was derived from endoscopic surgical techniques (35, 36). Transanal endoscopic microsurgery (TEM) has been used for excision of early stage rectal cancers since 1983 (37). The subsequently developed transanal minimally invasive surgery (TAMIS) is a hybrid between TEM and the use of a single-port laparoscopy platform (38). The experience gained with the use of these single-port laparoscopic platforms used for local excision enabled the introduction of TaTME. Initial reports on TaTME showed promising short-term outcomes. Noteworthy are the lower conversion rates (39, 40), as well as higher rates of complete specimen (41) and lower CRM involvement rates (42). When a two-team approach is used (laparoscopically from above and TaTME from below) operating time can be reduced (43). Another argument in favour of TaTME is that it does not require distal cross stapling. This prevents the creation of dog-ears that could become ischemic, therefore enabling the creation of a (low) anastomosis (44). However, TaTME is a challenging technique, which comprises a steep learning curve of 40-45 procedures (43). And intra-operative complications such as ureteral injury and CO2 embolus were seen during implementation of TaTME (45, 46).

More recently, literature has emerged that offers contradictory oncological results after TaTME. Initial reports showed acceptable intermediate term oncological results after TaTME (39, 45, 47-49). By contrast, early local recurrence rates of 9.5% were seen during implementation of TaTME in Norway (50). This led to a halt of TaTME in Norway (51). Research to date regarding long-term oncological outcome after TaTME are scarce and the technique requires further investigation.

PREOPERATIVE IMAGING

Better understanding of the preoperative imaging might lead to better treatment outcome. Most studies use arbitrary cut-off points in centimetres from the anal verge

to define rectal cancer. A large international consensus group proposed the sigmoid take-off as definition of the rectum, based on preoperative imaging (52). This definition is gradually being implemented in literature and guidelines and might have implications for treatment because a part of the former rectal cancers will now be treated as colon cancers. Stage III colon cancer is usually treated with adjuvant chemotherapy, whereas the role of chemotherapy in rectal cancer is debated (53). Another definition being implemented is the LOREC definition for low rectal cancer, based on anatomical landmarks where the tapering of the mesorectum starts (54). In this group of patients there is limited space for mobilising the rectum during TME which leads to a more difficult dissection and the risk of positive resection margins. The implications of the introduction of both definitions remain unclear.

DIVERTING ILEOSTOMY

Regardless of the approach used, a much debated question is whether a temporary diverting ileostomy should be created. When a sphincter preserving TME is performed with creation of an anastomosis, there is a risk of anastomotic leakage. Anastomotic leakage is a common and severe complication, and therefore an important source of morbidity after sphincter preserving surgery (17). Sphincter preserving surgery is most often combined with the creation of a temporary ileostomy. The theory behind this is to bypass the colonic anastomosis, allowing it to heal without passage of faecal material and subsequent less risk of infection. Therefore, an ileostomy might decrease the consequences of an anastomotic leakage (55, 56). On the other hand, the stoma itself can induce significant morbidity and discomfort and requires a second operation for stoma closure (57, 58). In some patients, the stoma is never closed (59). Despite the construction of a stoma, the risk of anastomotic leakage remains (56). There appears to be a large variation in practice (60). Some surgeons are in favour of routine diversion, whereas others argument selective diversion might be safe (61, 62).

OUTLINE OF THE THESIS

The **first part** of this thesis focusses on the implementation of robot-assisted and TaTME. **Chapter 2** represents the long-term oncological outcomes after TaTME in two large volume tertiary referral centres with at least three years of follow up. **Chapter 3** describes the results of an external audit in 120 patients in a multicentre structured training cohort during the implementation of TaTME. This is done with focus on loco regional recurrence rates during the implementation phase. In **chapter 4** six hospitals that had prolonged

experience with TaTME were externally audited. To investigate the implementation of robot-assisted TME, **chapter 5** contains the results of an implementation cohort of robotic-assisted TME by multiple surgeons in a large teaching hospital.

The **second part** of this thesis includes a comprehensive comparison of laparoscopic, robot-assisted and TaTME. Data was collected from patients operated on between 2015 and 2017 in eleven Dutch hospitals with profound experience in either laparoscopic, robot-assisted or TaTME. Each centre was considered beyond the learning curve for one of the techniques, thereby eliminating a learning curve effect. **Chapter 6** is a comparison of short-term outcomes of each technique after propensity score matching. **Chapter 7** is a comparison of three year oncological results after each technique. **Chapter 8** is a comparison of the three techniques for MRI-defined low-rectal cancer. **Chapter 9** looks at the effect of the implementation of the sigmoid take-off definition for rectal cancer, based on preoperative imaging.

The **third part** of this thesis concentrates on the benefits and harms of diverting ileostomy creation in sphincter preserving TME. In **chapter 10** a comparison is made depending on whether an ileostomy was constructed during sphincter preserving TaTME. Ileostomy related morbidity and hospital costs are evaluated. In **chapter 11** a comparison is made depending on whether an ileostomy was constructed during sphincter preserving laparoscopic, robot-assisted and TaTME. Ileostomy related morbidity and risk of permanent stoma after ileostomy are evaluated.

Chapter 12 contains a summary and discussion of this thesis, focussing on the future perspectives of minimally invasive approaches for total mesorectal excision.

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PART 1

IMPLEMENTATION OF ROBOT-ASSISTED AND TRANSANAL TOTAL MESORECTAL EXCISION

CHAPTER 2

LONG-TERM ONCOLOGICAL RESULTS AFTER TRANSANAL TOTAL MESORECTAL EXCISION FOR RECTAL CARCINOMA

JC Hol, SE van Oostendorp, JB Tuynman, C Sietses

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ABSTRACT

Introduction: Transanal total mesorectal excision (TaTME) for mid and low rectal cancer has shown to result in benefits in short-term outcomes, mostly reflected by lower conversion rates and with improved quality of the specimen. However, robust long-term oncological data supporting the encouraging clinical and pathologic outcomes are lacking.

Methods: All consecutive patients undergoing TaTME with curative intent for mid or low rectal cancer in two referral centers in The Netherlands between January 2012 and April 2016 with a complete and minimum follow-up of 36 months were included. The primary outcome was local recurrence rate. Secondary outcomes were disease-free survival, overall survival and development of metastasis.

Results: There were 159 consecutive patients. Their mean age was 66.9 (10.2) years and 66.7% of all patients were men. Pathological analysis showed a complete mesorectum in 139 patients (87.4%), nearly complete in 16 (10.1%) and an incomplete mesorectum in 4 (2.5%). There was involvement of the CRM (< 1 mm) in one patient (0.6%) and no patients had involvement of the distal margin (< 5 mm). Final postoperative staging after neoadjuvant therapy was stage 0 in 11 patients (6.9%), stage I in 73 (45.9%), stage II in 31 (19.5%), stage III in 37 (23.3%) and stage IV in 7 (4.4%). The 3-year local recurrence rate was 2.0% and the 5-year local recurrence rate was 4.0%. Median time to local recurrence was 19.2 months. Distant metastases were found in 22 (13.8%) patients and were diagnosed after a median of 6.9 months (range 1.1–50.4) months. Disease-free survival was 92% at 3 years and 81% at 5 years. Overall survival was 83.6% at 3 years and 77.3% at 5 years.

Conclusion: The long-term follow-up of the current cohort confirms the oncological safety and feasibility of TaTME in two high volume referral centers for rectal carcinoma. However, further robust and audited data must confirm current findings before widespread implementation of TaTME.

INTRODUCTION

Transanal Total Mesorectal Excision (TaTME) has the potential to lower the local recurrence rate after radical resection of mid and low rectal cancer. Currently available evidence shows an improvement in the quality of the surgical specimen and reduced number of R1 resections by lower distal margins in initial cohort studies (1-3). Therefore, TaTME has the potential to lower the local recurrence rate after radical resection of mid and low rectal cancer. However, long-term data of local recurrence rates confirming the encouraging pathologic outcomes are lacking (4). Over the past decades, adaptation of Total Mesorectal Excision (TME) as surgical principle has reduced local recurrence rates and improved cancer free survival rates (5). Combined with neoadjuvant chemoradiation the local recurrence rates have been reduced to 5% as demonstrated in a large randomized clinical trial (6).

Even though laparoscopic surgery has improved the short-term results after rectal cancer surgery, the expected oncological benefits are modest (6-8). Laparoscopic TME is a difficult technique and this may negatively influence the results of surgery, especially as regards the lower part of the rectum. In male patients with a small narrow pelvis, there is a limited space to mobilize the rectum with intact mesorectum.

In TaTME, the rectum is approached both from above and below, preferably at the same time (1). Because the distal part of the rectum is approached from below, it is more accessible and the surgical planes are better visualized. The technique appears to be feasible and short-term outcomes seem promising in expert centers. However, the learning curve is steep which might influence the results in low volume centers (3, 9)**.** Recently, Norway TaTME data revealed 9,5% local recurrences leading to a nationwide stop and thorough investigation (10). The results of the official investigations are eagerly awaited. Other single center series have reported local recurrence rates ranging from 2.3 to 5.7% with a median follow-up of 15–32 months (2, 11-15). The aim of this study was to investigate the long-term oncological results after TaTME surgery in a large consecutive cohort from the two hospitals that started TaTME in The Netherlands with a minimum follow-up of 36 months.

MATERIALS AND METHODS

Patients

Between January 2012 and May 2016, all patients in the Gelderse Vallei Hospital, Ede, The Netherlands and Amsterdam UMC, location VUmc, Amsterdam, The Netherlands with

histological proven distal or mid rectal carcinomas, who had elective TaTME, were included. Exclusion criteria were recurrent and/or locally advanced tumors with persistent threatened margins after neoadjuvant radiotherapy and palliative resections. Patients with curative resection of synchronous liver metastasis were included.

Preoperative assessment included magnetic resonance imaging (MRI) for local staging, computed tomography (CT) scan of the abdomen, CT scan or conventional X-ray of the chest to detect distant metastasis, and blood tests including serum carcinoembryonic antigen (CEA) levels. Each patient was discussed by a local multidisciplinary cancer board. Patients at medium risk, i.e., those with cT3b+ N0 or cT2–3 N1 tumors received preoperative radiotherapy with 5 Gy daily for five consecutive days. Patients with N2 disease or tumors with threatened margins (< 1.0 mm) to the mesorectal fascia were treated with chemoradiation therapy for 25 days with 2 Gy daily combined with administration of oral 5-fluorouracil.

The study was approved by the Ethics Committees of the participating centers. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Surgical procedure

TaTME was performed as described previously (2). The first patients were operated on by a single surgeon, performing both phases of the procedure sequentially. After the initial learning curve, the two team approach was introduced, with simultaneous abdominal and the transanal dissection. The splenic flexure was mobilized in the majority of the patients. Ligation of the inferior mesenteric vein was done near the pancreas.

The transanal phase consists of a thorough washout and the introduction of the anal platform; in the majority of the cases the GelPOINT Path Transanal Access Platform (Applied Medical, Rancho Santa Margarita, CA, USA) was used. In the first patients, a regular laparoscopic CO2 insufflator was used. In all other patients, the AirSeal insufflator (ConMed, Utica, NY, USA) was used. The purse-string location changed from the initial position directly behind the dentate line to a 3 cm higher position above the anorectal junction (if applicable for the location of the tumor, in proximal tumors it was placed below the tumor). Dissection was performed in a standardized fashion, starting the dissection dorsally and ventrally and thereafter dissecting the lateral plane. The abdominal and transanal team joined anteriorly. Specimen extraction was performed, after wound protection, through a Pfannenstiel incision. The anastomosis was preferably made side to end using a 31 EEA or 33 EEA hemorrhoid stapler (Medtronic, Dublin, Ireland).

Data collection

Baseline data were collected regarding age, sex, American Society of Anesthesiologists (ASA) classification, body mass index (BMI), distance of the tumor from the anal verge, preoperative clinical staging and preoperative chemoradiation therapy. Pathological outcomes included pathological staging, macroscopic completeness of the resection, number of lymph nodes harvested and circumferential resection margin (CRM) involvement. All patients have had follow-up carried out according to the Dutch National Guidelines for Colorectal Cancer for a period of 5 years at the outpatient clinic. For this cohort, a full 36-month follow-up was available for all patients. Primary outcome was locoregional recurrence. Secondary outcomes included distant metastasis, disease-free and overall survival. Recurrent disease was defined as the presence of locoregional recurrence, distant metastases or death from rectal cancer.

Statistical analysis

All data collection and statistical analysis were carried out using SPSS Statistics version 24 (IBM, Chicago, IL, USA). After analysis of numbers and percentages or median and range for each variable, a univariate binary regression analysis was performed for possible risk factors for local recurrence. Kaplan–Meier survival analysis was performed for local recurrence-free survival rates, disease-free survival rates and overall survival rates.

RESULTS

Patients characteristics and clinical outcomes

From January 2012 to May 2016, a total of 159 consecutive patients underwent TaTME. 110 underwent surgery in Gelderse Vallei Hospital, Ede, The Netherlands, and 49 in Amsterdam UMC, location VUmc, Amsterdam, the Netherlands. Their mean age was 66.9 (10.2) years and 66.7% of all patients were men. The follow-up data for 36-month follow-up was complete for all patients. Neoadjuvant radiotherapy was administered in 112 patients (70.4%) and 117 received a primary anastomosis during surgery (73.6%). Thirty-nine patients (24.5%) encountered postoperative complications graded as Clavien–Dindo grade 3 or higher. Patient characteristics and short-term clinical outcomes are summarized in Table 1.

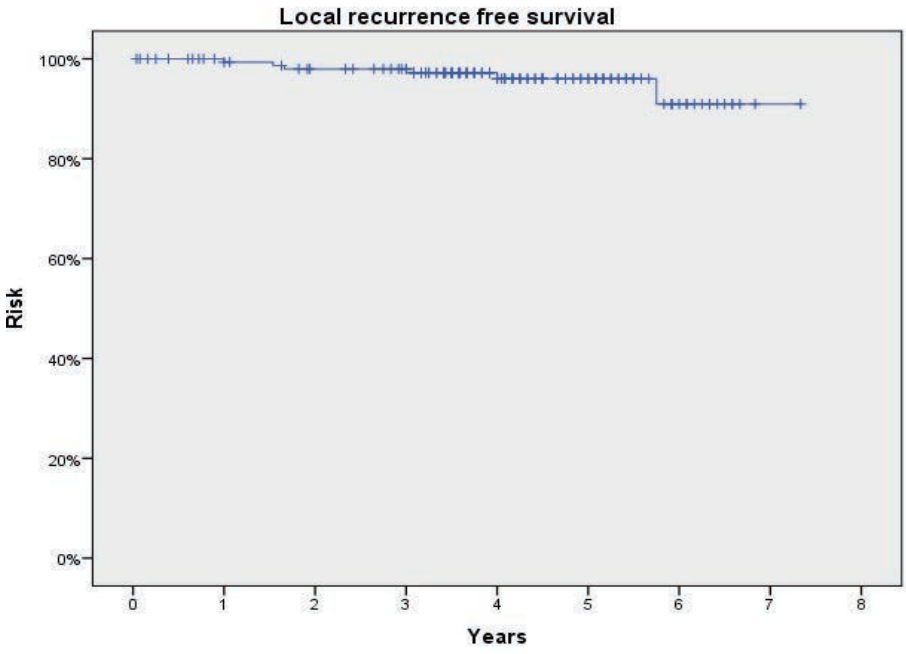
Oncologic outcomes

Pathological analysis showed a complete mesorectum in 139 patients (87.4%), nearly complete in 16 (10.1%) and an incomplete mesorectum in 4 (2.5%). There was involvement of the CRM (< 1 mm) in one patient (0.6%) and no patients had involvement of the distal margin (< 5 mm).

Table 1 Patient characteristics and clinical outcome

		n=159
Sex	*Male*	106 (66.7)
	Female	53 (33.3)
BMI (mean) (±SD)		26.4 (4.3)
Age (years) (mean) (±SD)		66.9 (10.2)
ASA	*I*	33 (20.8)
	II	100 (62.9)
	III	26 (16.4)
Height from AV (cm)	mean (±SD)	5.7 (3.5)
	median (range)	6 (0-15)
Height from AV <4cm	yes	47 (29.6))
Clinical Tumor stage	*T1*	2 (1.3)
	T2	39 (24.5)
	T3	103 (64.8)
	T4	11 (6.9)
	Tx	4 (2.5)
Clinical Nodal stage	*N0*	82 (51.6)
	N1	47 (29.6)
	N2	26 (16.4)
	Nx	3 (1.9)
Synchronous Metastasis	*M+*	7 (4.4)
MRF threatened (before RT)	*No*	125 (78.6)
	Yes	34 (21.4)
Preoperative therapy	*RT*	112 (70.4)
	CRT	43 (27.0)
Anastomosis	*primary anastomosis*	117 (73.6)
	end-colostomy	42 (26.4)
Performed operation	*LAR TaTME*	133 (83.6)
	ISR/APE TaTME	26 (16.4)
Intra-operative complications	*Rectal perforation*	2(1.3)
	Purse-string failure	1(0.6)
	Carbon dioxide (CO_2) embolus	1(0.6)
Postoperative morbidity	*No complications*	46 (47.8)
	Minor Clavien Dindo 1-2	44 (27.7)
	Severe Clavien Dindo ≥3	39 (24.5)
	Reoperation	36 (22.6)
Anastomotic leakage		10 (6.3)
Presacral abcess		14 (8.8)

Numbers in parentheses are percentages, unless mentioned otherwise
BMI body mass index (kg/m^2), *SD* standard deviation, *ASA* American Society of Anesthesiologists, *cm* centimeters, *AV* anal verge, *MRF* mesorectal fascia, *RT* radiotherapy, *CRT* chemoradiotherapy, *LAR* low anterior resection, *ISR* intersphincteric resection, *APE* abdominoperineal excision, *Tx* or *Nx* means stage unknown based on preoperative MRI



Years	0	1	2	3	4	5	6	7
No at Risk	159	149	140	133	80	41	14	1

Figure 1 Kaplan-Meier curve of local recurrence-free survival after TaTME

Pathological staging showed T0 in 13 patient (8.2%), T1 in 15 (9.4%), T2 in 74 (46.5%), T3 in 55 (34.6%) and T4 in 2 (1.3%). N stage was N0 in 118 patients (74.2%), N1 in 28 (17.6%) and N2 in 13 (8.2%). Final postoperative staging after neoadjuvant therapy according to the fifth AJCC classification was stage 0 in 11 patients (6.9%), stage I in 73 (45.9%), stage II in 31 (19.5%), stage III 37 (23.3%) and stage IV in 7 (4.4%).

The mean long-term follow-up was 54.8 months (range 36–88 months). The overall local recurrence rate was 3.8%, and median time to local recurrence was 19.2 months (range 5.9–30.0 months). Figure 1 shows a Kaplan–Meier (KM) curve of local recurrence. The local recurrence rate was 2.0% at 3 years and 4.0% at 5 years. An overview of all six cases of local recurrence and treatment can be seen in Table 2.

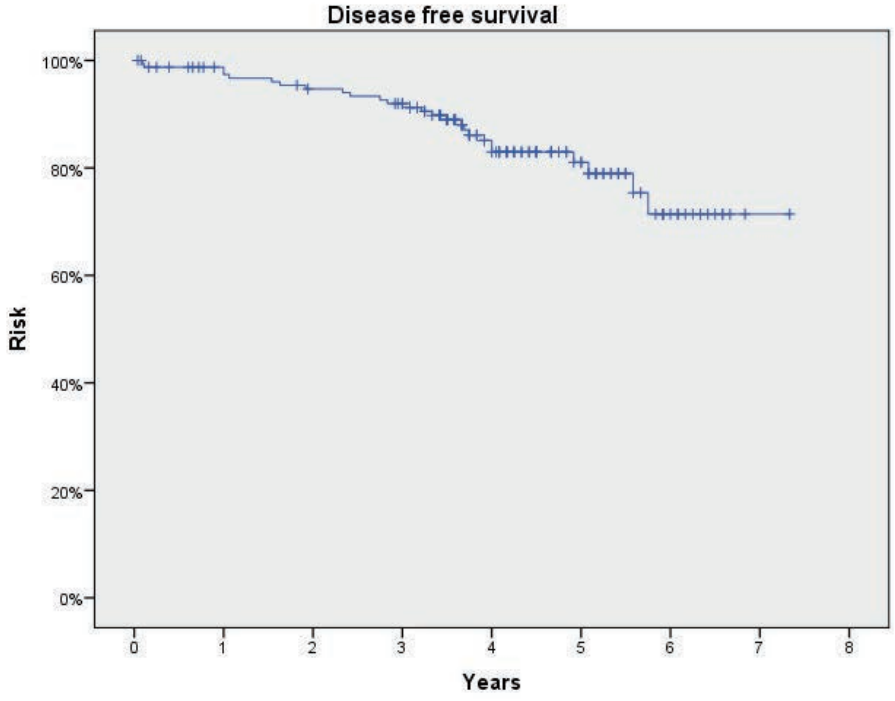
Risk factors for local recurrence

Univariate binary logistic regression analysis for local recurrence showed no significant difference for sex, obesity, low tumor, threatened mesorectal fascia, preoperative

Table 2 Overview of cases with local recurrence

	Surgery	p Stage	Complications	R	Neoadjuvant	Interval	Location	Treatment	Survival
1	2012	T3N2	**Presacral abscess**	R0	radiotherapy	18 months	presacral	palliative chemotherapy	57 months
2	2013	T2N1	**none**	R0	none	8 months	presacral	stoma and palliative chemotherapy	alive, remission
3	2014	T3N0	**Presacral abscess**	R1	chemoradiation	6 months	presacral	palliative treatmet	12 months
4	2016	T3N0	**Anastomotic leakage**	R0	chemoradiation	30 months	presacral	APE	alive
5	2014	ypT0N0	**Presacral abscess**	R0	radiotherapy	19 monhts	vesiculae	APE and debulking	alive
6	2015	pT3N1	**none**	R0	none	27 months	presacral	CRTX, excenteration	alive

APE abdomino perineal excision, *CRTX* chemoradiation therapy



Years	0	1	2	3	4	5	6	7
No at Risk	159	147	139	133	80	41	14	1

Figure 2 Kaplan-Meier curve of disease free survival after TaTME

Table 3 Pathologic and long-term outcomes

		n =159
Pathologic T-stage	*(y)pT0*	13 (8.2)
	(y)pT1	15 (9.4)
	(y)pT2	74 (46.5)
	(y)pT3	55 (34.6)
	(y)pT4	2 (1.3)
Pathologic N-stage	*N0*	118 (74.2)
	N1	28 (17.6)
	N2	13 (8.2)
Quality of specimen (Quirke)	*Incomplete*	4 (2.5)
	Nearly complete	16 (10.1)
	Complete	139 (87.4)
CRM +	*<1 mm*	1 (0.6)
DRM +	*<5mm*	0 (0.0)
Follow-up (months)	*Mean (±SD) **	54.8 (13.1)
	*Median (range) **	52.0 (36.0-88.0)
Local Recurrence overall	*no*	153 (96.2)
	yes	6 (3.8)
Interval to local recurrence (months)	*Median (range)*	19.2 (5.9-30.0)
Distant metastasis	*no*	137 (86.2)
	yes	22 (13.8)
Interval to distant metastasis (months)	*Median (range)*	6.9 (1.1-50.4)
Disease recurrence	*no*	133 (83.6)
	yes	26 (16.4)
Interval to disease recurrence	*months*	8.2 (1.1-50.4)
Overall survival		124 (78.0)
Deceased		35 (22.0)
Interval to death (months)	*Median (range)*	28.0 (0.5-61)

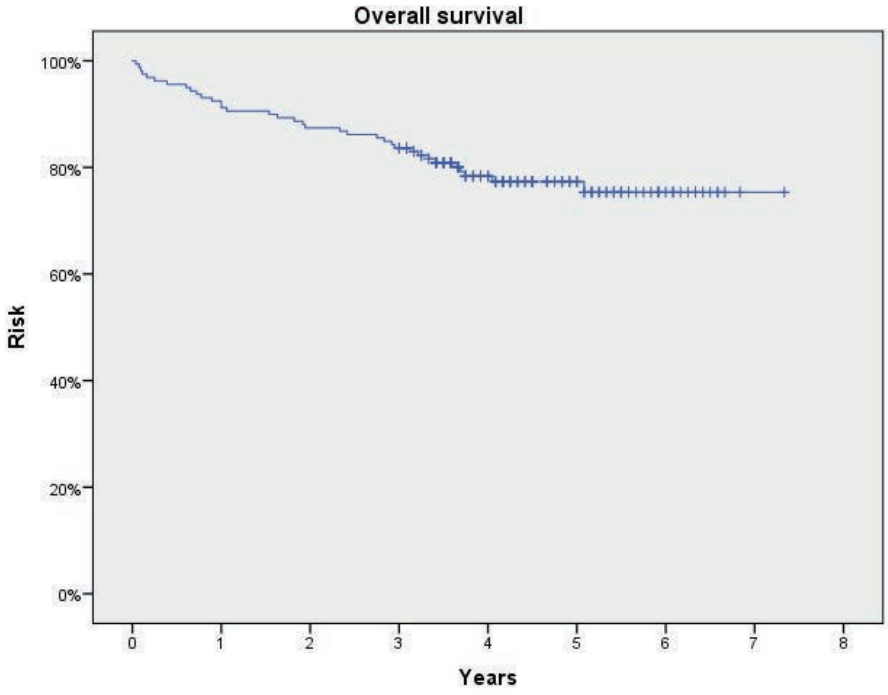
Numbers in parentheses are percentages, unless mentioned otherwise
*Mean/median range does not include diseased patients

radiotherapy, (y)pT4 stage, (y)pN2 stage, positive CRM, incomplete mesorectum, intraoperative perforation, intraoperative purse-string failure, carbon dioxide embolus, synchronous metastasis, anastomotic leakage and reoperation. There was a significant risk for pathologic stage T3 or 4 tumors, RR 0.103 (0.012–0.904), p = 0.040, complications grade 3 or higher according to Clavien–Dindo RR 0.148 (0.026–0.844), p = 0.031 and presence of presacral abscess RR 0.077 (0.014–0.430), p = 0.003. The patient with intraoperative purse-string failure did not develop presacral abscess or local recurrence. Results of the univariate analysis for risk factors are summarized in Table 4.

Table 4 Univariate analysis of risk factors for local recurrence

		LR	Total	RR	95% CI lower	95% CI upper	P-value
Sex	*Female*	3	53	ref			
	Male	3	106	2,06	0,401	10,573	0,386
BMI >25	*no*	4	66	ref			
	yes	2	93	2,935	0,522	16,522	0,222
Low tumor <4cm from AV	*no*	4	112	ref			
	yes	2	47	0,833	0,147	4,713	0,837
MRF threatened on MRI	*no*	4	125	ref			
	yes	2	34	0,529	0,093	3,018	0,473
Preoperative radiotherapy	*no*	2	47	ref			
	yes	4	112	1,200	0,212	6,787	0,837
pathologic stage T3-4	*no*	1	102	ref			
	yes	5	57	0,103	0,012	0,904	0,040
pathologic stage T4	*no*	6	157	ref			
	yes	0	2		0,000		0,999
pathologic stage N2	*no*	5	146	ref			
	yes	1	13	0,426	0,046	3,943	0,452
CRM+	*no*	5	158	ref			
	yes	1	1	0,000	0,000		1,000
incomplete mesorectum	*no*	6	155	ref			
	yes	0	4		0,000		0,999
Intra-operative perforation	*no*	6	157	ref			
	yes	0	2		0,000		0,999
Purse-string failure	*no*	6	158	ref			
	yes	0	1		0,000		1,000
CO2 embolus	*no*	6	158	ref			
	yes	0	1		0,000		1,000
Synchronous metastasis	*no*	5	152	ref			
	yes	1	7	0,204	0,021	2,029	0,175
complications CD 3 or higher	*no*	2	120	ref			
	yes	4	39	0,148	0,026	0,844	0,031
anastomotic leakage	*no*	5	149	ref			
	yes	1	10	0,313	0,033	2,965	0,311
presacral abscess	*no*	3	145	ref			
	yes	3	14	0,077	0,014	0,430	0,003
reoperation	*no*	3	123	ref			
	yes	3	36	0,275	0,053	1,426	0,124

Abbreviations: BMI = Body Mass Index (kg/m2), AV = Anal verge, MRF= mesorectal fascia, CRM+ = involvement of the circumferential resection margins (<1mm), CD = Clavien Dindo.



Years	0	1	2	3	4	5	6	7
No at Risk	159	147	139	133	80	41	14	1

Figure 3 Kaplan-Meier curve of overall survival after TaTME

DISCUSSION

This study of 159 TaTME procedures for rectal cancer shows that TaTME is associated with low local recurrence rate; the 3-year local recurrence rate was 2.0% with complete follow-up and the 5-year local recurrence rate was 4.0%. The median time to local recurrence was 19.2 months (range 5.9–30.0 months). To the best of our knowledge this is the largest series with a complete and long follow-up of more than 3 years after TaTME.

The 3-year local recurrence rate in this study is relatively low compared to the laparoscopic TME long-term outcome data of the COLOR II, ALaCART and ACOSOG Z6051 trials, which show a 3-year local recurrence rate of 5% (6-8). In accordance with previous literature, high tumor stage, severe postoperative complications and presence of a presacral abscess were risk factors for local recurrences (16). A multivariate analysis was not possible due to the low number of events.

One of the potential benefits of TaTME for mid and low rectal cancer is a better specimen quality and better radicality. Incomplete mesorectum is a known risk factor for local and overall recurrence (17). In our study 97.5% of the specimens had a good quality specimen, which is comparable to our previous study by Velthuis et al. in which 100% of the specimens after TaTME were of good quality, while in the traditional laparoscopic group 80% were of good quality (18).

Although TaTME was introduced in 2010, ample data on long-term outcome are currently limited. In contrast, a considerable amount of case series describing single center experiences focus merely on short-term and pathological outcomes (19). Although there is a growing interest in TaTME in rectal cancer surgery, it is still not widely implemented and concerns persist regarding the adequacy of oncological resection. Our study adds long-term outcome data to support the potential benefits of TaTME for mid and low rectal cancer: increased quality of the mesorectum, low number of positive CRM and corresponding low local recurrence rate.

Although the results from our study are encouraging, it only includes data from the two hospitals that started TaTME in The Netherlands which are high volume tertiary referral centers. The oncological results of widespread adoption of TaTME have not yet been demonstrated. Early adopters of TaTME recognized the high complexity of the procedure (20). Therefore, several countries started a nationwide structured training program including proctoring to guarantee safe implementation of the procedure (21, 22). The technique has a learning curve associated with substantial morbidity. Surgeons have to perform at least 40 cases to reach competency, based on acceptable morbidity or good pathologic outcome (9, 23). Furthermore, higher volumes are associated with better outcome in terms of conversion, severe complications and quality of the mesorectum (3). Our results do not support the concern that TaTME leads to an increased risk for local recurrence, as suggested by Norwegian data (10)**.** It is to be imagined that poor quality TaTME does negatively influence local recurrence rates. It is to be imagined that poor quality TaTME does negatively influence local recurrence rates. A review focusing on outcomes of TaTME in low volume centers was associated with a relatively high recurrence rate of 8.9% versus 2.8% in high volume centers (3).

This indicates that a steep learning curve might seriously hamper both short- and long-term outcome. Inadequate dissection, perforation and/or insufficient closure of the rectum before dissection all have the potential for tumor spill (24).

The Idea, Development, Exploration, Assessment and Long-term follow-up (IDEAL) framework aims to prevent surgical innovation from being implemented too early

(25). While the TaTME is still in the developmental stage and no global consensus and standardization has been reached, one could argue that the surgical community has proceeded to the adoption of this technique too early. This means exposing patients to potential intraoperative complications and short-term morbidity. Furthermore, long-term oncological safety of the technique must be established to avoid events comparable to the port-site metastasis setback seen in laparoscopic surgery (26). The international TaTME registry is a useful instrument for capturing real-time data of the early adoption of TaTME and has signaled a 15.7% anastomotic failure rate (27). The long-term follow-up data of the international registry are awaited, although the completeness of data will be a potential problem and source of bias.

Although the results of our study are promising, oncological safety after TaTME surgery remains to be proven in a multicenter international setting. The next crucial step in implementing this technique is an international randomized controlled trial such as the COLOR III trial, which is currently enrolling and is designed to assure high-quality evidence by implementing a pretrial showing surgical competency, central review of MRI, assessment of procedural video, re-evaluation of the specimen and obligatory upload and central review of MRI 3 years after surgery (28).

CONCLUSION

TaTME is associated with relatively low local recurrence rate at 3 years and 5 years. This shows that in experienced hands with high volume, TaTME is safe and is associated with good long-term outcome.

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CHAPTER 3

LOCOREGIONAL RECURRENCES AFTER TRANSANAL TOTAL MESORECTAL EXCISION OF RECTAL CANCER DURING IMPLEMENTATION

SE van Oostendorp, HJ Belgers, BT Bootsma, **JC Hol**, EJTH Belt, W Bleeker, FC den Boer, A Demirkiran, MS Dunker, HFJ Fabry, EJR de Graaf, JJ Knol, SJ Oosterling, GD Slooter, DJA Sonneveld, AK Talsma, HL van Westreenen, M Kusters, R Hompes, HJ Bonjer, C Sietses, JB Tuynman

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ABSTRACT

***Background*:** Transanal total mesorectal excision (TaTME) has been proposed as an approach in patients with mid and low rectal cancer. The TaTME procedure has been introduced in the Netherlands in a structured training pathway, including proctoring. This study evaluated the local recurrence rate during the implementation phase of TaTME.

***Methods*:** Oncological outcomes of the first ten TaTME procedures in each of 12 participating centres were collected as part of an external audit of procedure implementation. Data collected from a cohort of patients treated over a prolonged period in four centres were also collected to analyse learning curve effects. The primary outcome was the presence of locoregional recurrence.

***Results*:** The implementation cohort of 120 patients had a median follow up of 21.9 months. Short-term outcomes included a positive circumferential resection margin rate of 5.0 per cent and anastomotic leakage rate of 17 per cent. The overall local recurrence rate in the implementation cohort was 10.0 per cent (12 of 120), with a mean(s.d.) interval to recurrence of 15.2(7.0) months. Multifocal local recurrence was present in eight of 12 patients. In the prolonged cohort (266 patients), the overall recurrence rate was 5.6 per cent (4.0 per cent after excluding the first 10 procedures at each centre).

***Conclusion*:** TaTME was associated with a multifocal local recurrence rate that may be related to suboptimal execution rather than the technique itself. Prolonged proctoring, optimization of the technique to avoid spillage, and quality control is recommended.

INTRODUCTION

The transanal total mesorectal excision (TaTME) technique has been introduced for patients with low rectal cancer, with the aim of improving clinical outcomes, such as a greater degree of radical resection, lower rates of anastomotic leakage, more sphincter-saving procedures, better functional results and, most importantly, similar or lower local recurrence rates (1, 2). Direct visualization facilitates purse-string suture placement. The technique has been met with tremendous enthusiasm in the colorectal surgical community, and more than 300 centres worldwide have implemented the technique (3). In expert centres, TaTME is associated with promising pathological and clinical outcomes (4-8). The first long-term outcome data from two expert centres showed a favourable low recurrence rate of 2 per cent after 3 years (9).

Despite these positive results, it is also acknowledged that TaTME is a difficult technique and has a long learning curve with associated morbidity (10, 11). The international TaTME registry (3) and a systematic review (4) have shown that widespread adoption results in less favourable clinical outcomes than reported in the initial cohorts treated in expert centres. The TaTME registry (3), representing more than 300 centres voluntarily entering data, recorded an anastomotic failure rate of 15.6 per cent among 1594 patients, which is higher than rates from expert centres. In addition, a population-based study (12) documented an overall morbidity rate of 42.3 per cent, anastomotic leakage in 16.0 per cent and a circumferential resection margin (CRM)-positive rate of 4.4 per cent. These latter studies show that the promise of TaTME has not yet been met on a large scale.

The long-term oncological safety of TaTME remains to be proven. Although the first report with long-term outcome data showed a low level of local recurrence, the question remains whether such results can be achieved with more widespread adoption of TaTME (9). As TaTME is substantially different from abdominal techniques in terms of open access to the tumour, purse-string closure and a subsequent endoluminal approach to the mesorectal dissection, it is especially important to assess long-term outcomes properly. RCTs such as COLOR III (13) and GRECCAR 11 (14) are investigating long-term outcomes of TaTME, and are currently including patients. Recently, concern has been raised by the first report (15) of national Norwegian data which showed an increase in the incidence of local recurrence with an extensive or multifocal pattern following TaTME, leading to a national halt to TaTME (16).

In the Netherlands, a structured training pathway, including proctoring sessions by dedicated trainers, has been set up to ensure safe implementation of TaTME and minimization of learning curve effects (17). A collective review of the short-term outcomes of the first

ten patients in 12 proctored centres revealed a major morbidity rate of 19.2 per cent and involved CRMs in 5.0 per cent of patients (17). The aim of the present study was to evaluate the oncological outcomes of the initial patients who underwent TaTME within the structured training pathway. In addition, a cohort treated over a prolonged period after the implementation of TaTME in four high-volume centres was evaluated to analyse learning curve effects in terms of local recurrence rates.

METHODS

Structured training pathway

The structured training pathway was set up in the Netherlands in 2014 as a programme for postgraduate colorectal surgeons in centres with an annual volume of total mesorectal excision (TME) surgery for rectal cancer of 20 procedures or more and with known proficiency in laparoscopic TME. The clinical data from patients in the structured training pathway was collected prospectively, as described previously (17). The first five procedures were discussed with and assisted by an experienced proctor, after which the following procedures were performed independently. The first ten patients in each of centres that completed the structured training pathway were included to evaluate clinical outcomes during the implementation of TaTME (17). In addition, a larger cohort of patients from four centres that continued TaTME after training, with a procedure volume greater than 45, was collected to assess learning curve effects. Long-term clinical data were obtained as part of an external audit to assure high quality and completeness of the data set. The anonymized operative notes and full imaging reports of locoregional recurrences were obtained and audited by senior TaTME surgeons. All patients consented to a TaTME procedure as required under the Dutch national patient–physician relation regulations. The Medical Ethics Review Board of Amsterdam UMC, Location VUmc, approved the study and waived the need for additional informed consent for the present study

Outcomes

The primary outcome of this study was the incidence of local recurrence confirmed by either imaging (MRI, CT or PET–CT) and/or pathology (biopsy, salvage surgery). A local recurrence was defined as a mass in the pelvis with a biopsy positive for adenocarcinoma, or growth on sequential imaging in the absence of histopathological confirmation. A multifocal local recurrence was defined by the presence of two or more separate foci of recurrence in the pelvic area, as seen on MRI or PET–CT. Secondary outcomes included location of local recurrence and distant metastasis, treatment of recurrence and distant metastasis, and overall mortality. All potential risk factors were evaluated

for an association with recurrence. Pelvic sepsis was defined by the occurrence of early anastomotic leakage, early pelvic abscess or late complications (leakage, abscess or presacral sinus occurring more than 30 days after operation) (18). Complications were graded according to the Clavien–Dindo classification (19). Rectal perforation, purse-string failure and an insufficient anastomosis requiring reinforcement or refashioning were deemed to increase the risk of spillage of tumour cells into the pelvis. A positive CRM was defined by the presence of tumour cells 1 mm or less from the circumferential plane.

Statistical analysis

Categorical data are shown as number with percentage, whereas continuous outcomes are recorded as mean(s.d.) or median (range). Dichotomous and categorical values were analyzed using Pearson's χ^2 square test or Fisher's exact test. Comparison of continuous data was done using the independent Student's *t* test, or Mann–Whitney *U* test if the data were not distributed normally.

Univariable logistic regression analysis was performed to identify potential risk factors for local recurrence. Multivariable analysis was not possible because the event rate did not exceed the threshold for entry of multiple univariable significant predictors into a multivariable model. Case–control analysis between the present TaTME group and the laparoscopic TME group from the original COLOR II study was performed by matching sex, age, tumour height, neoadjuvant chemoradiotherapy, type of procedure (low anterior resection or abdominoperineal resection) and pathological risk factors, R1 and CRM and pT4 category (20, 21). Patients with a final pT4 category or positive margins were excluded to enable evaluation of the technique as a potential individual risk factor for recurrence. For all tests, two-sided $P \leq 0.050$ was considered statistically significant. Statistical analyses were done using SPSS® version 24 for Windows® and Mac® (IBM, Armonk, New York, USA).

RESULTS

Baseline characteristics and clinical outcomes

A cohort of 120 patients, comprising the first ten patients in each of 12 centres who underwent TaTME between March 2015 and October 2018, was included. Median follow-up was 21.9 (range 2.0–46.7) months. The median interval between the first and tenth procedures in each hospital was 12.5 (range 3.5–35.5) months. Baseline characteristics have been published previously and are shown in *Table 1* (17).

Table 1 Patient characteristics

	No. of patients* (*n* = 120)
Age (years)†	65.4(9.6)
Sex ratio (M : F)	91 : 29
BMI (kg/m²)†	26.9(4.1)
ASA fitness grade	
I	26 (21.7)
II	77 (64.2)
III	17 (14.2)
Tumour height from anal verge (cm)†	6.9(3.1)
Clinical tumour category	
ycT1	7 (5.8)
ycT2	24 (20.0)
ycT3	89 (74.2)
Clinical node category	
cN0	52 (43.3)
cN1	44 (36.7)
cN2	24 (20.0)
Persistent MRF+ after RT‡	6 (5.0)
Preoperative therapy	
None	43 (35.8)
RT	41 (34.2)
CRT	36 (30.0)
Transanal total mesorectal excision	
Low anterior resection	110 (91.7)
Intersphincteric resection	10 (8.3)

*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.). ‡All patients with a persistent threatened mesorectal fascia (MRF+) initially had cT3 tumours (3 anterior, 2 lateral, 1 unknown). RT, radiotherapy; CRT, chemoradiotherapy.

Short-term outcomes are summarized in *Table 2*. The overall 30-day morbidity rate was 45.0 per cent, including an anastomotic leakage rate of 17 per cent and pelvic sepsis in 17.5 per cent. The involved CRM rate was 5.0 per cent; no patient had an involved distal resection margin. The quality of the specimen was rated as complete in 89.2 per cent of procedures and nearly complete in 10.8 per cent; none of the specimens were considered incomplete.

Table 2 Short-term clinicopathological outcomes

	No. of patients (*n* = 120)
Intraoperative events	
Purse-string failure	1 (0.8)
Perforation	1 (0.8)
Reinforcement	3 (2.5)
30-day mortality	0 (0)
30-day overall morbidity	54 (45.0)
Major morbidity (Clavien–Dindo grade ≥ III)	23 (19.2)
30-day anastomotic leakage	17 of 98 (17)
Pelvic sepsis (early leak, abscess and late sinus*	21 (17.5)
Pathological tumour category	
(y)pT0	11 (9.2)
(y)pT1	16 (13.3)
(y)pT2	34 (28.3)
(y)pT3	59 (49.2)
(y)pT4	0 (0)
Quality of specimen (Quirke)*	
Complete	107 (89.2)
Nearly complete	13 (10.8)
Incomplete	0 (0)
CRM involvement ≤ 1 mm	6 (5.0)
DRM involvement < 5 mm	0 (0)

Values in parentheses are percentages. *All patients (anastomosis and colostomy). CRM, circumferential resection margin; DRM, distal resection margin.

Long-term outcomes

Long-term outcomes are shown in *Table 3*. Twelve of 120 patients (10.0 per cent) developed local recurrence, which was multifocal in eight patients. The median interval to local recurrence was 15.9 months, ranging from 6.0 to 26.4 months (*Table 4*). The recurrences were located presacrally (2), anterior (1), at the rectal stump (1) or in multiple regions in the pelvis (8). Nine of the 12 patients with local recurrence presented with or developed distant metastasis, whereas only 14 of 108 patients without local recurrence had distant metastases diagnosed ($P < 0.001$).

The local recurrences were distributed over the 12 participating sites as follows: three in one centre, two in three centres, one in three centres and none in five centres. There was no relationship between the time to include ten procedures and the incidence of local recurrence.

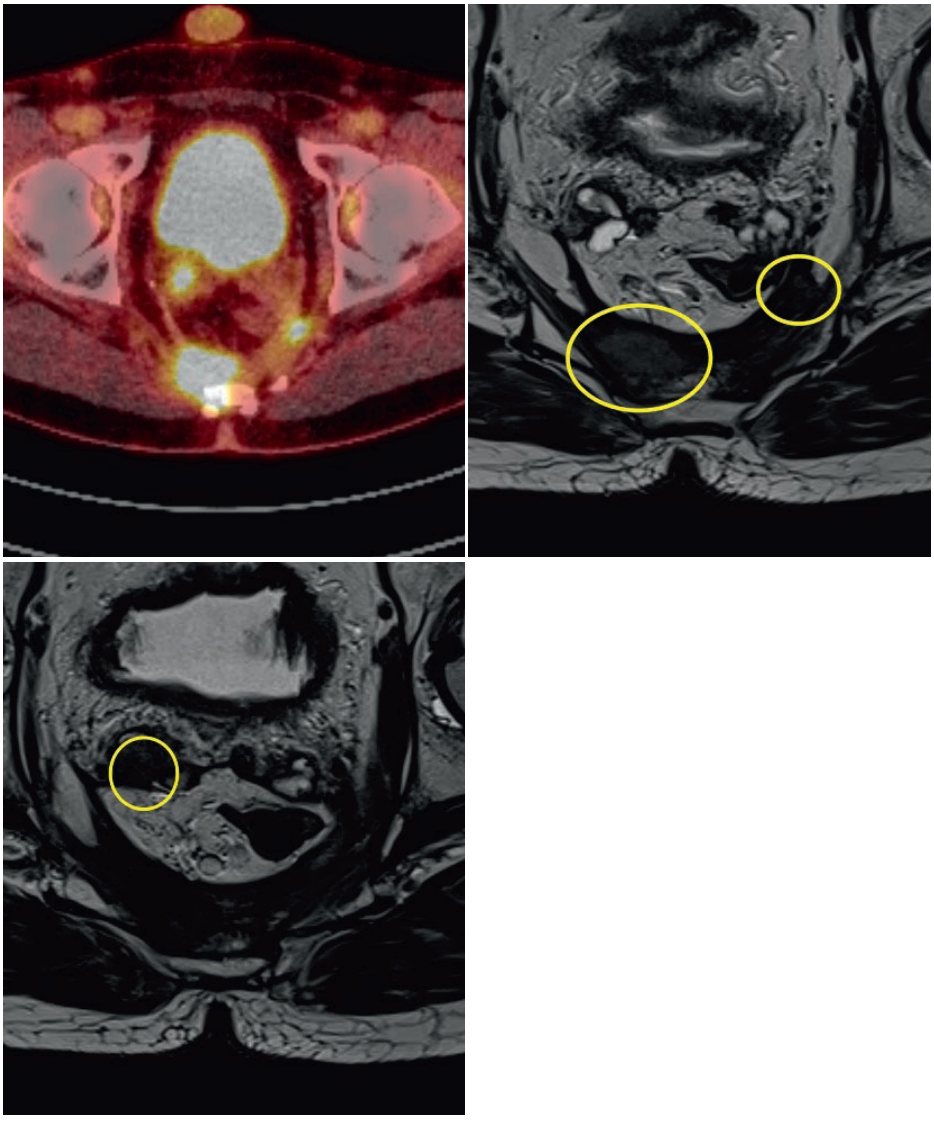

Figure 1 Images from a patient with multifocal recurrence after transanal total mesorectal excision **a** PET images showing multifocal recurrence. **b**,**c** T2-weighted axial MRI images showing left lateral and presacral local recurrence (**b**) and recurrence in right seminal vesicle (**c**).

Details of the 12 patients who developed local recurrence are shown in *Table 5*. Two patients initially presented with a synchronous liver metastasis which was treated by a liver-first approach. One of these developed lung metastasis simultaneous with the local recurrence. Pathological examination showed two poorly differentiated tumours, and three patients had an involved margin, one due to perineural growth that intersected the circumferential plane.

Table 3 Long-term outcomes

	No. of patients* (*n* = 120)
Follow-up (months)	
Mean(s.d.)	23.4(9.5)
Median (range)	21.9 (2.0–46.7)
Local recurrence (total)	12 (10.0)
Multifocal local recurrence	8 of 12 (67)
Interval to local recurrence (months)†	15.2(7.0)
Overall distribution of disease (recurrence and metastasis)	
Isolated local	3 (12)
Local + liver	4 (15)
Local + lung	2 (8)
Local + liver + lung	2 (8)
Local + lung + peritoneal + brain	1 (4)
Liver + lung	4 (15)
Isolated liver	5 (19)
Isolated lung	5 (19)
Disease-free survival	94 (78.3)
Overall survival	115 (95.8)

*With percentages in parentheses unless indicated otherwise; †values are mean(s.d.).

Treatment of recurrences

Of the 12 patients with local recurrence, five with unresectable and/or systemic disease received palliative treatment. Six patients had local exenterative surgery with curative intent. Four patients underwent exenteration (1 combined with intraoperative radiotherapy (IORT)), one had abdominoperineal excision with IORT and one had cytoreductive surgery with hyperthermic intraperitoneal chemotherapy as salvage surgery. At the time of writing, the final patient was receiving further chemoradiotherapy before salvage surgery.

Risk factors for recurrence

Risk factors for recurrence were identified by univariable logistic regression analysis. Prognostic factors associated with local recurrence (12 patients) were: positive CRM (odds ratio (OR) 11.67; $P = 0.006$), intraoperative complication (OR 7.00; $P = 0.005$), (y)pT3 category (OR 6.02; $P = 0.025$) and pelvic sepsis (OR 4.12; $P = 0.029$) (*Table S1*, supporting information). Risk factors associated with multifocal recurrence (8 patients) were: intraoperative complication (OR 12.11; $P = 0.013$), positive CRM (OR 9.00; $P = 0.022$), pathological N-positive status (OR 6.88; $P = 0.022$), (y)pT3 category (OR 3.34; $P = 0.150$) and pelvic sepsis (OR 5.59; $P = 0.023$) (*Table S2*, supporting information).

Table 4 Location and treatment of local recurrences

	No. of patients* (*n* = 12)
Interval to local recurrence (months)	
Mean(s.d.)	15.2(7.0)
Median (range)	15.9 (6.0–26.4)
Location	
Presacral	2
Anterior	1
Rectal stump	1
Multiple sites	8
Focality (no. of sites)	
1	4
2	4
3	4
Treatment	
Exenteration†	4
CRS + HIPEC	1
Abdominoperineal resection + IORT	1
Palliative chemotherapy	5
Further CRT; multivisceral resection planned	1

*Unless indicated otherwise. †Also intraoperative radiotherapy (IORT) in one patient. CRS + HIPEC, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; CRT, chemoradiotherapy.

Proctoring effect

There were four patients with local recurrence among the first five proctored TaTME procedures per centre (4 of 60 overall) and eight occurred in the second five proctored TaTME procedures (8 of 60) ($P = 0.362$). Clinicopathological outcomes for the first and second five procedures per centre were an intraoperative complication rate of 3 *versus* 5 per cent respectively, an anastomotic leakage rate of 19 *versus* 16 per cent, and involved CRM rate of 2 *versus* 8 per cent.

Comparative case-matched analysis of transanal versus laparoscopic total mesorectal excision

To focus on the procedure itself rather than pathological risk factors for local recurrence, case-matched pairing of patients with good-quality specimens and no CRM involvement yielded two groups of 109 patients with similar baseline characteristics, abdominoperineal resection rate and incidence of anastomotic leakage (*Table S3*, supporting information). The pathological outcomes were comparable in terms of stage, and no patient in either matched group had a non-radical resection or incomplete specimen.

Table 5 Details of patients with local recurrence

Patient no.	Baseline data (sex, age, tumour height, cTNM stage)	Neoadjuvant treatment, MRF status*	Surgery	Anastomotic leakage	Pathological stage	Differentiation	CRM (mm)	Follow-up details	Treatment	Outcome
1	M, 68 years, 2 cm from AV, cT2 N0 M0	No, MRF–	LAR + diversion	No	pT3 N0	W/M	10	18 months LR (multifocal) + M (hepatic)	Metastasectomy, APR + IORT	M+ (pulmonary), palliative chemotherapy. Alive at 35 months
2	F, 50 years, 8 cm from AV, cT3 N2 M1 (hepatic)	CRT, MRF–	Liver-first laparoscopic segmentectomy VI + VII. LAR + diversion	Yes	pT3 N0	W/M	5	19 months LR (unifocal)	Exenteration	Further recurrence after 3 months. Alive at 28 months
3	F, 54 years, 3 cm from AV, cT3 N0 M0	No, MRF–	LAR + diversion	No	pT3 N0	W/M	3	26 months LR (unifocal) + M (hepatic)	Metastasectomy, exenteration	Disease-free. Alive at 39 months
4	M, 65 years, 4 cm from AV, cT3 N1 M0	CRT, MRF–	LAR, no stoma	No	pT2 N1	Poor	3	12 months LR (multifocal)	Exenteration (R1)	M+ (hepatectomy) after 5 months, palliative chemotherapy. Died 36 months after TME
5	M, 55 years, 8 cm from AV, cT3 N0 M0	5 × 5, MRF–	LAR, no stoma	Yes	pT3 N1	W/M	4	7 months LR (multifocal) + M (hepatic)	Palliative	Alive at 23 months
6	M, 40 years, 8.3 cm from AV, cT3 N2 M0	CRT, MRF–	LAR + diversion	No	pT3 N2	W/M	7	14 months LR (multifocal) + M (pulmonary)	Further CRT, systemic chemotherapy	Progression, palliative. Alive at 25 months

Table 5 Details of patients with local recurrence (continued)

Patient no.	Baseline data (sex, age, tumour height, cTNM stage)	Neoadjuvant treatment, MRF status*	Surgery	Anastomotic leakage	Pathological stage	Differentiation	CRM (mm)	Follow-up details	Treatment	Outcome
7	M, 85 years, 2 cm from AV, cT3 N2 M0	CRT, MRF–	LAR + colostomy	No	pT3 N0	Poor	0	10 months LR (unifocal)	Palliative	Died 15 months after TME
8	M, 51 years, 5 cm from AV, cT3 N2 M1 (hepatic)	CRT, MRF–	Liver-first laparoscopic segmentectomy IVb. LAR + diversion	No	pT3 N1	W/M	< 1	8 months LR (multifocal) + M (pulmonary)	Pulmonary RT. Response to induction chemotherapy. Recurrent M+ (pulmonary)	Palliative chemotherapy. Alive at 34 months
9	F, 54 years, 3 cm from AV, cT3 N1 M0	CRT, MRF–	LAR + diversion	No	pT3 N1	W/M	> 10	25 months LR (multifocal)	Induction chemotherapy + further CRT. CRS + HIPEC (R0)	Alive 36 at months
10	M, 60 years, 7 cm from AV, cT3 N1 M0	5 × 5, MRF–	LAR + diversion; air leak reinforced by sutures	Yes	pT3 N0	W/M	> 10	20 months LR (multifocal)	Induction chemotherapy + further CRT. Exenteration (R0)	Alive at 22 months
11	F, 75 years, 5 cm from AV, cT3 N1 M0	5 × 5, MRF–	LAR, no stoma; air leak reinforced by sutures	Yes	pT3 N1	W/M	0†	19 months LR (multifocal) + M (pulmonary). Also previous 10 months M (hepatic)	Work-up to plan treatment for LR + M (pulmonary)	Alive at 22 months
12	M, 73, 10cm AV, cT3 N1 M0	5 ×5, MRF–	LAR + diversion	No	pT3 N1	W/M	7	6 months LR (unifocal) + M (pulmonary, peritoneal, brain)	Palliative	Alive at 18.5 months

*After neoadjuvant treatment if applicable. †Perineural growth. MRF, mesorectal fascia; CRM, circumferential resection margin; AV, anal verge; MRF–, MRF not threatened; LAR, low anterior resection; W/M, well to moderate; LR, local recurrence; M, distant metastasis; APR, abdominoperineal resection; IORT, intraoperative radiotherapy; CRT, chemoradiotherapy; TME, total mesorectal excision; 5 × 5, short-course radiotherapy (RT) 5 × 5 Gy; CRS + HIPEC, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

The overall local recurrence rate was higher for TaTME than laparoscopic TME: 8.3 per cent (nine patients) and 1.8 per cent (2) respectively.

Long-term outcomes of four hospitals with experience of more than 45 procedures

A prolonged cohort from four hospitals with experience of more than 45 procedures included a total of 266 patients who underwent TaTME for primary rectal cancer. Median follow-up was 23.8 (range 1.0–62.4) months. The crude local recurrence rate was 15.0 per cent after the first ten procedures in each centre, 4.2 per cent after procedures 11–40, and 3.8 per cent for procedure 41 onwards (*Table 6*). Overall, 15 patients (5.6 per cent) in this cohort of 266 patients who underwent TaTME developed local recurrence.

Table 6 Local recurrence according to number of transanal total mesorectal excision procedures at each centre in prolonged cohort

	Local recurrence rate			
	Procedures 1–10	**Procedures 11–40**	**Procedures ≥ 41**	**Total**
Centre A	2 of 10	2 of 30	0 of 31	4 of 71 (6)
Centre B	1 of 10	2 of 30	3 of 28	6 of 68 (9)
Centre C	2 of 10	0 of 30	1 of 7	3 of 47 (6)
Centre D	1 of 10	1 of 30	0 of 40	2 of 80 (3)
Overall	6 of 40 (15)	5 of 120 (4.2)	4 of 106 (3.8)	15 of 266 (5.6)

Values in parentheses are percentages.

DISCUSSION

In this study, the local recurrence rate during the learning curve was 10.0 per cent, despite the low positive CRM rate and the presence of a structured training pathway, including on-site proctoring. The multifocal pattern of recurrence seemed to be substantially different from that after abdominal TME (open, laparoscopic or robotic) and confirmed the pattern encountered in Norway (15), which calls for further evaluation of the safety of TaTME. TaTME has been shown to be a difficult technique with a relatively long learning curve and associated morbidity (10). Therefore, it was expected that some learning curve-related problems would be encountered in the present cohort, despite the presence of a structured training pathway aimed at minimizing harm during implementation.

The effect of the learning curve is demonstrated by the relatively high rate of anastomotic leakage and relatively high rate of local recurrences in the longer term. The present cohort size in each centre was inadequate for cumulative sum analysis with the endpoint

local recurrence, but an increased recurrence rate among the first ten patients was clearly shown. This could reflect difficulties with poor execution of the technique causing unwanted tumour spillage. These data also demonstrate that the structured training as set out in this programme was not capable of diminishing all adverse outcomes, and should therefore be made more extensive for centres implementing this technique in the future. Proctoring of more than ten procedures should be advised until proficiency is met according to independent competency assessment using video analysis (22).

Execution of the procedure rather than the technique itself may explain the observed recurrences. This is supported by the results of univariable analysis, which identified intraoperative events as the biggest risk factor. Two expert centres reported a 3-year local recurrence rate of 2.0 per cent (9). In the present study, long-term outcomes from four centres with experience of more than 45 TaTME procedures after training indicated that the first ten procedures (early experience) are more at risk of local recurrence than the following 30. The 4.0 per cent local recurrence rate achieved after exclusion of the first ten procedures at each centre is more in line with the results reported by Hol et al. for the two expert centres starting this technique in the Netherland (9). Longer follow-up is needed to confirm the present recurrence rates, which should be interpreted with caution owing to inclusion of more challenging cases (23).

The learning curve for implementation of new surgical techniques and its influence on long-term oncological outcome is an important issue. Data are scarce, but a study of laparoscopic TME surgery demonstrated a significantly higher recurrence rate among the first 100 procedures compared with the following 200 (10.5 *versus* 4.9 per cent respectively) (24). Robotic-assisted TME surgery is being implemented worldwide, but data on the learning curve have focused on duration of operation, involved CRM rates and/or complications, and not on long-term recurrence rates. A series by Polat et al., reporting the first 77 procedures, documented a recurrence rate of 9.5 per cent despite a relatively low positive margin rate. This relatively high local recurrence rate was probably related to suboptimal technical execution within the learning curve (25).

The full report of the National Norwegian audit of 157 TaTME procedures revealed 12 local recurrences (7.6 per cent) after a median follow-up of 19 months, with an estimated local recurrence rate of 11.6 per cent at 2.4 years according to Kaplan–Meier analysis (16). Wasmuth et al. stated that TaTME was responsible for the increased local recurrence rate, and that poor outcome could not be attributed to the learning curve effect because several of these recurrences occurred late in the series (16). However, four high-volume centres performed 152 procedures over 4 years, which breaks down to an average annual volume of 9.5 procedures. This raises the question of whether the learning curve had

been completed owing to the low exposure. A high rate of positive margins despite low tumour stage, the high rate of permanent stomas and perioperative morbidity may be indicative of suboptimal TaTME procedures. An unsupervised learning curve without proctoring, as shown by experienced single-port surgeons, takes over 40 procedures (10, 11).

The crucial difference in the TaTME technique is the endoluminal approach and potential direct contact with the tumour, whereas in the other abdominal techniques distal closure is assured by stapling below the tumour (26). Poor tumour handling and inadequate closure of the lumen by failing purse strings could lead to tumour cells spilling into the pelvic dissection area during the procedure causing (multifocal) recurrences. This could be a similar mechanism to that described in early reports of laparoscopy demonstrating port-site metastasis (27). Careful evaluation led to the acknowledgement of tumour cell aerosolization combined with a chimney effect at the trocar sites. After implementation of sufficient training and clinical trials, it has now been proven that laparoscopy is safe when executed proficiently.

The multifocal local recurrence shown in this series and reported by Larsen and co-workers seems to be a new pattern (15). In the Dutch TME trial (28), the multifocality of recurrences was not evident on review of the imaging of patients with local recurrence. Other data regarding the incidence of multifocal local recurrences are scarce; large trials have not reported multifocality as a separate entity. In the present study, seven of 12 patients with local recurrence developed distant metastasis, similar to rates found in the Dutch TME and COLOR II trials, in which 50–60 per cent of patients with local recurrence also had distant metastasis (21, 29). The question remains whether recurrence is related to the biology of the cancer rather than the surgical technique driving distant haematogenous spread of the disease (30).

The explanation for both the high rate of multifocal recurrences and the local recurrence rate of 10.0 per cent, despite a relatively low CRM positivity rate of 5.0 per cent in this implementation cohort, could be multifactorial. Theoretically, unsuccessful execution of a TaTME procedure might result in inadequate purse-string closure of the lumen. During the subsequent pelvic dissection, spilled tumour cells might be scattered as a result of the continuous high-flow insufflation used in the dissection area in TaTME, leading to multifocal local recurrence. A high rate of positive bacterial cultures during TaTME, as reported by Velthuis and colleagues (31), might provide support for this hypothesis. The authors have preliminary data showing that cancer cells can be cultured from rectal wash-out (J. Tuynman; unpublished observation). Although the exact aetiology remains to be proven, all COLOR III sites have been instructed to secure the purse-string closure

with a second over-running suture after the rectotomy with a secondary wash-out (32). Intraoperative perforation of the rectal tube in conventional TME might be regarded as a similar mechanism whereby tumour cells can seed in the pelvic cavity. In the present risk analysis, occurrence of intraoperative complications was the strongest predictor of multifocal local recurrence and second strongest for overall local recurrence. A previous study by Eriksen and colleagues (33) showed a tremendous negative impact of perforation on 5-year local recurrence, with the incidence rising from 9.9 per cent to 28.8 per cent in the presence of perforation ($P < 0.001$). The relatively high rate of pelvic sepsis (17.5 per cent) in the present learning curve cohort might also have contributed to the increased recurrence rate. A consistent hypothesis is that pelvic sepsis leads to an increased inflammatory reaction, and increased levels of growth factors associated with stimulation of adhesion and seeding of tumour cells (34-36).

A potential weakness of this cohort study is the possible inclusion of some patients with advanced-stage disease in the learning curve cohort. Overall, selection bias could be present within these data, but all patients who underwent TaTME for primary rectal cancer were included consecutively and the data were audited externally by an independent clinical researcher. Furthermore, case-matched analysis of TaTME and laparoscopic TME procedures, excluding CRM-positive and T4 tumours, demonstrated that TaTME during the learning curve was the only risk factor for local recurrence and not the pathology, showing that case selection was not an issue in the present cohort. Video analysis with surgical quality assessment could have revealed potential risk features for local recurrence. Quality assessment of every procedure is the central ingredient in the current COLOR III trial (22), in which all data including MRI and the entire video of each procedure are captured centrally.

As stated in the IDEAL framework, a new innovation or technique should be evaluated stepwise, and not be implemented broadly before standardized indications and procedures have been developed. In this way, adverse effects and consistent outcomes can be established during the learning curve, which new centres can set as a benchmark (37). The surgical community should focus on demonstrating oncological safety rather than surrogate endpoints for new innovative surgical techniques for patients with cancer. High-quality data accrual in a clinical (randomized) trial is key, including establishing a safety commission and frequent external data monitoring (38). The international TaTME guidance also states that TaTME should be implemented only in centres with a high volume of TME practice and with adequate training, including individual proctoring (2).

CONTRIBUTORS

Other proctors in the training pathway: H. B. A. C. Stockmann, R. C. L. M. Vuylsteke (Spaarne Hospital, Hoofddorp); P. G. Doornebosch (IJsselland Hospital, Cappelle aan den IJssel).

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CHAPTER 4

THE LEARNING CURVE OF TATME FOR RECTAL CANCER IS ASSOCIATED WITH LOCAL RECURRENCE: RESULTS FROM A MULTICENTRE EXTERNAL AUDIT

SE Van Oostendorp*, HJ Belgers*, **JC Hol**, PG Doornebosch, EJT Belt, SJ Oosterling, M Kusters, HJ Bonjer, C Sietses, JB Tuynman
* shared first authorship

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ABSTRACT

Aim: Transanal total mesorectal excision (TaTME) has been suggested as a potential solution for the resection of challenging mid and low rectal cancer. This relatively complex procedure has been implemented in many centres over the last years, despite the absence of long-term safety data. Recently, concern has arisen because of an increase in local recurrence in the implementation phase. The aim of this study was to assess the correlation between accumulated experience and local recurrences.

Method: An independent clinical researcher performed an external audit of consecutive series of all TaTME procedures in six centres in the Netherlands. Kaplan–Meier estimated local recurrence rates were calculated and multivariate Cox proportional hazards regression analysis performed to assess risk factors for local recurrence. Primary outcome was the local recurrence rate in the initial implementation (cases 1–10), continued adoption (cases 11-40) and prolonged experience (case 41 onward).

Results: Six hundred and twenty-four consecutive patients underwent TaTME for rectal cancer with a median follow-up of 27 months (range 1–82 months). The estimated 2- and 3-year local recurrence rates were 4.6% and 6.6%, respectively. Cox proportional hazards regression revealed procedural experience to be an independent factor in multivariate analysis next to advanced stage (ycMRF+, pT3-4, pN+) and pelvic sepsis. Corrected analysis projected the 3-year local recurrence rates to be 9.7%, 3.3% and 3.5% for the implementation, continued adoption and prolonged experience cohorts, respectively.

Conclusion: This multicentre study shows a high local recurrence rate (12.5%) after implementation of TaTME which lowers to an acceptable rate (3.4%) when experience increases. Therefore, intensified proctoring and further precautions must be implemented to reduce the unacceptably high risk of local recurrence at units starting this technique.

WHAT DOES THIS PAPER ADD TO THE LITERATURE?

This study describes the results from six centres in the Netherlands. The audit shows that despite efforts at structured training and proctoring, the implementation phase of transanal total mesorectal excision (TaTME) was associated with an increased risk of local recurrence which improved with accumulated experience. This emphasizes the need to refine structured training programmes and extend the duration of proctoring, the importance of case selection and above all the absolute need for robust audited data from prospective trials to determine the role of TaTME in the treatment of rectal cancer.

INTRODUCTION

The transanal approach for total mesorectal excision (TaTME) has been introduced to improve both clinical and long-term outcomes for patients with low and mid rectal cancer (1). Early adopters of the TaTME technique in high-volume centres claimed promising clinicopathological results in selected TaTME cohorts compared with matched or historic cohorts of laparoscopic TME (2, 3). These promising results provoked the interest of colorectal surgeons in using the TaTME technique for mid and distal rectal cancer. Nevertheless, the surgical community acknowledged that the technique is highly complex and requires training (4). Subsequently it was considered that widespread implementation might have been premature pending robust data on reproducible long-term outcomes (4, 5). In particular, high-quality evidence regarding long-term outcomes after TaTME is still missing.

In-depth analysis to quantify the learning curve by means of a cumulative sum (CUSUM) method has identified that an unsupervised 'autodidact' learning curve with the primary outcome of morbidity constitutes approximately 40 cases in centres with extensive experience in both single-port and minimally invasive surgery (6, 7). In another CUSUM-based analysis of anastomotic leakage risk a tipping point was identified at 50 cases (8). Interestingly, Persiani et al. found two cut-off points: an initial reduction in both operation time and major complications was seen after 54 cases, and a further decrease in major complications at 69 cases and operating time at 87 cases (9). In addition, specific intraoperative complications such as urethral injury in male patients and systemic carbon dioxide emboli have been collectively reported by early adopters and seem to relate to an unfamiliar bottom-up approach to the pelvic anatomy with risk of entering a wrong plane and different technical aspects, such as the continuous high-flow insufflation in a confined space (10, 11). This indicates that TaTME is a substantially different surgical concept rather than a modification of approach or instruments, and has created awareness of the potential hazards of widespread adoption. Therefore, multiple nations have initiated structured training pathways in order to safely implement the technique in new centres (12-16). These programmes consist of detailed study of the anatomy, observation of live surgery, cadaver training and, ideally, on-site proctoring. Proctorship by an experienced surgeon aims to prevent intraoperative mistakes and improve surgical technique, which ought to limit exposure of patients to hazardous and long learning curves for individual surgeons (4, 17).

Despite these unprecedented implementation measures, a concerning local recurrence rate of 10% in the first series of 10 patients in 12 Dutch centres occurred in a structured training programme (18). In addition, the Norwegian colorectal cancer group declared

a moratorium on TaTME following a nationwide audit which revealed an estimated local recurrence rate of 11.6% at 2.4 years (19). Interestingly, a majority of the local recurrences in both studies showed a multifocal pattern, which led to speculation about the potential presence of technical or executional issues (18, 19). In contrast to the aforementioned studies, multiple respectably sized cohorts of TaTME procedures with a median follow-up of approximately 2 years showed that good local recurrence rates, ranging from 2% to 6%, can be achieved in dedicated centres (8, 20-24).

The present audit study aimed to assess the local recurrence rate during the initial implementation, continued adoption and prolonged experience of TaTME in six hospitals in the Netherlands.

METHODS

The primary endpoint was local recurrence rate in relation to surgical experience and the secondary endpoint was anastomotic take down and end colostomy rate in restorative procedures in relation to surgical experience.

An external audit of the full electronic patient records of a prospectively tracked series of all consecutive TaTME procedures was performed in six high-volume hospitals (one started 2012, one in 2013, one in 2014, two in 2015 and one in 2016) including all the original imaging reports, operation notes and pathology reports. Preoperative work-up and follow-up were performed according to the national guidelines. In summary, this constitutes a full colonoscopy with biopsy of the lesion, MRI of the rectum, carcinoembryonic antigen (CEA) and imaging of the liver and thorax by CT scan or ultrasound and x-ray, respectively. Neoadjuvant long-course chemoradiotherapy was given in case of threatened margin to the mesorectal fascia (MRF) or cN2 disease. For frail patients, short-course radiotherapy with a long interval to surgery was considered as an alternative option. Short-course 5 × 5 Gy neoadjuvant radiotherapy has been given for those with clinical T3 disease with more than 5 mm extramural invasion and/or cN1 disease. Follow-up was according to the national guidelines, which recommend 6-monthly imaging of chest and liver and CEA during the first 2 years and thereafter yearly up to 5 years (25).

The cumulative local recurrence rate was estimated by the Kaplan–Meier method and inter-group difference was assessed by log-rank test. A separate subgroup analysis was performed for patients in whom initial or restage MRI after neoadjuvant therapy if applicable showed no threatened margin to the MRF. For comparative analysis of increasing institutional experience, case sequence numbers were categorized into

initial implementation (cases 1–10), continued adoption (cases 11–40) and prolonged experience (case 41 onward). Cut-off values were established in advance based on the first 10 to make a comparison with the previous report of the Dutch structured training pathway and the second cut-off at 40 based on previous evaluation of the learning curve (6, 18). To identify risk factors for local recurrence, the effects of covariates were analysed using a univariate Cox proportional hazards regression model. Covariates with an effect of $p < 0.10$ were subsequently entered into a multivariable Cox proportional hazards regression model in which a p-value of <0.05 was considered significant.

RESULTS

A total of 624 patients who underwent TaTME for rectal cancer entered this cohort with a median follow-up of 27 months (range 1–82 months). All consecutive cases of TaTME for primary rectal cancer since the start of this technique in each of the six centres were included; the date of surgery ranged from March 2012 to May 2020. The caseload among the six participating centres ranged between 47 and 227. The three cohorts defined as the initial implementation (cases 1–10), continued adoption (cases 11–40) and prolonged experience (case 41 onward) constituted 60, 180 and 384 patients, respectively.

Baseline

The majority of included patients were men (73.7%) and 19.4% of the study population was classified as obese [body mass index (BMI) ≥30 kg/m2]. Almost half of all tumours (46.3%) were located below or within 3 cm of the anorectal junction (ARJ). Clinical tumour staging showed cT4 in 6.0% and cT3 in 66.8%. The MRF was threatened in a quarter of the cohort (n = 154, 24.7%) of which less than half (n = 68, 10.9%) showed a persistent threatened margin to the MRF upon restaging after neoadjuvant treatment. Synchronous distant metastases were present in 47 patients (7.5%); these were mostly hepatic followed by a pulmonary location (Table 1).

Operative details

A low anterior TME resection was performed in 539 patients (86.4%) in this cohort. In these a primary anastomosis was constructed without diversion in 103 (16.5%), anastomosis with a diverting ileostomy in 337 (54.0%) and nonrestorative end-colostomy (Hartmann) in 99 patients (15.9%). An intersphincteric resection with creation of an end-colostomy was performed in 80 patients (12.5%) and a TaTME resection as part of a proctocolectomy was done in five patients. Intraoperative complications are listed in Table 2 and comprised 1 urethral injury, 5 carbon dioxide emboli, 11 cases of pelvic bleeding, 14 documented purse-string failures and 21 intraoperative rectal perforations.

Table 1 Patient characteristics (*N* = 624)

Characteristic		*n* or value
Sex, *n* (%)	Male	440 (70.5%)
	Female	184 (29.5%)
BMI (kg/m^2), mean ± SD		26.7 ± 4.2
Age (years), mean ± SD		66.0 ± 10.9
ASA classification, *n* (%)	I	106 (17.0%)
	II	401 (64.3%)
	III	116 (18.6%)
	IV	1 (0.2%)
Height from ARJ (cm), mean ± SD		3.7 ± 2.7
Clinical tumour stage (cT), *n* (%)	cTis/TVA hgr	3 (0.5%)
	cT1	21 (3.4%)
	cT2	145 (23.3%)
	cT3	415 (66.8%)
	cT4	37 (6.0%)
	Missing	3 (–)
Clinical nodal stage (cN), *n* (%)	N0	297 (48.1%)
	N1	186 (30.1%)
	N2	135 (21.8%)
	Missing	6 (–)
Synchronous metastasis (cM), *n* (%)	No	577 (92.5%)
	Yes	47 (7.5%)
MRF threatened, *n* (%)	Pre-neoadjuvant (c-) RT	154 (24.7%)
	Persistent upon restaging	68 (10.9%)
Preoperative therapy, *n* (%)	None	220 (35.3%)
	5 × 5 short interval	137 (22.0%)
	5 × 5 long interval	76 (12.2%)
	Chemoradiotherapy	190 (30.4)
	Systemic chemotherapy	1 (0.2%)

Abbreviations: ARJ, anorectal junction; ASA, American Society of Anesthesiologists; BMI, body mass index; CRT, chemoradiotherapy; MRF, mesorectal fascia; RT, radiotherapy; SD, standard deviation; TVA hgr, tubulovillous adenoma with high-grade dysplasia.

Postoperative morbidity

The overall postoperative morbidity rate was 53.7%; this was further classified according to Clavien–Dindo grades as shown in Table 3. Short-term anastomotic leakage and/or pelvic abscess occurred in approximately one out of five of both restorative and non-restorative procedures. Anastomotic takedown and creation of an end-colostomy due to septic complications occurred in 42 out of 443 (9.5%) restorative procedures. The anastomotic takedown rate following septic anastomotic complications decreased from 13.5% in the first 25 restorative TaTME procedures to 11.5% in the second and 7.6% in the third 25, and to 2.2% in procedures 76–100 (p = 0.023).

Table 2 Operation details (*N* = 624)

		***n* (%)**
Procedure	LAR	103 (16.5%
	LAR – ileostomy	337 (54.0%)
	LAR – colostomy	99 (15.9%)
	ISR – colostomy	80 (12.8%)
	Proctocolectomy	5 (0.8%)
Anastomosis	Not performed	180 (29.0%)
	Stapled	378 (60.9%)
	Hand-sewn	63 (10.1%)
	Missing	3 (–)
Conversion	No conversion	595 (95.4%)
	Laparotomy	15 (2.4%)
	Pfannenstiel	5 (0.8%)
	Laparoscopy	7 (1.1%)
	Open APR	1 (0.2%)
Extraction site	Transanal	204 (34.8%)
	Pfannenstiel	271 (46.2%)
	(Contralateral) McBurney	33 (5.6%)
	Umbilical trocar site	15 (2.6%)
	Laparotomy	13 (2.2%)
	Stoma site	42 (7.2%)
	Missing	38 (–)
Intraoperative complications	Urethral injury	1 (0.2%)
	CO_2 embolus	5 (0.8%)
	Pelvic bleeding	11 (1.8%)
	Visceral injury	7 (1.1%)
	Purse-string failure	14 (2.2%)
	Rectal perforation	21 (3.4%)
	Anastomotic problem	62 (10.0%)
	Technical problem transanal phase	3 (0.5%)

Abbreviations: APR, abdominoperineal resection; ISR, intersphincteric resection; LAR, low anterior resection.

Pathology

An involved circumferential margin was observed in 20 cases (3.2%) and a positive distal margin in 4 (0.6%). Major defects of the specimen were reported in 19 cases (3.1%; Table Table 4).

Primary outcome: local recurrence

Thirty patients developed a local recurrence (4.8%) after a median interval of 17 months (range 5–61 months) from index surgery. The predominant location was presacral (n = 16; 53%) while a multifocal pattern was observed in six local recurrences (20%; Table 5) Kaplan–Meier survival analysis showed an estimated local recurrence rate in the

Table 3 Morbidity (*N* = 624)

		***n* (%)**
Postoperative complications (30 day)	None – CD 0	289 (46.3)
	CD I	57 (9.1%)
	CD II	120 (19.2%)
	CD IIIa	24 (3.8%)
	CD IIIb	93 (14.9%)
	CD IV	36 (5.8%)
	CD V	5 (0.8%)
Major surgical morbidity (30 day)	CD ≥III	149 (23.9%)
Short-term leakage or abscess (30 day)	Anastomosis (*N* = 443)	89 (20.1%)
	Non-restorative (*N* = 181)	31 (17.1%)
Overall pelvic sepsis[a]		140 (22.4%)
Anastomotic takedown[b] (*N* = 443)		42 (9.5%)

Abbreviation: CD, Clavien–Dindo.
[a] Includes early and late complications (leakages, abscess and/or sinus).
[b] Unintended take down of anastomosis and creation of end colostomy due to septic complications.

Table 4 Pathology (*N* = 624)

		***n* (%)**
Pathological T-stage	(y)pT0	63 (10.1%)
	(y)pT1	66 (10.6%)
	(y)pT2	248 (39.8%)
	(y)pT3	242 (38.8%)
	(y)pT4	4 (0.6%)
	Missing	1 (–)
Quality of specimen (Quirke)	No defects	539 (87.2%)
	Minor defects	60 (9.7%)
	Major defects	19 (3.1%)
	Not reported	6 (–)
CRM involvement (≤1 mm)a		20 (3.2%)
DRM involvement (≤1 mm)		4 (0.6%)
Nodal stage	pN0	446 (71.5%)
	pN1	138 (22.1%)
	pN2	40 (6.4%)
Nodes harvested (mean ± SD)[b]		16.9 ± 7.6

Abbreviations: CRM, circumferential resection margin; DRM, distal resection margin; SD, standard deviation.
[a] One missing.
[b] Excluding five proctocolectomies.

Table 5 Follow-up (*N* = 624)

Follow-up (months)	Mean ± SD)	29.0 ± 18.3
	Median (range)	26.8 (1–82)
Local recurrence, *n* (%)	Overall	30 (4.8%)
Interval to local recurrence (months)	Median (range)	17 (5–61)
Location of local recurrence[a], *n* (%)	Presacral	16 (53.3%)
	Anterior	1 (3.3%)
	Lateral	2 (6.7%)
	Anastomosis	3 (10.0%)
	Rectal stump	2 (6.7%)
	Multifocal	6 (20.0%)

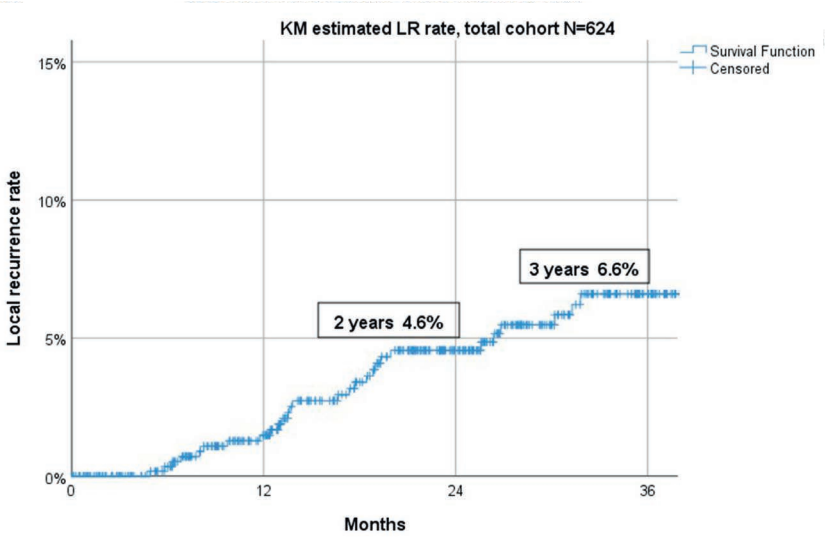
Abbreviations: SD, standard deviation.
[a] Denominator is total local recurrence (*N* = 30).

total study population of 4.6% at 2 years and 6.6% at 3 years (Figure1A). Comparative analyses of the three predefined cohorts showed a 3-year local recurrence rate of 14.0% in the initial implementation, 5.3% during continued adoption and 5.9% with prolonged experience (p = 0.036) (Figure 2A). Exclusion of patients with a persistent threatened margin after neoadjuvant therapy showed a Kaplan–Meier estimated local recurrence rate of 3.7% at 2 years and 5.6% at 3 years (see Figures 1B and 2B).

Cox proportional hazard regression analysis to identify predictive risk factors for local recurrence revealed experience to be a consistent independent predicting factor in uni- and multivariate analysis next to a persistent threatened margin to the MRF following neoadjuvant therapy, advanced stage pT3-4, presence of pathological lymph nodes and pelvic sepsis. (Table 6). Adjusted Cox regression analysis to correct for case mix projected the 3-year local recurrence rate to be 9.6%, 2.9% and 3.1% for the three cohorts, respectively. Both the continued adoption phase [hazard ratio (HR) 0.290, 95% CI 0.108–0.780, p = 0.014] and prolonged experience (HR 0.318, 95% CI 0.127–0.795, p = 0.014) had a significant lower hazard of developing a local recurrence compared with the initial implementation cohort (Figure 3, Table 6).

Pelvic sepsis and an unintended intraoperative connection between the rectal lumen and pelvic cavity (purse-string failure, rectal perforation or anastomotic defect) were additionally assessed as potential risk factors. Twelve local recurrences occurred in patients with pelvic sepsis (12 out of 140, 8.6%) versus 18 in patients without pelvic sepsis (18 out of 484, 3.7%). Five local recurrences occurred after an unintended open connection (5 out of 86, 5.8%) versus 25 local recurrences without a connection (25 out of 535, 4.7%). In uni- and multivariate Cox regression, pelvic sepsis was related to an increased risk of local recurrence (HR 2.530, 95% CI 1.159–5.472, p = 0.018) while an open connection did not show a significantly increased risk for the development of local recurrence.

A



Time	Start	12 months	24 months	36 months
No at risk	624	492	347	200
Cumulative LR	0	8	22	28
LR rate	0%	1.5%	4.6%	6.6%

B

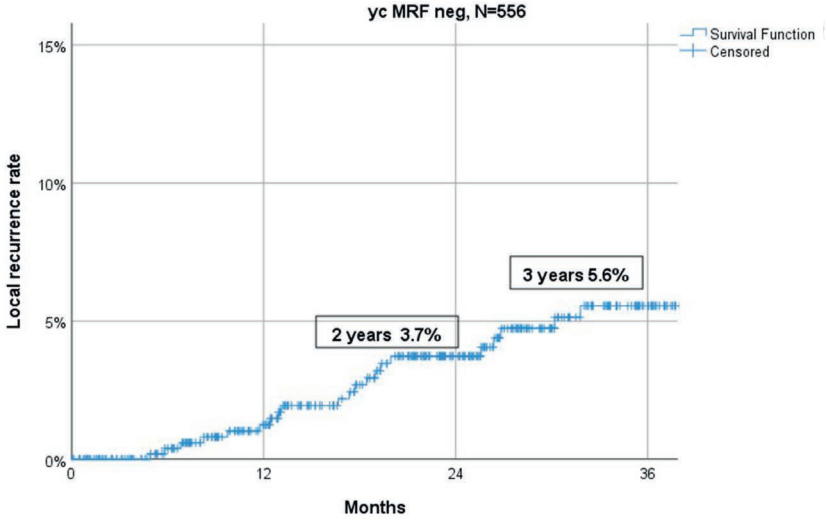
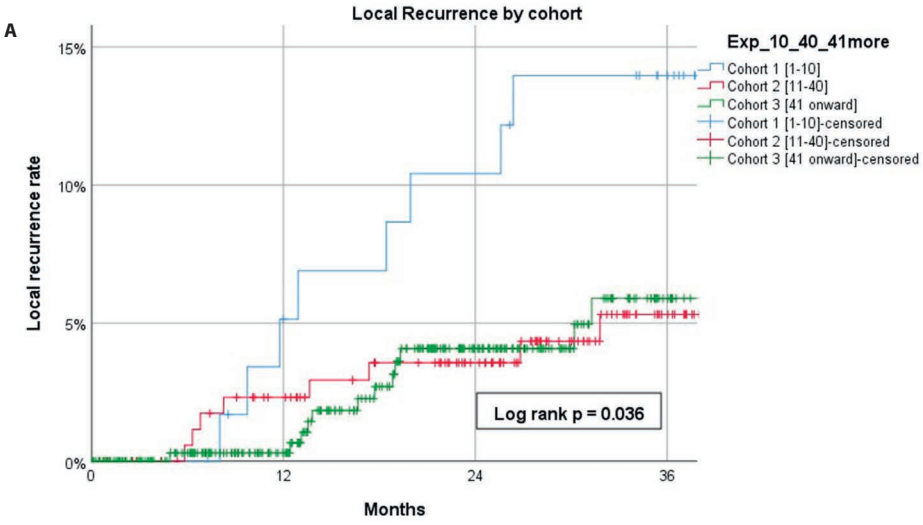


Figure 1 (A) Kaplan–Meier (KM) estimated local recurrence (LR) rate, total cohort (n = 624), (B) Kaplan–Meier (KM) estimated local recurrence (LR) rate, subgroup of non-threatened margin to the mesorectal fascia (n=556)



Cohort (no at risk, LR rate)	Start	12 months	24 months	36 months
1	60	54	51	43
	0%	5.1%	10.4%	14.0%
2	180	163	138	80
	0%	2.3%	3.5%	5.3%
3	384	275	157	76
	0%	0.3%	4.1%	5.9%

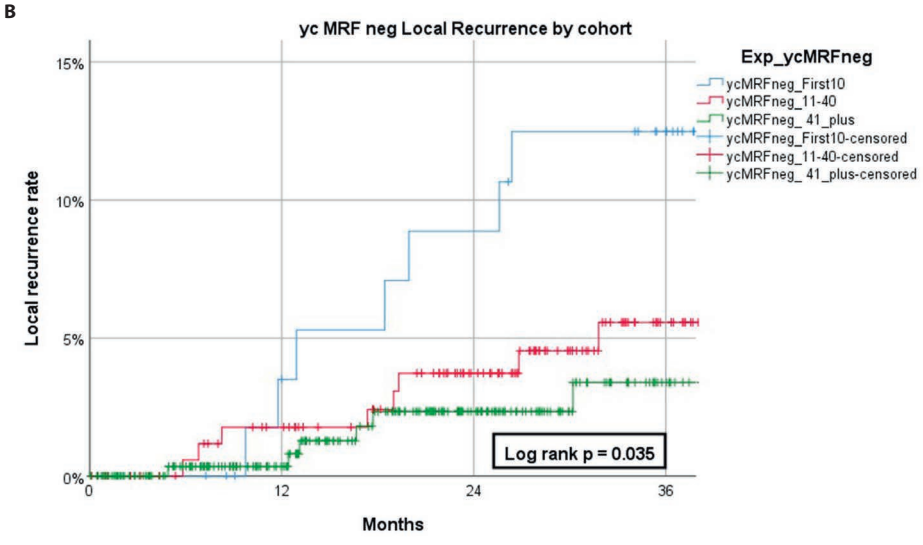
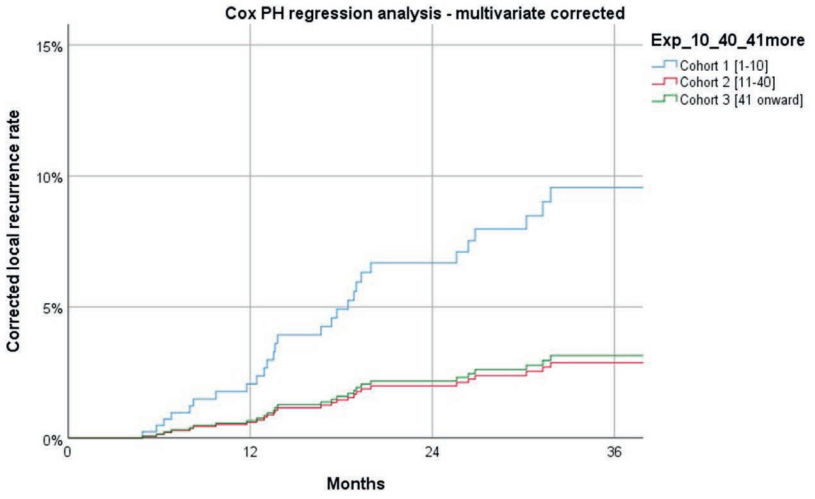


Figure 2 (A) Local recurrence rate by experience of total cohort (N = 624) (cohort 1 cases 1–10, cohort 2 cases 11–40, cohort 3 case 41 onwards). (B) Local recurrence rate by experience, subgroup of non-threatened margin to the mesorectal fascia (n = 566). Cohorts as in (A). Log rank test for comparative analysis



Cohort (no at risk, LR rate)	Start	12 months	24 months	36 months
1	60	54	51	43
	0%	2.1%	6.7%	9.6%
2	180	163	138	80
	0%	0.6%	2.0%	2.9%
3	384	275	157	76
	0%	0.6%	2.1%	3.1%

Figure 3 Corrected Cox proportional hazards (PH)multivariate regression analysis. Corrected for variables significant ($p < 0.05$) in multivariate analysis (Table 6)

DISCUSSION

This external audit of a prospective multicentre consecutive cohort of TaTME procedures (N = 624) shows that the incidence of local recurrence following TaTME for rectal cancer is associated in multivariate analysis with surgical experience in addition to advanced pT- and pN-stage and pelvic sepsis. A relatively high rate of LR in the initial implementation phase was observed which diminished to a low percentage during further implementation in the six centres. These results show that the learning curve is partially responsible for the increased risk of local recurrences for the TaTME procedure. For cases without a threatened margin, the local recurrence rate for the first 10 procedures was 13% but below 5% for the following series (Figure 2B). This learning curve effect was also visualized for conversion (10%, 6% and 3% for the three groups, respectively) and for anastomotic takedown due to septic complications (Supplementary Material). Centres currently planning or starting with TaTME should be cautious, and adequate training, patient selection and case volume seem very relevant for obtaining safe results.

Table 6 Cox proportional hazards regression analysis

			UNIVARIATE			MULTIVARIATE		
		Event / Total	HR	95% c.i.	P value	HR	95% c.i.	P value
Experience	Case 1 - 10	9 / 60	*1.0 (ref)*	.		*1.0 (ref)*		
	Case 11 - 40	8 / 180	0.339	0.130 - 0.881	0.026	0.290	0.108 - 0.780	0.014
	Case 41- onward	13 / 384	0.394	0.165 - 0.939	0.035	0.318	0.127 - 0.795	0.014
Sex	female	9 / 184	*1.0 (ref)*	.		NA	.	
	male	21 / 440	0.978	0.448 - 2.136	0.955	NA	.	
BMI	< 30	24 / 503	*1.0 (ref)*	.		NA	.	
	≥ 30	6 / 121	0.976	0.399 - 2.389	0.958	NA	.	
Height	>3 cm from ARJ	12 / 335	*1.0 (ref)*	.		NA	.	
	≤3 cm from ARJ	18 /289	1.802	0.868 - 3.742	0.114	NA	.	
Previous local excission	no	29 / 569	*1.0 (ref)*	.		NA	.	
	yes	1 / 55	0.397	0.054 - 2.914	0.363	NA	.	
Clinical M1	no	27 / 577	*1.0 (ref)*	.		NA	.	
	yes	3 / 47	2.151	0.649 - 7.126	0.210	NA	.	
Chemoradiotherapy	no	15 / 434	*1.0 (ref)*	.		*1.0 (ref)*	.	
	yes	15 / 190	2.471	1.205 - 5.066	0.014	1.894	0.854 - 4.201	0.116
Post CRT MRF+	no	23 / 556	*1.0 (ref)*	.		*1.0 (ref)*	.	
	yes	7 / 68	2.990	1.274 - 7.017	0.023	2.774	1.055 - 7.299	0.039
(y)pT-stage	0-2	8 / 378	*1.0 (ref)*	.		*1.0 (ref)*	.	
	3-4	22 /246	4.668	2.077 - 10.490	< 0.001	2.562	1.077 - 6.092	0.033
CRM involved (<1mm)	no	27 / 603	*1.0 (ref)*	.		*1.0 (ref)*	.	
	yes	3 / 20	5.073	1.529 - 16.828	0.008	2.020	0.561 - 7.276	0.282

Table 6 Cox proportional hazards regression analysis (continued)

		UNIVARIATE				MULTIVARIATE		
		Event / Total	HR	95% c.i.	P value	HR	95% c.i.	P value
DRM involved	no	30 / 617	*1.0 (ref)*	.		NA	.	
	yes	0 / 4	0.049	0.000 - 2.7 e^7	0.740	NA	.	
pN stage	negative	12 / 447	*1.0 (ref)*			*1.0 (ref)*	.	
	positive	18 / 177	4.213	2.027 - 8.756	< 0.001	3.127	1.447 - 6.759	0.004
IO-defect	no	25 / 532	*1.0 (ref)*			NA	.	
	yes	5 / 89	1.595	0.607 - 4.188	0.344	NA		
Pelvic Sepsis	no	18 / 488	*1.0 (ref)*			*1.0 (ref)*	.	
	yes	12 / 140	2.147	1.033 - 4.464	0.041	2.530	1.169 - 5.472	0.018

Abbreviations: HR= Hazards ratio, *BMI* = Body Mass Index (kg/m^2), *cm* = centimeters, *ARJ* = anorectal junction, Clinical M1 = synchronous distant metastasis, *CRT* = chemoradiotherapy, MRF = mesorectal fascia, CRM = circumferential resection margin, DRM = distal resection margin, IO – defect = composite of either intra-operative rectal perforation, purse string failure or defects of the anastomosis, pelvic sepsis = composite of short and long-term anastomotic leakage, pelvic abscess or presacral sinus

After the declared moratorium on TaTME in Norway various renowned centres for minimally invasive rectal cancer surgery have published (multi-)institutional cohort studies with a 2%–6% crude local recurrence (8, 20-24). In response to the audit of the Dutch structured training pathway revealing a crude 10% local recurrence rate in the first 10 consecutive patients, Warrier et al. reported a 2% local recurrence rate among 300 patients at a minimum of 2 years follow-up within the Australasian structured training pathway for TaTME (26). In-depth analysis of the organization of the Australasian and UK implementation pathway might show particular differences in entry criteria, training, case selection, technique and competency sign-off which could offer insights into the diverging oncological results (13, 15, 26). The structured training pathway in the Netherlands is currently on hold and will need further refinement and more strict governance upon its restart (12). In addition to annual volume requirements and an extended duration of proctoring, continued quality assurance by video assessment and repeated external audit of clinical outcomes might be beneficial (27, 28).

The introduction of TaTME (implementation) has been transparently studied and evaluated by a global collaborative, with unprecedented public sharing (i.e. data and videos at conferences) of early unfavourable outcomes in order to improve the technique. Moreover, extensive training and other precautions, which have tried to adhere to the IDEAL framework, have nevertheless failed to prevent the current setback and scepticism about the oncological safety of the technique (29). The current detailed findings of TaTME-associated local recurrences in the start of the learning curve should be compared with laparoscopic and robotic-assisted TME resection, of which the long-term data on local recurrence during the implementation phase are not well registered.

The expected benefits in especially difficult low rectal cancer cases have tempted participating centres to select challenging cases even early in the learning curve. From the implementation cohort (the first 10 cases in each centre), 15 out of 60 (25%) patients would not have met the eligibility criteria (cT4 or cT3 ≤2 mm to the MRF, previous local excision or synchronous metastasis) of the current benchmark for laparoscopic TME surgery, namely the COLOR 2 trial (Supplementary Material).(30) Unfortunately, in the early phase of TaTME patients with low tumours, a narrow pelvis and threatened margins were offered this novel technique, which would currently be highly disputed since the learning curve should not incorporate such difficult cases (31). Moreover, included cases were often more advanced in terms of difficulty compared with selected cohorts as seen in the ALaCaRT, ACOSOG Z6051 and COLOR II trials since the participating centres have become referral centres for patients in pursuit of a restorative or sphincter-saving procedure (30, 32, 33). Nevertheless, patients should be fully informed and consent to undergo any surgical procedure, and especially a new surgical technique including potential

unknown hazards and uncertain long-term outcomes (34). The potential negative effects are mostly present in difficult cases: a small pelvis, high BMI, anterior or low situated tumours. For mid rectal cancer, an immediate bailout when encountering any difficulties can be made by converting to the standard technique, laparoscopic abdominal TME, and it is recommended to do this with a low threshold.

For optimal assessment of the local recurrence rate, adequate follow-up for a minimum of 3 years for an entire cohort is desirable; this is not yet available. Given the current debate on the safety of TaTME with respect to (multifocal) local recurrence postponing the publication of our current results was considered unethical. Multiple groups have assessed the learning curve by CUSUM analysis to be around 40–50 procedures (6-9, 35). Therefore, the chosen cut-off of 40 cases, next to the first cut-off at 10 procedures to serve as reference from the previous audit of 12 centres was considered appropriate. A learning curve is generally measured by CUSUM analysis rather than a case ranking method including an arbitrary cut-off to define subgroups as performed in this study. However, such analysis requires an extensive cohort, ideally of a single surgeon. Another limitation is that the current study did not assess the volume effect, i.e. cases per time unit, on (long-term) outcome since we focused on institutional rather than individual surgeon experience.

When introducing new techniques, a thorough and well-designed scientific evaluation according to the IDEAL framework is essential to guarantee patient safety (34). Equipoise towards an intervention should be based on reliable data which the surgical community should prove using registries and clinical trials with a high standard of data quality. Clinical trials with quality assurance are ongoing but it must be acknowledged that the adoption of TaTME without proper audit might have gone too fast (36).

CONCLUSION

TaTME is a complex procedure with a learning curve that not only affects short-term morbidity but is also associated with an increased risk of local recurrence; however, this improves both in terms of lower morbidity and local recurrence rates with greater experience.

COLLABORATORS

EJ Boerma, MN Sosef, D Creemers, EJ De Graaf, EP van der Stok, JAB van der Hoeven, HBAC Stockmann, RCLM Vuylsteke

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SUPPLEMENTARY MATERIAL

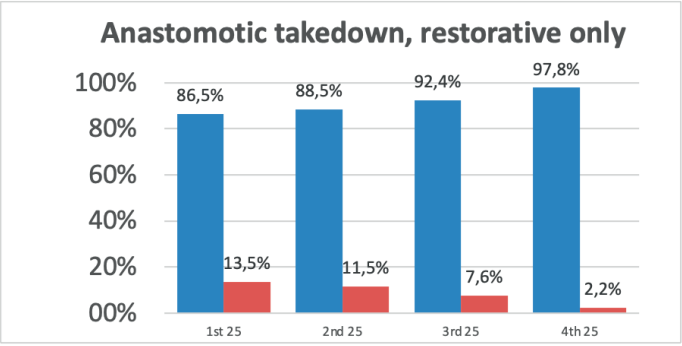

Figure S1 Effect of experience on anastomotic takedown rate

Table S1 Effect of experience on anastomotic takedown rate

P = 0.023	1st 25	2nd 25	3rd 25	4th 25
Anastomosis preserved	128	100	73	45
	86,5%	88,5%	92,4%	97,8%
Takedown & end-colostomy	20	13	6	1
	13,5%	11,5%	7,6%	2,2%

Table S2 Groups baseline and outcome

		Total cohort	**Case #1-10**	**Case #11-40**	**Case #41**	**P value**	**Statistical Test**
		N = 624	**n=60**	**n= 180**	**N = 384**		
Median FU in months		**26.8**	**47.3**	**33.8**	**21.3**		
Sex	Female	184 (29.5)	10 (16.7)	64 (35.6)	110 (28.6)	**0.018**	**Chi square**
	Male	440 (70.5)	50 (83.3)	116 (64.4)	274 (71.4)		
BMI	< 30	503 (80.6)	48 (80.0)	137 (76.1)	318 (82.8)	0.172	Chi square
	≥ 30	121 (19.4)	12 (20.0)	43 (23.9)	66 (17.2)		
Height	>3 cm from ARJ	335 (53.7)	29 (48.3)	80 (44.4)	226 (58.9)	**0.004**	**Chi square**
	≤3 cm from ARJ	289 (46.3)	31 (51.7)	100 (55.6)	158 (41.1)		
Clinical Tumor stage (cT)	cT0 - Tis	3 (0.5)	0 (0)	0 (0)	3 (0.8)	0.405	Fishers exact
	cT1	21 (3.4)	2 (3.3)	6 (3.4)	13 (3.4)		
	cT2	145 (23.3)	11 (18.3)	51 (28.8)	83 (21.6)		
	cT3	415 (66.8)	45 (75.0)	113 (63.8)	257 (66.9)		
	cT4	37 (6.0)	2 (3.3)	7 (4.0)	28 (7.3)		

Table S2 Groups baseline and outcome (continued)

		Total cohort	Case #1-10	Case #11-40	Case #41	P value	Statistical Test
		N = 624	n=60	n= 180	N = 384		
Clinical Nodal stage (cN)	*N0*	297 (48.1)	29 (48.3)	83 (46.9)	185 (48.6)	0.986	Chi square
	N1	186 (30.1)	17 (28.3)	56 (31.6)	113 (29.7)		
	N2	135 (21.8)	14 (23.3)	38 (21.5)	83 (21.8)		
Clinical M stage	No	577 (92.5)	57 (95.0)	172 (95.6)	348 (90.6)	0.100	Fishers exact
	Yes	47 (7.5)	3 (5.0)	8 (4.4)	36 (9.4)		
Initial MRI MRF+	no	470 (75.3)	51 (85.0)	145 (80.6)	274 (71.4)	**0.011**	**Chi square**
	yes	154 (24.7)	9 (15.0)	35 (19.4)	110 (28.6)		
Persisting MRF+ after (Chemo)RTX	no	556 (89.1)	58 (96.7)	164 (91.1)	334 (87.0)	**0.043**	**Fishers exact**
	yes	68 (10.9)	2 (3.3)	16 (8.9)	50 (13.0)		
Chemoradiotherapy	no	434 (69.6)	42 (70.0)	120 (66.7)	272 (70.8)	0.604	Chi square
	yes	190 (30.4)	18 (30.0)	60 (33.3)	112 (29.2)		
Restorative procedure	No	181 (29.0)	14 (23.3)	61 (33.9)	106 (27.6)	0.185	Chi square
	Yes	443 (71.0)	46 (76.7)	119 (66.1)	278 (72.4)		
Conversion	No	593 (95.5)	54 (90.0)	169 (93.9)	370 (97.1)	**0.022**	**Fishers exact**
	Yes	28 (4.5)	6 (10.0)	11 (6.1)	11 (2.9)		
(y)pT-stage	0-2	378 (60.6)	32 (53.3)	120 (77.7)	226 (58.9)	0.102	Chi square
	3-4	236 (39.4)	28 (46.7)	60 (33.3)	158 (41.1)		
(y)pN-stage	negative	447 (71.6)	42 (70.)	130 (72.2)	275 (71.6)	0.954	Chi square
	positive	177 (28.4)	18 (30.0)	50 (27.8)	109 (28.4)		
CRM involved	no	603 (96.8)	58 (96.7)	174 (96.7)	371 (96.9)	0.999	Fishers exact
	yes	20 (3.2)	2 (3.3)	6 (3.3)	12 (3.1)		
Quality - major defects	no	599 (96.9)	56 (100)	170 (94.4)	373 (97.6)	0.067	Fishers exact
	yes	19 (3.1)	0 (0)	10 (5.6)	9 (2.4)		
Postoperative moribidty	No	301 (48.3)	31 (51.7)	89 (49.4)	181 (47.3)	0.761	Chi square
	Yes	322 (51.7)	29 (48.3)	91 (50.6)	202 (52.7)		
Major Surgical morbidity	No	475 (76.1)	44 (73.3)	134 (74.4)	297 (77.3)	0.652	Chi square
	Yes	149 (23.9)	16 (26.7)	46 (25.6)	87 (22.7)		
Pelvic Sepsis	No	484 (77.6)	44 (73.3)	135 (75.0)	305 (79.4)	0.366	Chi square
	yes	140 (22.4)	16 (26.7)	45 (25.0)	79 (20.6)		
Anastomotic failure	no	401 (90.5)	39 (84.8)	102 (85.7)	260 (93.5)	0.020	Chi square
	yes	42 (9.5)	7 (15.2)	17 (14.3)	18 (6.5)		

CHAPTER 5

IMPLEMENTATION OF ROBOT-ASSISTED TOTAL MESORECTAL EXCISION BY MULTIPLE SURGEONS IN A LARGE TEACHING HOSPITAL: MORBIDITY, LONG-TERM ONCOLOGICAL AND FUNCTIONAL OUTCOME

JC Hol, K Dogan, CFJM Blanken-Peeters, RRJP van Eekeren, MAJ de Roos, C Sietses, EJ Spillenaar Bilgen, BPL Witteman

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ABSTRACT

***Background*:** Robot-assisted total mesorectal excision (TME) might offer benefits in less morbidity, better functional and long-term outcome over laparoscopic TME.

***Methods*:** All consecutive patients undergoing robot-assisted TME for rectal cancer during implementation between May 2015 and December 2019 performed by five surgeons in a single centre were included. Outcomes included local recurrence rate at 3 years, conversion rate, circumferential resection margin (CRM) positivity rate, 30-day postoperative morbidity and outcomes of low anterior resection syndrome (LARS) questionnaires.

***Results*:** In 105 robot-assisted TME, local recurrence rate at 3 years was 7.4%, conversion to open surgery rate was 8.6%, CRM positivity rate was 5.7%, 73.3% had good quality specimen, postoperative morbidity rate was 47.6% and anastomotic leakage rate was 9.0%. Incidence of major LARS was 55.3%.

***Conclusions*:** results of this study described acceptable morbidity, functional and long-term outcome during implementation of robotic TME for rectal cancer by multiple surgeons in a single centre.

1 INTRODUCTION

Total mesorectal excision (TME) surgery is the golden standard these days for rectal cancer surgery. The past decade, there has been a shift from traditional open surgery to laparoscopic TME surgery (1). However, laparoscopic TME is challenging due to the narrow and confined area of the pelvis. It is not proven superior to open surgery in terms of oncological outcome (1).

Working in a small confined space where nerves could risk adverted damage, injury to the autonomic nerves along the pelvic side-wall, and in close proximity to the prostate in male, may readily occur in pelvic dissection, leading to sexual and urinary dysfunction (2). Another major source of comorbidity is the high prevalence of Low Anterior Resection Syndrome (LARS) (3). This is a major source of comorbidity following TME surgery and has a significant impact on quality of life (3). Other risk factors for LARS are: distal anastomosis, type of anastomosis and preoperative radiotherapy (3, 4).

Robot-assisted TME was developed complementary to laparoscopic TME. It has three dimensional enlarged vision, instruments with seven degrees of freedom of motion that truly mimic the movements made by a surgeon's hand, lack of tremor and superior ergonomics. The robotic system could therefore help overcome limitations of laparoscopy in the narrow pelvis and could result in a benefit to the patient by means of improved oncologic and functional outcomes. Potential benefits of robot-assisted TME are faster recovery, faster return of sexual function and more restored sexual function in general [5]. However, these potential benefits were not seen in a large randomized controlled trial [6].

Previous reports show a relatively short learning curve for robot-assisted rectal cancer surgery of around 20 cases for surgeons with previous laparoscopic experience. However, these reports mostly consists of large series by single surgeons with extensive experience in laparoscopic surgery and focus on intra-operative vectors such as duration of surgery, blood loss, conversion rates and intra- or postoperative complications and pathological outcomes, since these are immediately available following the procedure (5-8).

The evaluation of safety of the learning curve should be confirmed by long-term oncological results rather than short-term surrogate outcomes. Short-term clinic-pathological parameters such as (intra-operative) complications, operating time, circumferential margin and quality of the specimen are widely used because they are readily available (9, 10). However, in order to help policy makers develop well-informed decisions on the use of a new technique, long-term safety must be proven by data on (loco regional)

recurrences of the technique. Furthermore, robot-assisted has the potential to be more nerve-sparing by more meticulous dissection and therefore may result in less erectile dysfunction, LARS or urological complaints. These functional outcomes should be evaluated during implementation as well.

The present study aimed to assess the long-term oncological and functional outcome during implementation of robot-assisted TME surgery for rectal cancer defined by sigmoidal take-off in a large Dutch teaching hospital by multiple surgeons.

2 MATERIALS AND METHODS

2.1 Patients

All consecutive patients who underwent robot-assisted TME for histologically proven rectal cancer between May 2015 and December 2019 in a single centre (Rijnstate Hospital, Arnhem, The Netherlands) were included. Rijnstate Hospital is a large teaching hospital, with 5 dedicated rectal surgeons performing a total of over 50 TME procedures each year. Rectal cancer was defined according to the sigmoidal take-off based on pretreatment MRI (11). Patients undergoing laparoscopic approach (N=83) without use of the robot in the study period were excluded. The number of robotic cases increased and in 2019 no cases were performed laparoscopically.

All patients had preoperative MRI and were presented in a multidisciplinary meeting, to discuss the treatment according to the Dutch National Guidelines for Colorectal Cancer (12). All patients have had follow-up carried out according to the Dutch National Guidelines for Colorectal Cancer for a period of 5 years. Clinical data were obtained in August 2020 from patient electronic medical records. Functional outcome assessments were obtained by questionnaires in patients with a follow up of at least 1 year after their primary operation or stoma reversal in case of deviating ileostomy in April 2020. Patients with end colostomy were excluded from functional outcome assessment.

2.2 Procedures

Operations were performed by five surgeons trained for robotic surgery. Each surgeon had gained sufficient proficiency in laparoscopic TME surgery prior to start of robot-assisted TME. Robot-assisted surgery was performed using the daVinci Xi system with a single console (Intuitive Surgical). Each surgeon completed the online modules for the robotic Xi system. This included an online assessment and a 2-h course on the robotic Xi system, followed by simulation training and case observations. After completing the Intuitive program, all robotic resections were performed by two surgeons together. Each

surgeon enrolled the structured training programme for teaching and training, including on-site proctoring by other Dutch surgeons from a national proctoring program. During this implementation period, all five surgeons performed other robotic colorectal surgery as well (e.g. left-sided colectomies and sigmoid resections).

Procedures were performed according to standardized principles, using a single-docking totally robotic approach. Medial to lateral approach or lateral to medial approach was used, and splenic flexure was done in accordance with the preference of individual surgeons and/or length of the sigmoid to create a tension-free anastomosis. Port placement was as following for the daVinci Xi: a 12mm laparoscopic assistance port at the right flank, three 8mm ports along a diagonal line from subxiphoidal to the right iliac region, and a 12mm trocar at the right iliac region. Depending on the height of the tumor and preoperative anorectal function, either TME resection with primary anastomosis (LAR) was performed or intersphincteric TME resection with definitive end colostomy (ISR) was performed. Abdominoperineal resections were not performed in this centre. In case of LAR after neoadjuvant chemoradiation or low tumor a deviating ileostomy was constructed. Following TME by careful dissection ensuring to avoid injuring the pelvic autonomous nerves, distal stapling was performed using a 45mm linear laparoscopic or robotic stapler. The number of staple firings differed; in most cases, two staple firings were used. The specimens were extracted through a Pfannenstiel incision or at an ileostomy site after placement of a wound protector. In case of primary anastomosis, a circular stapled anastomosis was performed. A second layer suture was performed to support the ventral staple line in all cases. All patients received postoperative care according to the same local Enhanced Recovery After Surgery (ERAS) protocol.

2.3 Endpoints

Baseline characteristics of patients were collected, including: age, sex, BMI, American Society of Anesthesiologists (ASA) classification, history of abdominal surgery, history of previous transanal surgery, tumor height based on pretreatment MRI according to LOREC criteria(13), clinical TNM staging based on MRI (14), mesorectal fascia (MRF) involvement on MRI and administration of preoperative (chemo)radiation therapy.

All pretreatment MRIs were reviewed by one of the researchers with extensive training in sigmoidal take-off and LOREC criteria. A low rectal tumour was defined according to LOREC: "tumour with its lower border at or below the origin of the levators on the pelvic sidewall" (13).

Details on operation included construction of an anastomosis and/or stoma, type of operation (LAR or ISR), operation time and conversion. Operation time was defined in

minutes as the time from incision to wound closure. Conversion was defined as the use of laparotomy for the mesorectal dissection.

Hospital stay was defined as the number of days between surgery and discharge. Reoperation, reintervention and readmission were recorded within the first 30 days. Postoperative morbidity was categorized according to the Clavien-Dindo classification (15). Anastomotic leakage was defined as clinical or radiological evidence of a defect of the integrity of the intestinal wall at the anastomotic site. A presacral abscess was defined as a pelvic collection visible on radiological evaluation.

Pathology outcomes included AJCC (American Joint Committee on Cancer) fifth edition staging, pathological T stage, N stage, completeness of the specimen defined according to Quirke (incomplete, near complete or complete)(16), circumferential resection margin (CRM) involvement defined as <1mm and distal resection margin (DRM) involvement defined as <5mm.

Long term recurrence was confirmed by either imaging (MRI, CT or PET-CT) and/or pathology (biopsy, salvage surgery). A local recurrence was defined as a mass in the pelvis with a biopsy positive for adenocarcinoma or growth on sequential imaging in absence of histopathologic confirmation.

A low anterior resection syndrome (LARS) questionnaire was used to identify the rate of low anterior resection syndrome (4). It consists of five questions of rectal and bowel function after rectal cancer surgery, leading to a total score. This score was then categorized into no LARS (0–20 points), minor LARS (21–29 points), and major LARS (30–42 points). An International Prostate Symptom Score (IPSS) questionnaire was taken in all male subjects and consists of seven questions leading to a score. The urinary dysfunction was then categorized into mild (0–7), moderate (8–19), or severe (20–35) (17). The sexual function in female was assessed using the Female Sexual Function Index (FSFI) questionnaire, consisting of 18 questions, leading to a total score with higher scores indicating better function on a scale of 2-36) (18). Questionnaires were sent to patients who had primary operation or stoma reversal at least 1 year ago.

Primary outcome was local recurrence rate at 3 years. Secondary outcomes were rate of conversion to open surgery, CRM positivity rate, 30-day postoperative morbidity and outcomes of LARS, IPSS and FSFI questionnaires.

2.4 Statistical analysis

Categorical data were displayed as number (%), continuous variables were displayed as mean (standard deviation) or median (range) in case of non-normal distribution. A Kaplan-Meier analysis was used to analyze local recurrences, disease-free survival and overall survival. All analyses were performed using IBM SPSS software (version 25 Chicago, IL, USA).

The study was approved by the ethical board of Radboudumc Nijmegen, the Netherlands (registration number 2020-6149), and was approved by the local Institutional Review Board of Rijnstate hospital (study number 2019-1541). Patients who filled in the questionnaires also signed an informed consent form.

3 RESULTS

3.1 Baseline and clinical outcome

A total of 105 patients underwent robot-assisted TME for rectal cancer according to sigmoidal take-off definition during the study period. The number of distal tumours according to LOREC definition was 26 (24.8%). Mean distance to the anal verge in centimetres on MRI was 9.1 (2.9). Six (5.7%) patients had synchronous metastases, 40 (38.1%) had neoadjuvant radiation therapy and 19 (18.1%) had neoadjuvant chemoradiation therapy administered. A primary anastomosis was constructed in 89 (84.8%) patients.

Nine patients (8.6%) underwent conversion to open surgery. There was no conversion to conventional laparoscopy. Reason for conversion was lack of progression in five patients, complications in two (bleeding, perforation of colon), no safe margin in T4 tumour in one and no space for stapling in one. Eight patients (9.0% of patients with a primary anastomosis) had an anastomotic leakage. Anastomotic leakage was managed with antibiotics in one patient and four patients were treated by relaparoscopy with drainage and a deviating ileostomy. Four patients had occult leakage discovered on routine imaging before deviating ileostomy reversal, and stoma reversal was postponed. An overview of all clinical outcome of the cohort can be seen in Table 1. Six (5.7%) underwent a reoperation. Reasons for reoperation were anastomotic leakage in four, and trocar hernia in two patients. Fifteen patients had a readmission. Reason for readmissions were: high output stoma with dehydration in four, anastomotic leakage in three, pneumonia in two, infected hematoma in one, pelvic abscess in two, pain in one and ileus in one patient.

Table 1 Baseline and clinical outcome

		N=105	%
Sex	*Male*	66	62.9
	Female	39	37.1
BMI (mean) (±SD)		27.04(4.55)	
Age (years) (mean) (±SD)		65.60(9.98)	
ASA	*I*	8	7.6
	II	71	67.6
	III	24	22.9
	IV	2	1.9
Previous abdominal surgery	*yes*	22	21.0
Previous transanal surgery	*yes*	11	10.5
Distal tumor according to LOREC definition	*yes*	26	24.8
Tumor distance to anal verge on MRI (cm)		9.1(2.9)	
Detected in population screening	*yes*	45	42.9
Clinical Tumor stage	*T1*	4	3.8
	T2	33	31.7
	T3	65	62.5
	T4	1	1.0
	Unkown	1	1.0
Clinical Nodal stage	*N0*	71	68.3
	N1	21	20.2
	N2	12	11.5
Synchronous Metastasis*	*M+*	6	5.7
MRF threatened (before RT)	*yes*	15	14.6
Preoperative therapy	*RT*	40	38.1
	CRT	19	18.1
Anastomosis	*primary anastomosis*	89	84.8
	end-colostomy	16	15.2
Performed operation	*LAR*	103	98.1
	ISR	2	1.9
Conversion to laparotomy	*Yes*	9	8.6
Diverting ileostomy	*Yes*	64	61.
Operation time (minutes)	*mean (±SD)*	243(64)	
Posterative morbidity	*No complications*	55	52.4
	Minor Clavien Dindo 1-2	45	42.9
	Severe Clavien Dindo ≥3	5	4.8
	Reoperation	6	5.7
Length of hospital stay (days)	*mean (±SD)*	9.86(10.86)	
	median (range)	7(3-106)	
Readmission		15	14.3
Anastomotic leakage**		8	9.0**
Presacral abcess		6	5.7

Numbers in parentheses are percentages, unless mentioned otherwise. Abbreviations: BMI = Body Mass Index (kg/m2), SD = standard deviation, ASA = American Society of anesthesiologists, MRF = mesorectal fascia RT = radiotherapy, CRT = chemoradiotherapy, LAR= Low anterior resection, ISR= Intersfincteric resection. *All synchronous liver metastasis, treated with curative intention. **Percentage of patients with anastomosis.

3.2 Pathological outcome

Pathological outcome can be seen in Table 2. The rate of good quality specimen was 73.3%, near complete was 12.4% and incomplete was 14.3%. Six had CRM positivity (5.7%).

Table 2 Pathological outcome

		N=105	%
Pathologic staging acording to AJCC	*I*	42	40.0
	II	25	23.8
	III	29	27.6
	IV	3	2.9
Pathologic T-stage	*pT0*	6	5.7
	pT1	11	10.5
	pT2	39	37.1
	pT3	47	44.8
	pT4	2	1.9
Pathologic N-stage	*N0*	72	68.6
	N1	23	21.9
	N2	10	9.5
Quality of specimen (Quirke)	*Incomplete*	15	14.3
	Nearly complete	13	12.4
	Complete	77	73.3
CRM +	*<1 mm*	6	5.7
DRM +	*<5mm*	1	1.0

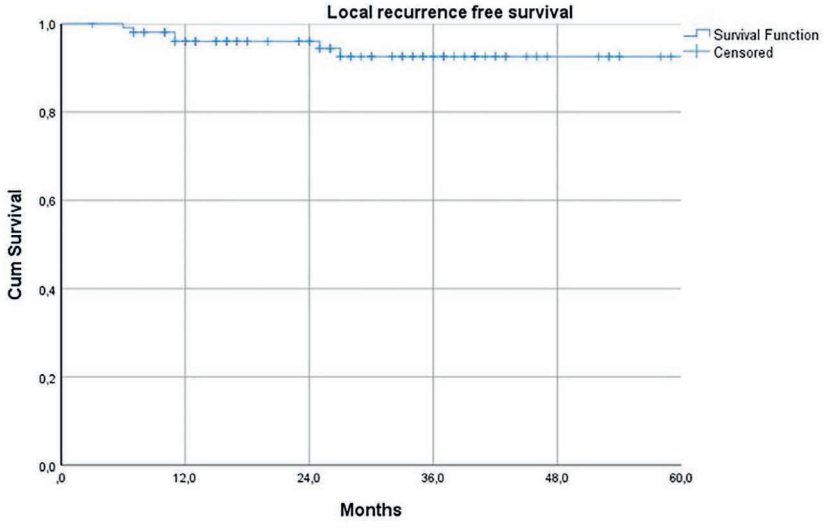
Numbers in parentheses are percentages, unless mentioned otherwise
Abbreviations: AJCC=American Joint Committee on Cancer, CRM=circumferential resection margin, DRM=distal resection margin

3.3 Long-term oncologic outcome

Median follow-up was 28[3-62] months. Local recurrence rate at 3 years was 7.4%, see Figure 1. An overview of all cases with local recurrences can be seen in Table 3. Disease-free survival rate at 3 years was 79.1%, see Figure 2. Overall survival rate at 3 years was 88.8%, see figure 3.

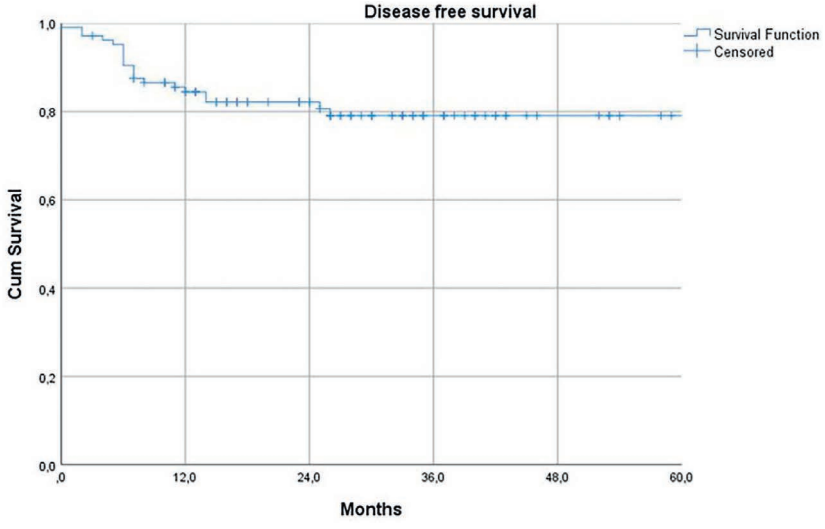
3.4 Functional outcome

Of 70 patients eligible for inclusion, who underwent (continuity) surgery at least 1 year ago, functional outcome data was collected from 43 patients (61.4%). Twenty-seven (38.6%) did not participated for various reasons: 22 did not respond, 2 already partici-



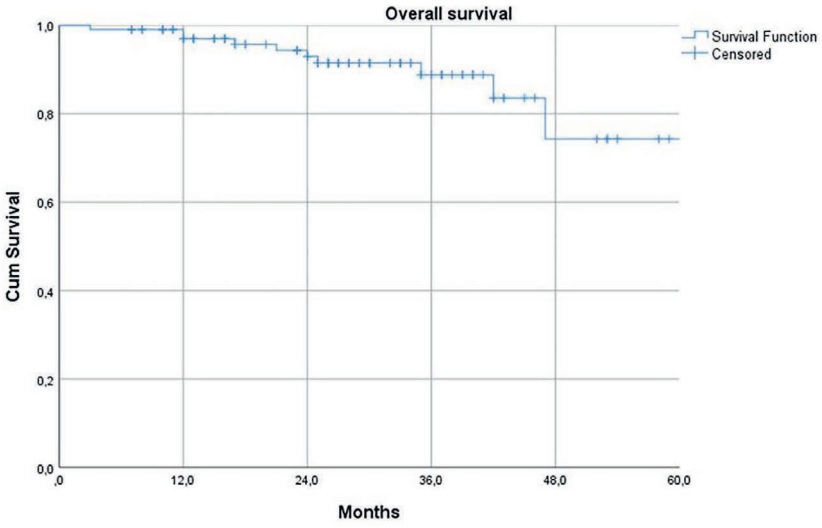
Years	0	1	2	3	4	5
Months	0	12	24	36	48	60
Number at risk	105	90	64	29	8	1
Local recurrence rate %	0	4.0	4.0	7.4	7.4	7.4

Figure 1 Kaplan–Meier of local recurrence free survival after robot-assisted total mesorectal excision



Years	0	1	2	3	4	5
Months	0	12	24	36	48	60
Number at risk	105	80	57	24	8	1
Disease free survival %	100	85.5	82.1	79.1	79.1	79.1

Figure 2 Kaplan–Meier of disease free survival after robot-assisted total mesorectal excision



Years	0	1	2	3	4	5
Months	0	12	24	36	48	60
Number at risk	105	94	67	31	8	1
Overall survival %	100	99.0	94.3	88.8	74.3	74.3

Figure 3 Kaplan–Meier curve of overall survival after robot-assisted total mesorectal excision

pated in other studies, 1 because of mental state and 2 because of severe comorbidity. Mean follow-up time after surgery was 28.8(11.2) months.

Thirty eight out of 43 patients (88.4%) completed the LARS questionnaire. Twenty-one out of 38 (55.3%) responders had major LARS, 6 out of 38 (15.8%) had minor LARS and 11 out of 43 (28.9%) had no LARS. Mean LARS score was 28.1(12.1). In male patients, 32 completed the IPSS questionnaire (72.7%). Mean IPSS score was 9.94(7.33). Three out of 32 (9.4%) responders had severe urinary dysfunction, 16 out of 32 (50%) had moderate dysfunction and 13 out of 32 (40.6%) had mild dysfunction. In female patients, 8 completed the FSFI questionnaire (18.6%). Mean overall FSFI score was 18.6(8.8).

DISCUSSION

In this single centre series of 105 robot-assisted TME, performed by 5 surgeons during implementation, conversion to open surgery rate was 8.6%, CRM positivity rate was 5.7%, postoperative morbidity rate was 47.6% and local recurrence rate at 3 years was 7.4%. Incidence of major LARS was 55.3%.

Table 3 Overview of cases with local recurrence

	Surgery	p Stage	Complications	R	Neoadjuvant	Interval	Location	Treatment	Survival
1	2015	pT2N1	No	R0	No	6	Anastomosis	Laparoscopic APE	Died after
		Poorly differentiated				months	And liver metastasis	Resection of liver metastasis	42 months
2	2017	pT3N0	No	R0	No	11	Anastomosis	Chemotherapy, planned for surgery	Alive
		Moderately differentiated				months			
3	2018	pT3N0	No	R0	CRTX	11	Presacral	Chemotherapy	Alive
		Moderately differentiated				months	And liver metastasis	RFA of liver metastasis	
4	2018	pT2N1a	High-output	R0	No	12	Two presacral lesions	Chemotherapy and planned	Alive
		Moderately differentiated	stoma			months	And in blind loop	for surgery	
5	2018	pT3N2b	No	R0	RTX short-term	7	Pelvic lymph nodes	Palliative chemotherapy	Alive
		Moderately differentiated				months	And liver and lung metastasis		
6	2018	pT3N2b	No	R1	No	3	Anastomosis	Chemotherapy	Alive
		Moderately differentiated		CRM+		months			

Abbreviations: APE = abdomino perineal excision, CRTX=chemoradiation therapy

The encountered local recurrence rate we saw in this implementation phase of robot-assisted TME is comparable to the laparoscopic TME long-term data of the COLOR II, ALaCaRT and ACOSOG Z6051 trials, which show a local recurrence rate of 5% (1, 19, 20). One Dutch series of robotic rectal surgery reported a local recurrence rate of 9.5% despite a low positive margin rate (21). This was possibly related to suboptimal technical execution within the learning curve. The CRM involvement rate of 5.7% in the present study was comparable to 5.1% CRM involvement rate in the ROLARR trial (22). Moreover, the number of patients with good quality specimen was comparable to the ROLARR trial (22) and in other series of robotic learning curves (23). It should be noted that case selection, rate of low rectal cancer with sphincter saving surgery in this cohort is not directly comparable to study populations in the aforementioned trials. We used the sigmoid take-off as definition for the rectum, probably including less proximal tumours and more distal and more complex resections.

The ROLARR trial is the largest randomized trial comparing robot-assisted with laparoscopic rectal resection. Conversion rates in the ROLARR trial were 8.1% in the robotic group and 12.2% in the laparoscopic group (22). The 8.6% total conversion rate in the present study was comparable to the ROLARR trial. One of the biggest methodological issues in the ROLARR trial was the study contained a learning curve effect. Surgeons were required to perform at least 10 robotic procedures before participating in the ROLARR trial. This a rather small amount, given the earlier published learning curves of up to 30-40 procedures for robotic surgery (8, 22). Previous studies similar to the present study showed lower conversion rates (below 3%) in robot-assisted TME (21, 24, 25). This study could not reproduce this rate. Most conversions were due to a lack in progression and not because of intra-operative complications, indicating safe implementation of the technique. Additionally, these numbers are comparable to laparoscopic rectal cancer trials (COLOR II, ALaCaRT, ACOSOG Z6501), which is still common practice in most hospitals (20, 26, 27). The effect of the learning curve was neither reflected by the rate of anastomotic leakage. Although the observed 84.8% rate of primary anastomosis was higher than the ROLARR trial (78%) and COLOR II (66%), the 9.0% rate of anastomotic leakage was lower than ROLARR (12.2%), Kim et al (12.1%) and COLOR II (13%) (22, 26, 28). This indicates relatively safe surgery, despite the implementation phase. The rate of primary anastomosis was also higher than the observed 70% in previous studies based on a national audit. A potential benefit of the robotic technique is safe creation of an anastomosis (including second layer suturing additional to stapling), by overcoming technical limitations of laparoscopy by superior view and better instrument handling.

Although representing the implementation phase, the incidence of major LARS seems to be comparable with previous studies (29, 30). A potential explanation could be the

learning curve. Incidence of major LARS was comparable to 53% at 12 months after robotic surgery described by Harslof et al (29). Similar results were seen for urogenital function as well. IPSS score was comparable to several previous studies (31, 32). FSFI score was comparable to ROLARR trial (22). These data must be interpreted with caution because response rates were low. Although laparoscopic and robotic TME surgery can result in bladder and sexual dysfunction, some studies suggest recovery is earlier for robot-assisted compared to laparoscopic surgery (32, 33). In one study erectile dysfunction was completely recovered at 1 year (34). Therefore we chose a cut-off of at least 12 months after surgery for questionnaires, as functional outcomes after this period are unlikely to change, as they may be attributed to permanent nerve injury (32). We did not included patients with end colostomy in functional outcome analysis in order to create a more homogeneous group. Robotic TME offers technologic advantages, including: enlarged 3D-vision, instruments with seven degrees of freedom that mimic movements made by a surgeons hand, lack of tremor and superior ergonomics (22, 28). These characteristics have the potential over laparoscopy to provide better visualization of the pelvic structures, especially the autonomic nerves. Key is to identify and to preserve pelvic autonomic nerves to avoid urinary and sexual dysfunction. The hypogastric plexus is located very close to the rectum. These nerves are easily damaged during rectal dissection, particularly by an imprecise or rough technique (35). This should be taken into consideration, as robot-assisted surgery comes at a higher cost, which may balance out financial benefits in improving postoperative functional complaints.

Certain limitations should be taken into consideration. First, all clinical outcome data were collected retrospectively. Second, functional scores were collected at different length of follow-up, which could have led to selection bias. However, all questionnaires were obtained at least one year after surgery. Since further recovery after this time period is unlikely, it should be considered as reliable outcomes (32). Moreover, baseline functional outcomes are missing, which could have led to confounding. Unfortunately, the robotic approach was employed at the end of the study period and became the preferred approach for TME procedures, which did not allow comparison of the laparoscopic technique. There also was a large case mix variation in both groups; initially there were more distal tumors and more APR in the laparoscopic group, which changed during the study period. Data from a large obligatory national audit prior to start of the implementation of robotic surgery showed similar long-term oncologic outcomes.

Most surgeons in our hospital operated in alternating pairs, where one surgeon took place at the robotic console and another surgeon assisted at the table, therefore participating in more procedures than mentioned, which might have contributed to their learning curve as well. Most learning curve analysis focusses on data from single centres

and generalized. Most cohort studies are series of a single surgeon with extensive experience in laparoscopic surgery (24, 36). Those series are not representative to daily practice in most hospitals, since multiple colorectal surgeons perform these operations. Multiple studies have tried to assess the learning curve for laparoscopically experienced surgeons by CUSUM analysis of operative time, pathologic outcome and intra- and postoperative outcomes to be around 20 to 25 procedures to reach proficiency (5, 6, 34). Therefore the number of around 20 procedures per surgeon was considered appropriate. A learning curve is generally measured by CUSUM analysis. However, such analysis requires an extensive cohort, ideally of a single surgeon, and was therefore not suitable for our study. It should be noted that intra-operative parameters including operative time did not differ between surgeons. Blood loss was generally low (below 150cc) except for cases that had undergone conversion. Furthermore, evaluation of safety of the learning curve is often based on short-term surrogate outcomes (25). This is one of the first studies to conform favourable results during implementation of robotic TME by functional and long-term outcomes (21). It should be noted we used sigmoidal take-off as definition for the rectum, allowing for a more standardized comparison with other centres excluding any sigmoid tumours (11). This study gives real-life data of the implementation phase as T4 tumours, stadium IV rectal cancer and T3 tumours with close mesorectal fascia involvement after neoadjuvant treatment are often not included in randomized trials (1).

Surgical treatment of rectal cancer remains challenging due to anatomical, oncological and technical constraints. Besides sufficient experience in laparoscopic TME surgery, surgeons in our team had access to robotic surgical system on a regular basis, with a credible and competent team and surgical set-up. We evaluated the data presented in this study with the entire staff-board to assess how future results might be enhanced. After this evaluation we decided to re-introduce rectal washout with povidone-iodine as a proportion of local recurrences in this cohort were located near the anastomosis. Although local recurrence is multifactorial, previous literature suggests the incidence of this type of recurrence might be reduced by rectal washout (37, 38).

In conclusion, the results of the present study showed acceptable morbidity, oncological and functional outcome during implementation of robot-assisted TME surgery for rectal cancer according to sigmoidal take-off in an experienced laparoscopic centre. Local recurrence rate at 3 years was 7%. Despite the implementation phase, functional outcomes seemed comparable to current literature. However, it might be too preliminary to conclude whether the technological advantages of the robotic surgical system can ultimately translate to better oncological and functional outcomes. We therefore plan to further evaluate robot-assisted TME by means of functional outcome in a prospective study which is currently enrolling.

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PART 2

COMPARISON OF ROBOT-ASSISTED AND TRANSANAL TOTAL MESORECTAL EXCISION

CHAPTER 6

COMPARISON OF LAPAROSCOPIC *VERSUS* ROBOT-ASSISTED *VERSUS* TATME SURGERY FOR RECTAL CANCER: A RETROSPECTIVE PROPENSITY SCORE MATCHED COHORT STUDY OF SHORT-TERM OUTCOMES

J C Hol, TA Burghgraef, MLW Rutgers, RMPH Crolla, NAW van Geloven, R Hompes, JWA Leijtens, F Polat, A Pronk, AB Smits, JB Tuynman, EGG Verdaasdonk, ECJ Consten, C Sietses

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ABSTRACT

Background: Laparoscopic total mesorectal excision (TME) surgery for rectal cancer has important technical limitations. Robot-assisted and transanal TME (TaTME) may overcome these limitations, potentially leading to lower conversion rates and reduced morbidity. However, comparative data between the three approaches are lacking. The aim of this study was to compare short-term outcomes for laparoscopic TME, robot-assisted TME and TaTME in expert centres.

Method: Patients undergoing rectal cancer surgery between 2015 and 2017 in expert centres for laparoscopic, robot-assisted or TaTME were included. Outcomes for TME surgery performed by the specialized technique in the expert centres were compared after propensity score matching. The primary outcome was conversion rate. Secondary outcomes were morbidity and pathological outcomes.

Result: A total of 1078 patients were included. In rectal cancer surgery in general, the overall rate of primary anastomosis was 39.4, 61.9 and 61.9 per cent in laparoscopic, robot-assisted and TaTME centres respectively ($P < 0.001$). For specialized techniques in expert centres excluding abdominoperineal resection (APR), the rate of primary anastomosis was 66.7 per cent in laparoscopic, 89.8 per cent in robot-assisted and 84.3 per cent in TaTME ($P < 0.001$). Conversion rates were 3.7 , 4.6 and 1.9 per cent in laparoscopic, robot-assisted and TaTME respectively ($P = 0.134$). The number of incomplete specimens, circumferential resection margin involvement rate and morbidity rates did not differ.

Conclusion: In the minimally invasive treatment of rectal cancer more primary anastomoses are created in robotic and TaTME expert centres.

INTRODUCTION

Total mesorectal excision (TME), combined with neoadjuvant therapy, has reduced locoregional recurrence rates after rectal cancer surgery (1, 2). The introduction of laparoscopic TME was expected to improve oncological results even further. However, to date, oncological superiority compared to an open technique has not been shown (3, 4). A laparoscopic approach has been shown to reduce morbidity, infection rates and duration of postoperative hospital stay (5, 6). These benefits have led to the laparoscopic approach being the preferred approach in many countries, including the Netherlands (3, 4).

Despite short-term advantages, laparoscopic TME is considered a difficult technique, due to the technical limitations of laparoscopy and the challenge of operating in the confined space of the pelvis. As a consequence, conversion rates of more than 10 per cent are common (5, 7). Conversion is associated with increased morbidity and worse oncological outcome (5, 8). Transanal TME (TaTME) and robot-assisted TME attempt to overcome the technical limitations of laparoscopy.

In TaTME the most difficult part of the rectal dissection is performed from below. Published data to date report that TaTME is safe in expert hands and has reduced conversion rates (9-12), but recent reports have raised concerns about oncological safety during the learning curve (13, 14). Robot-assisted TME also aims to overcome the technical limitations of laparoscopy in the narrow pelvis. Even in the low pelvis, accurate dissection is feasible thanks to the use of three-dimensional vision, lack of tremor, superior ergonomics and instruments with high degrees of freedom that mimic movements made by a surgeon's hands(15, 16). Previous studies report lower conversion rates in robot-assisted TME compared with laparoscopic TME, but no oncological benefit has been found (16-18). A large randomized controlled trial (ROLARR) found no difference in conversion rates, intraoperative or postoperative complications between robot-assisted and laparoscopic TME, although the learning curve may have impacted upon these results (19).

A concern about previous studies of robot-assisted TME and TaTME is that the surgeons performing these techniques were not as experienced as those performing laparoscopic surgery. This may underestimate the benefits of these new techniques (16, 19). In addition, there are no data comparing all three techniques (20). Therefore, the aim of this retrospective cohort study is to compare intra- and postoperative complications between laparoscopic, robot-assisted and TaTME performed in expert centres.

METHODS

A retrospective multicentre cohort study was performed in 11 centres with a large experience in one of the three techniques: three TaTME expert centres, three robot-assisted expert centres and five laparoscopic expert centres. All participating hospitals were considered high volume, with at least 40 TME procedures per year (21, 22). 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 medical ethics committee (AW 19.023/W18.100) and was approved by the local ethics boards of all participating centres.

Study design

Patients were divided according to the type of expert technique used in each centre, irrespective of the actual approach used. For further analysis, only low anterior resections (LARs) executed in expert centres with the corresponding technique were included (that is, robot-assisted only from centres where the standard technique was robot-assisted TME, laparoscopic only from centres with laparoscopic TME as standard and TaTME from centres where TaTME was standard). Each centre had to perform at least 30 procedures per year using the expert technique. For two centres that began to use the expert technique as late as 2014 (one robot-assisted and one TaTME centre), procedures from 2015 were excluded because the learning curve was not considered to have been completed. Abdominoperineal resections (APRs) were excluded from this analysis.

Patients

All patients 18 years or older diagnosed with rectal cancer according to the sigmoidal take-off definition (23), operated on between January 2015 and December 2017 in the 11 participating Dutch hospitals were included. All patients were operated upon with curative intent. Excluded from analysis were patients with distant metastasis (cM1 disease), palliative-intent treatment, synchronous colonic tumours, acute procedures and non-TME surgery (including local excision, transanal endoscopic microsurgery (TEM) or transanal minimally invasive surgery (TAMIS)). Each patient was discussed in a local multidisciplinary cancer meeting and neoadjuvant treatment used according to the current Dutch national guidelines for colorectal cancer (last updated in 2014) (24).

Data collection

Data for this multicentre cohort study were derived from the Dutch Colo Rectal Audit (DCRA), an obligatory nationwide registry reporting data related to the quality of colorectal resections (25). Missing data and additional information not present in the DCRA were added to the database using local electronic medical records. Patients were

anonymized before data collection from local records. All data were collected between January and April 2020 and stored in the data management system CASTOR.

Outcomes and definitions

The study primary outcome was the conversion rate, defined as conversion to laparotomy to complete the mesorectal dissection. Secondary outcomes were intraoperative complications, length of hospital stay, 30-day morbidity and mortality, circumferential resection margin (CRM) involvement rate, quality of TME specimen and primary anastomosis rate.

Data collected in the DCRA audit were baseline characteristics such as age, sex, BMI, ASA class, co-morbidities, prior abdominal surgery, tumour location, clinical and pathological TNM stage, neoadjuvant treatment, date of surgery, type of surgery, intraoperative details, 30-day morbidity and mortality, and pathological outcome of all patients.

The type of procedure was categorized as low anterior resection (LAR) with anastomosis, LAR with colostomy or APR. APR included any procedure with perineal dissection with complete proctectomy with definitive end colostomy. LAR included all sphincter-saving procedures, with primary anastomosis. LAR with definitive end colostomy was either a 'Hartmann's procedure' or a procedure with mucosectomy and closing of the rectal stump and anus. A rectal tumour was defined as a tumour with its lower border below the sigmoid take-off on cross-sectional imaging, according to the definition of D'Souza and colleagues, whereby the sigmoid take-off is defined as 'where the mesocolon elongates in ventral and horizontal course on axial and sagittal views on cross-sectional imaging' (23). In addition, a low rectal tumour was defined according to the LOREC definition, whereby the lower border of the cancer is 'at or below the origin of the levators on the pelvic sidewall' (26). Investigators involved in reviewing preoperative MRI images had extensive training in defining the definitions used. In cases of doubt, consensus was reached after discussion with radiologists.

Thirty-day morbidity was categorized according to the Clavien–Dindo classification (27). Anastomotic leakage was defined as anastomotic dehiscence or intra-abdominal abscess adjacent to the anastomotic site, requiring radiological or surgical intervention during follow-up, including those beyond 30 days. Leakages were graded according to need for intervention: grade A can be managed without change in management, grade B requires active therapeutic intervention but is manageable without re-laparotomy, and grade C requires re-laparotomy (28). Early stoma reversal was not defined as readmission or reoperation. A positive CRM was defined as a margin of 1 mm or less. The quality of the mesorectum was graded according to Quirke (29).

Statistical analysis

Three propensity score-matched groups of equal size for each technique were formed. First robot-assisted and TaTME were matched 1 : 1. Then, laparoscopic and TaTME were matched in a similar way. Robot-assisted and TaTME patients that were not included in the second match were excluded.

Propensity score matching was performed using 1 on 1 near-neighbour matching with a calliper of 0.1. The variables used for matching were age (years), BMI (kg/m2), sex (male/female), ASA class (I–IV), history of abdominal surgery (yes/no), distance to anal verge on colonoscopy in centimetres, MRI-defined low rectal tumour (LOREC), involvement of the mesorectal fascia on preoperative staging MRI of 1 mm or less (yes/no/unknown), clinical TNM stage, and neoadjuvant chemotherapy (yes/no). A standardized mean difference (SMD) less than 0.1 was deemed negligible, indicating appropriate matching. Missing data for the propensity score were imputed using multiple imputations if the type of missing data was missing at random or completely at random.

Data were presented as number and percentages for categorical variables. Continuous variables were presented as mean(s.d.) or median (i.q.r.), depending on the type of distribution. Univariable analysis of unmatched patients was done using the $\chi 2$ test for categorical data. The independent sample t-test or the Wilcoxon rank sum test, depending on the distribution, were used for continuous data. Analyses of matched patients was done using generalized linear modelling. $P < 0.050$ was considered significant. All statistical analysis was performed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) using the Matching and Mice packages.

RESULTS

A total of 1834 patients undergoing primary rectal resections were registered in the DCRA registry in the participating centres between January 2015 and December 2017. After excluding patients that were ineligible for inclusion, 1078 patients were included. The study flow chart is shown in Fig. 1.

Overall results per centre

Baseline characteristics for the unmatched cohorts for all rectal cancer surgery in each centre are shown in Table 1. There were 490 patients in laparoscopic centres, 344 in robot-assisted and 244 in TaTME centres. The rate of primary anastomosis was 39.4 per cent in laparoscopic, 61.9 per cent and robot-assisted and 61.9 per cent in TaTME centres ($P < 0.001$). The APR rate was 41.4 per cent in laparoscopic, 30.8 per cent in robot-assisted

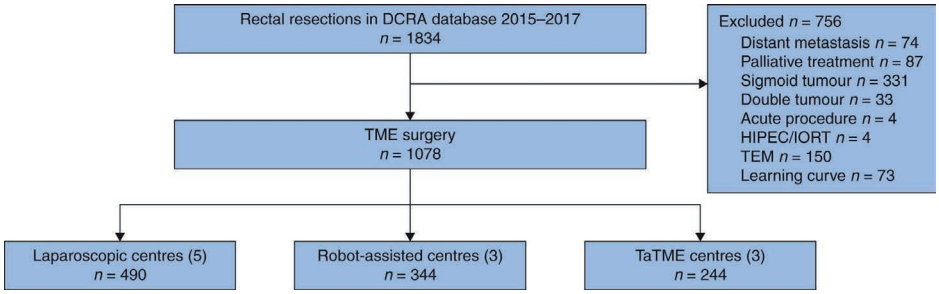

Fig. 1 Flow chart of patients
DCRA, Dutch Colo Rectal Audit; TEM, transanal endoscopic microsurgery; HIPEC, hyperthermic intraperitoneal; IORT, intra-operative radiotherapy; TME, total mesorectal excision

and 24.6 per cent in TaTME centres (P < 0.001). The rate of open TME approach was 5.5 per cent in laparoscopic, 1.5 per cent in robot-assisted and 3.3 per cent in TaTME centres (P < 0.001).

COMPARISON OF SPECIALIZED TECHNIQUES IN EXPERT CENTRES

Baseline

Baseline characteristics for unmatched and matched LAR by specialized technique in expert centres are presented in Table 2. Before matching there were 254 patients in the laparoscopic, 209 in the robot-assisted and 161 in the TaTME group. After matching 108 patients remained per group. There were minor differences in ASA grade (SMD 0.107). No difference was seen in other baseline comparisons after matching with SMD less than 0.1, indicating good-quality matching.

Intra operative parameters

Conversion rates were 3.7, 4.6 and 1.9 per cent in laparoscopic, robot-assisted and TaTME respectively (P = 0.518). The rate of primary anastomosis was highest in robot-assisted (89.8 per cent), followed by TaTME (84.3 per cent) and lowest in laparoscopic centres (66.7 per cent) (P < 0.001). Post hoc testing showed no difference between robot-assisted and TaTME (P = 0.227). End colostomy rate was highest in the laparoscopic group (33.3 per cent) compared with the robot-assisted (10.2 per cent) and TaTME (14.8 per cent). More diverting ileostomies were constructed in the robot-assisted surgery (60.2 per cent) compared to the laparoscopic (33.3 per cent) and TaTME (39.8 per cent) (P < 0.001). Mean operation time was longest in the TaTME group (mean(s.d.) 209(74) mins), compared with robot-assisted

Table 1 Unmatched rectal cancer surgery per type of centre

	Laparoscopy (*n*=490)	Robot (*n*=344)	TaTME (*n*=244)	SMD	*P*
Age (years)*	68 (9.8)	67 (10.6)	66 (11.0)	0.101	0.144
BMI (kg/m^2)*	26 (4.4)	26 (4.0)	26 (4.2)	0.076	0.255
Gender					
Male	311 (63.5)	218 (63.4)	158 (64.8)	0.019	0.930
Female	179 (36.5)	126 (36.6)	86 (35.2)		
ASA grade					
I	93 (19.0)	75 (21.8)	49 (20.1)	0.156	0.170
II	296 (60.4)	194 (56.4)	151 (61.9)		
III	94 (19.2)	75 (21.8)	43 (17.6)		
IV	7 (1.4)	0 (0.0)	1 (0.4)		
History of abdominal surgery	155 (31.6)	86 (25.0)	71 (29.1)	0.098	0.115
Tumour distance at coloscopy (cm)†	8 (4- 10)	7 (3–10)	5 (3-9)	0.185	0.002
LOREC					
Yes	319 (65.1)	178 (51.7)	140 (57.4)	0.223	0.001
Missing	7 (1.4)	8 (2.3)	1 (0.4)		
MRF involvement on MRI					
MRF involved	132 (26.9)	105 (30.5)	87 (35.7)	0.147	0.054
MRF not involved	352 (71.8)	232 (67.4)	155 (63.5)		
Missing	6 (1.2)	7 (2.0)	2 (0.8)		
cT stage					
1 or 2	155 (31.6)	117 (34.0)	75 (30.7)	0.129	0.280
3	297 (60.6)	188 (54.7)	147 (60.2)		
4	37 (7.6)	38 (11.0)	20 (8.2)		
cN stage					
0	219 (44.7)	149 (43.3)	132 (54.1)	0.145	0.023
1 or 2	271 (55.3)	195 (56.7)	112 (45.9)		
Neoadjuvant therapy					
None	196 (40.0)	128 (37.2)	96 (39.3)	0.184	0.035
(Chemo)radiation	280 (57.1)	214 (62.2)	148 (60.7)		
Missing	14 (2.9)	2 (0.6)	0 (0.0)		
Procedure					
APR	203 (41.4)	106 (30.8)	60 (24.6)	0.399	<0.0001
LAR + colostomy	94 (19.2)	25 (7.3)	33 (13.5)		
LAR + anastomosis	193 (39.4)	213 (61.9)	151 (61.9)		
Approach					
Open	27 (5.5)	5 (1.5)	8 (3.3)	0.354	<0.001
Laparoscopy	434 (88.6)	28 (8.1)	54 (22.1)		
TaTME	20 (4.1)	2 (0.6)	182 (74.6)		
Robot	9 (1.8)	309 (89.8)	0 (0.0)		

Values in parentheses are percentages, unless indicated otherwise;
*values are mean(s.d.), †values are median (i.q.r.). TaTME, transanal total mesorectal excision; SMD, standard mean difference; LOREC, low rectal cancer definition; MRF, mesorectal fascia; APR, abdomino-perineal resection; LAR, low anterior resection.

Table 2 Baseline characteristics of TME surgery before and after propensity score matching

	Unmatched cohort				Matched cohort			
	Laparoscopy (*n* = 254)	**Robot (*n*=209)**	**TaTME (n = 161)**	**SMD**	**Laparoscopy (n = 108)**	**Robot (n = 108)**	**TaTME (n = 108)**	**SMD**
Age (years)*	68 (9.7)	66 (10.3)	65 (10.9)	0.153	66 (10.1)	66 (10.3)	66 (10.4)	0.034
BMI (kg/m2)*	26 (4.3)	26 (3.9)	26 (4.3)	0.017	26 (4.4)	26 (3.7)	26 (4.3)	0.030
Gender								
Male	155 (61.0)	131 (62.7)	111 (68.9)	0.111	69 (63.9)	65 (60.2)	71 (65.7)	0.077
Female	99 (39.0)	78 (37.3)	50 (31.1)		39 (36.1)	43 (39.8)	37 (34.3)	
ASA grade								
I	58 (22.8)	46 (22.0)	35 (21.7)	0.133	27 (25.0)	21 (19.4)	25 (23.1)	0.107
II	140 (55.1)	125 (59.8)	96 (59.6)		60 (55.6)	68 (63.0)	62 (57.4)	
III	53 (20.9)	38 (18.2)	29 (18.0)		21 (19.4)	19 (17.6)	21 (19.4)	
IV	3 (1.2)	0 (0.0)	1 (0.6)		0 (0.0)	0 (0.0)	0 (0.0)	
History of abdominal surgery	80 (31.5)	48 (23.0)	38 (23.6)	0.128	25 (23.1)	29 (26.9)	26 (24.1)	0.057
Tumour distance at coloscopy (cm)†	10 [7, 12]	8 [6, 10]	6 [5, 10]	0.500	8 [5, 10]	8 [6, 10]	8 [5, 10]	0.025
LOREC								
Yes	118 (46.5)	73 (34.9)	78 (48.4)	0.219	49 (45.8)	44 (42.3)	48 (44.9)	0.047
Missing	3 (1.2)	7 (3.3)	1 (0.6)		0 (0.0)	0 (0.0)	0 (0.0)	
MRF involvement on MRI								
MRF involved	42 (16.5)	54 (25.8)	46 (28.6)	0.267	26 (24.1)	29 (27.1)	23 (21.5)	0.087
MRF not involved	212 (83.5)	150 (71.8)	114 (70.8)		82 (75.9)	78 (72.9)	84 (78.5)	
Missing	0 (0.0)	5 (2.4)	1 (0.6)		0 (0.0)	0 (0.0)	0 (0.0)	
cT stage								
1 and 2	88 (34.6)	72 (34.4)	49 (30.4)	0.188	38 (35.2)	39 (36.1)	35 (32.7)	0.087
3	157 (61.8)	119 (56.9)	104 (64.6)		66 (61.1)	64 (59.3)	69 (64.5)	
4	9 (3.5)	17 (8.1)	7 (4.3)		4 (3.7)	5 (4.6)	3 (2.8)	
Missing	0 (0.0)	1 (0.5)	1 (0.6)		0 (0.0)	0 (0.0)	0 (0.0)	
cN stage (%)								
0	109 (42.9)	89 (42.6)	87 (54.0)	0.154	51 (47.2)	50 (46.3)	49 (45.4)	0.025
1 and 2	145 (57.1)	120 (57.4)	74 (64.0)		57 (52.8)	58 (53.7)	59 (54.6)	
Neoadjuvant therapy								
None	112 (44.1)	84 (40.2)	65 (40.4)	0.147	48 (44.4)	44 (41.1)	46 (42.6)	0.045
(Chemo) radiation	138 (54.3)	123 (58.9)	96 (59.6)		60 (55.6)	63 (58.9)	62 (57.4)	
Missing	4 (1.6)	2 (1.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	

Values in parentheses are percentages, unless indicated otherwise; *values are mean(s.d.), †values are median (i.q.r.). TaTME, transanal total mesorectal excision; SMD, standard mean difference; LOREC, low rectal cancer definition; MRF, mesorectal fascia.

Table 3 Intra operative parameters after propensity score matching

	Matched Cohort				Post hoc testing		
	Laparoscopy (*n* = 108)	**Robot (*n* = 108)**	**TaTME (*n* = 108)**	***P***	***P*** **Laparoscopy *versus* robot**	***P*** **Laparoscopy *versus* TaTME**	***P*** **Robot *versus* TaTME**
Procedure							
LAR + colostomy	36 (33.3)	11 (10.2)	17 (15.7)	<0.001	<0.001	0.003	0.227
LAR + anastomosis	72 (66.7)	97 (89.8)	91 (84.3)				
Operating time (min)*	149 (53)	186 (59)	209 (74)	<0.001	<0.001	<0.001	0.015
Conversion	4 (3.7)	5 (4.6)	2 (1.9)	0.518			
Reason for conversion							
Extensiveness tumour	0 (0.0)	0 (0.0)	1 (50.0)				
Accessibility	3 (75.0)	5 (100.0)	1 (50.0)				
Preoperative complication	1 (25.0)	0 (0.0)	0 (0.0)				
Primary anastomosis	72 (66.7)	97 (89.8)	91 (84.3)	<0.001	<0.001	0.003	0.227
Stoma							
No stoma	29 (26.9)	32 (29.6)	48 (44.4)	<0.001	0.653	0.005	0.018
Deviating ileostomy	36 (33.3)	65 (60.2)	43 (39.8)	<0.001	<0.001	0.323	0.003
Deviating colostomy	7 (6.5)	0 (0.0)	1 (0.9)				
End colostomy	36 (33.3)	11 (10.2)	16 (14.8)		<0.001	0.003	0.291
Additional resection	2 (1.9)	6 (5.6)	6 (5.6)	0.303			
Intraoperative complication	3 (2.8)	5 (4.6)	4 (3.7)	0.771			

Values in parentheses are percentages, unless indicated otherwise;
*values are mean(s.d.). TaTME, transanal total mesorectal excision; LAR, low anterior resection.

Table 4 Postoperative parameters after propensity score matching

	Matched Cohort				Post hoc testing		
	Laparoscopy (n=108)	**Robot (n=108)**	**TaTME (n=108)**	***P***	***P* Laparoscopy *versus* Robot**	***P* Laparoscopy *versus* TaTME**	***P* Robot *versus* TaTME**
Complications	55 (50.9)	59 (54.6)	47 (43.5)	0.251			
Cardiac complications	6 (5.6)	4 (3.7)	1 (0.9)	0.167			
Pulmonary complications	6 (5.6)	9 (8.3)	9 (8.3)	0.667			
Surgical complications	42 (38.9)	46 (42.6)	30 (27.8)	0.063	0.580	0.084	0.023
Abscess	8 (7.4)	4 (3.7)	4 (3.7)	0.349			
Ileus	20 (18.5)	27 (25.0)	10 (9.3)	0.009	0.250	0.053	0.003
Wound infection	3 (2.8)	4 (3.8)	1 (0.9)	0.141			
Anastomotic leakage	17 (23.6)	21 (21.6)	16 (17.6)	0.619			
Anastomotic leakage grade							
A	3 (17.6)	1 (4.8)	4 (25.0)	0.290			
B	6 (35.3)	10 (47.6)	3 (18.8)				
C	8 (47.1)	10 (47.6)	9 (56.2)				
Clavien Dindo classification							
Major morbidity	23 (21.3)	19 (17.6)	22 (20.4)	0.776			
Minor morbidity	32 (29.6)	40 (37.0)	24 (22.2)				
No complication	53 (49.1)	49 (45.4)	62 (57.4)				
Reintervention	23 (21.3)	19 (17.6)	21 (19.4)	0.789			
Readmission	19 (17.6)	25 (23.1)	17 (15.7)	0.350			
LOS (days)*	6 (4-10)	6 (5-12)	6 (4-9)	0.742			
Mortality within 30 days	1 (0.9)	0 (0.0)	0 (0.0)	0.363			

Abbreviations: TaTME, transanal total mesorectal excision; LOS, length of hospital stay.

(186(59) mins) and laparoscopic (149(53) mins) ($P < 0.001$). The number of intraoperative complications was comparable for each group. In TaTME one patient had a carbon dioxide embolus, one had intraoperative bleeding and two had purse-string failure. In the robot-assisted TME, one patient had a bladder injury. Unintended small bowel injury occurred in two laparoscopic, four robot-assisted and two TaTME patients (Table 3).

Postoperative parameters

The overall complication rates were comparable between groups. Postoperative ileus rates were lower in TaTME (9.3 per cent) compared with laparoscopy (18.5 per cent) and robot-assisted TME (25.0 per cent) ($P = 0.003$). The rates of anastomotic leakage were 23.6, 21.6 and 17.6 per cent in laparoscopic, robot-assisted and TaTME respectively ($P = 0.619$). Grade of leakage did not differ. Median length of hospital stay was 6 days in each group (Table 4).

Pathology

No difference was seen in pathological outcomes, including histological type, grade of differentiation and pTNM stage (Table S1, supporting information). CRM involvement rates were 2.0, 2.0 and 4.0 per cent in laparoscopic, robot-assisted and TaTME respectively (SMD 0.598). Complete or near complete specimens were achieved in 96.2, 96.3 and 98.1 per cent in laparoscopic, robot-assisted and TaTME respectively (SMD 0.677). CRM involvement or incomplete specimen was found in 7.3, 7.0 and 6.3 per cent respectively (SMD 0.963).

DISCUSSION

This multicentre retrospective cohort evaluating laparoscopic, robot-assisted and TaTME operated on in expert centres found comparable short-term results between all three techniques. However, in robot-assisted and TaTME centres a higher percentage of patients had anastomoses created. This suggests that robot-assisted and TaTME may facilitate the safe creation of an anastomosis.

The overall rates of postoperative morbidity were similar between laparoscopic, robot-assisted and TaTME, with results in keeping with previously reported series that report morbidity rates of up to 40 per cent after laparoscopic TME (5). Previous randomized trials comparing robot-assisted with laparoscopic TME have shown no difference in morbidity (15, 16, 30) and some studies of TaTME have shown less short-term morbidity when compared with laparoscopy (31, 32).

Conversions in general and conversions due to intraoperative complications were rare in the present study. This is indicative of high-quality surgery and reflects that surgery was performed in expert centres. Previously reported conversion rates for laparoscopic TME vary from 0–16 per cent (2, 7). In the ROLARR trial the conversion rate was 8.1 per cent in the robot-assisted group, compared with 12.2 per cent in the laparoscopic group (16). However, the ROLARR trial was probably underpowered due to a higher anticipated difference based on a conversion rate of up to 25 per cent in the MRC CLASSICC trial (33). Another explanation for the higher conversion rate in the ROLARR trial might be that data were captured in the learning curve. The learning curve for robot-assisted and TaTME is at least 30–40 procedures (16, 22, 34, 35). Since centres in the current study performed at least 30 procedures in the year before inclusion, the learning curve effect was believed to be diminished. The results in this study are comparable to other studies on robot-assisted TME and TaTME in which only experienced surgeons participated (15, 17, 32, 36).

Significantly more primary anastomoses were made in robot-assisted and TaTME expert centres. Restorative rates were higher in all groups compared with a previous national snapshot study in which the anastomosis rate was only 50 per cent (37). The technological advantages of the new techniques could have contributed to these higher restorative rates. Both robot-assisted and TaTME provide better access to the distal rectum, enabling surgeons to complete the TME dissection safely and create an anastomosis. Robot-assisted TME can overcome the technical limitations of laparoscopy in the narrow pelvis by improved vision and superior instrument handling, while the transanal approach allows for direct access to the distal part of the rectum and eliminates cross stapling (9, 10, 15, 16). Olthof and colleagues also reported higher restorative rates in a robot-assisted implementation cohort (38). Other explanations for the higher restorative rate should be considered including patient-, surgeon- or centre-specific preferences. Furthermore, the construction of an anastomosis in patients who otherwise would undergo APR does not necessarily contribute to better functional outcome or quality of life (39).

The rate of anastomotic leakage in this study was in accordance with a large Dutch national audit in which anastomotic leakage was 20.0 per cent beyond 30 days (37). Another Dutch audit based on DCRA data reported similar results (10). It should be noted that all types of leakages, including occult leakages or leakages beyond 30 days, are included in this study. Furthermore, previous studies did not use a clear definition of the rectum, and might have included more proximal tumours, resulting in an underestimation of anastomotic leakage rate (40). In this study, rectal carcinoma was defined according to the MRI-based sigmoid take-off definition, thereby eliminating the inclusion of distal sigmoid tumours (23). Although the rate of primary anastomosis was higher in robot-assisted and TaTME centres, this did not lead to a higher rate of anastomotic leakage.

The most important predictor for local recurrence is the involvement of the CRM. In this study, CRM involvement rates for all three techniques were comparable: 2.0 to 4.0 per cent. In the ROLARR trial, a 5.1 per cent CRM involvement rate was seen with relatively proximal tumours. The exclusion of distal sigmoid tumours in the present study did not result in higher CRM involvement, indicating good-quality surgery for all three techniques. Specifically for TaTME, the observed positive CRM rates were lower than the 12.7 per cent encountered in Norway which led to a local recurrence rate of 11.6 per cent and a halt on TaTME in that country (41). The observed CRM rates in the present study are comparable with the results from early adopters in Australia and the Netherlands, which showed local recurrence rates to be 2–4 per cent (11, 42). One of the most important parameters in assessing the quality of each technique is whether a radical resection can be achieved, with complete resection of the mesorectum. The overall number of incomplete specimen in this study was less than 4%, and rates were comparable between groups. This is in line with previous research (43).

The most important limitation of this study is its retrospective nature; confounding by indication might therefore be apparent. In order to correct for confounding by indication, three balanced cohorts were created using propensity score matching. Studies comparing robot-assisted with TaTME are scarce (20). Some contain only small series of patients, while others lack important outcome measures such as conversion rate. Additionally, one of the most important drawbacks in previous research is the inability to take the learning curve into account (44). The effect of the learning curve was diminished in this study, by selection of experienced centres (45, 46). Further work is required to establish the potential benefits of each technique in the hands of experienced and less experienced surgeons.

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Supporting information: Table S1 Pathology outcome after propensity score matching

		Matched Cohort			
		Laparoscopy	**Robot**	**TaTME**	**SMD**
N		108	108	108	
Histological type (%)	Adenocarcinoma	104 (96.3)	102 (94.4)	105 (97.2)	0.571
	Mucinous type	4 (3.7)	6 (5.6)	3 (2.8)	
	Other	0 (0.0)	0 (0.0)	0 (0.0)	
Differentiation (%)	Well/moderate	97 (89.8)	97 (89.8)	102 (94.4)	0.687
	Poor	5 (4.6)	4 (3.7)	2 (1.9)	
	Unknown	6 (5.6)	7 (6.5)	4 (3.7)	
pT (%)	0	9 (8.4)	7 (6.5)	8 (7.5)	0.998
	1	11 (10.3)	13 (12.1)	13 (12.1)	
	2	42 (39.3)	39 (36.4)	38 (35.5)	
	3	43 (40.2)	46 (43.0)	45 (42.1)	
	4	2 (1.9)	2 (1.9)	3 (2.8)	
pN (%)	0	70 (64.8)	76 (71.0)	76 (70.4)	0.583
	1	29 (26.9)	21 (19.6)	20 (18.5)	
	2	9 (8.3)	10 (9.3)	12 (11.1)	
pM (%)	0	108 (100.0)	105 (98.1)	102 (99.0)	0.554
	1	0 (0.0)	1 (1.0)	1 (1.0)	
CRM ≤1 mm (%)	CRM involvement*	2 (2.0)	2 (2.0)	4 (4.0)	0.598
Quality of TME (%)	Complete/near complete	101 (96.2)	103 (96.3)	102 (98.1)	0.677
	Incomplete	4 (3.8)	4 (3.7)	2 (1.9)	
Composite outcome (%)	No CRM involvement and complete/near complete TME	89 (92.7)	93 (93.0)	89 (93.7)	0.963
	CRM involvement or incomplete TME	7 (7.3)	7 (7.0)	6 (6.3)	

Numbers in parentheses are percentages, unless mentioned otherwise
Abbreviations: CRM=circumferential resection margin, TME=total mesorectal excision
*=percentages excluding ypT0

CHAPTER 7

LAPAROSCOPIC VERSUS ROBOT-ASSISTED VERSUS TRANSANAL LOW ANTERIOR RESECTION: 3-YEAR ONCOLOGIC RESULTS FOR A POPULATION-BASED COHORT IN EXPERIENCED CENTERS

TA Burghgraef, **JC Hol**, ML Rutgers, RMPH Crolla, AAW van Geloven, R Hompes, JWA Leijtens, F Polat, A Pronk, AB Smits, JB Tuynman, EGG Verdaasdonk, PM Verheijen, C Sietses, E Consten

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ABSTRACT

Background: Laparoscopic, robot-assisted, and transanal total mesorectal excision are the minimally invasive techniques used most for rectal cancer surgery. Because data regarding oncologic results are lacking, this study aimed to compare these three techniques while taking the learning curve into account.

Method: This retrospective population-based study cohort included all patients between 2015 and 2017 who underwent a low anterior resection at 11 dedicated centers that had completed the learning curve of the specific technique. The primary outcome was overall survival (OS) during a 3-year follow-up period. The secondary outcomes were 3-year disease-free survival (DFS) and 3-year local recurrence rate. Statistical analysis was performed using Cox-regression.

Results: The 617 patients enrolled in the study included 252 who underwent a laparoscopic resection, 205 who underwent a robot-assisted resection, and 160 who underwent a transanal low anterior resection. The oncologic outcomes were equal between the three techniques. The 3-year OS rate was 90% for laparoscopic resection, 90.4% for robot-assisted resection, and 87.6% for transanal low anterior resection. The 3-year DFS rate was 77.8% for laparoscopic resection, 75.8% for robot-assisted resection, and 78.8% for transanal low anterior resection. The 3-year local recurrence rate was in 6.1% for laparoscopic resection, 6.4% for robot-assisted resection, and 5.7% for transanal procedures. Cox-regression did not show a significant difference between the techniques while taking confounders into account.

Conclusion: The oncologic results during the 3-year follow-up were good and comparable between laparoscopic, robot-assisted, and transanal total mesorectal technique at experienced centers. These techniques can be performed safely in experienced hands.

INTRODUCTION

The primary surgical treatment for rectal cancer is total mesorectal excision (TME) (1). After the introduction of laparoscopic TME (L-TME), large randomized trials showed that oncologic outcomes for minimally invasive L-TME are not superior to open TME (2-5). However, because L-TME has led to an improvement in short-term outcomes such as hospital length of stay (6), it has become the standard technique in most Western countries (7).

Despite its short-term benefits, laparoscopic surgery has not been proven superior to open surgery with regard to oncologic outcomes (2-5). Especially for distal tumors deep in the pelvis, the laparoscopic technique has technical limitations. To overcome these limitations, two new minimally invasive techniques have been introduced for the surgical resection of rectal carcinoma: robot-assisted TME (R-TME) and transanal TME (TaTME).

Adequate comparative studies investigating L-TME, R-TME, and TaTME are lacking. Most studies are single-center cohort series reporting on the comparison of only two techniques (8), whereas studies comparing all three minimally invasive techniques are scarce (9). Additionally, most studies did not take into account the learning curve of the new technique, which is associated with worse outcomes (10, 11). Despite the limited number of comparative studies, results show equality of the three techniques with regard to short-term results (8, 11-13).

Evidence regarding oncologic outcomes is scarce. Lately, case series have reported on the oncologic results of minimally invasive techniques for TME. High local recurrence rates have been found in series reporting on the initial cases managed using TaTME, leading to the suspension of TaTME in Norway (14, 15). Similarly, a high local recurrence rate has been reported in a comparative study of R-TME (16). On the other hand, low local recurrence rates for both techniques have been reported as well (17-20).

In conclusion, robust data comparing all three techniques regarding oncologic outcomes taking into account the learning curve are lacking. Therefore, this multicenter cohort study aimed to compare the 3-year oncologic outcomes of laparoscopic, robot-assisted, and transanal sphincter-saving TME performed by surgeons well beyond their learning curve.

METHODS

A retrospective multicenter cohort study was performed to compare L-TME with R-TME and TaTME performed in five dedicated laparoscopy centers, three dedicated robot-assisted centers, and three dedicated TaTME centers between 2015 and 2017. A protocol regarding the design, methods, and statistical analysis was composed before initiation of the study. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (21).

Design

Centers were able to participate in this multicenter population-based cohort if they were "dedicated centers" for L-TME, R-TME, or TaTME and only one of the techniques was the standard technique. In addition, colorectal surgeons performing TME in the specific center had to be well beyond the learning curve for the specific technique, which is estimated to be about 40 procedures for R-TME and TaTME (22-25).

The dedicated robot-assisted centers were three large teaching hospitals who started using R-TME in 2011, 2012, and 2014, respectively. The dedicated TaTME centers were three large teaching hospitals who started using TaTME in 2012, 2012, and 2014, respectively. With an average of 50 procedures per center annually and a maximum of two dedicated colorectal surgeons per center performing the procedure, it was estimated that all surgeons in the dedicated TaTME and robot-assisted centers that started using R-TME or TaTME in 2011 or 2012 were well beyond their learning curve at the beginning of the study. The two centers with start dates in 2014 fulfilled the learning curve in 2015. Therefore, in these centers, patients were included from 1 January 2016 until 31 December 2017. Finally, with more than 10 years of experience performing L-TME in the dedicated laparoscopic centers, these surgeons were estimated to be well beyond their learning curve as well. Altogether, 12 L-TME surgeons, 6 R-TME surgeons, and 6 TaTME surgeons participated in this study.

Patients

Patients were eligible for inclusion if they had a diagnosis of rectal cancer according to the new definition using the sigmoidal take-off on magnetic resonance imaging (MRI) or computed tomography (CT) (26), were older than 18 years, were registered in the prospective Dutch ColoRectal Audit (DCRA), and had undergone an L-TME in a dedicated laparoscopic center, an R-TME in a dedicated robot-assisted center, or a TaTME in a dedicated TaTME center. Patients were excluded if they had undergone surgery in an emergency setting, had a synchronous metastasis during diagnosis of rectal cancer, had undergone treatment with palliative intent, had more than one colorectal tumor

at diagnosis, had undergone hyperthermic intraperitoneal chemotherapy (HIPEC) or intraoperative radiotherapy (IORT), had undergone transanal minimally invasive surgery (TAMIS), had undergone an abdominal perineal resection (APR), or had a surgeon performing the procedure who did not fulfil the learning curve. Each patient was discussed by a local multidisciplinary cancer board, and neoadjuvant treatment was offered according to the current Dutch National guidelines for colorectal cancer (27).

Outcomes

The primary outcome was overall survival (OS) after the 3-year follow-up period. Overall survival was defined as being alive at the 3-year follow-up evaluation. The secondary outcomes were disease-free survival (DFS) after the 3-year follow-up period, systemic recurrence after the 3-year follow-up period, local recurrence after the 3-year follow-up period, pattern of local recurrence, location of distant metastasis, and permanent stoma rate at the end of the follow-up period. Disease-free survival was defined as being alive without recurrent disease after the 3-year follow-up period. Systemic recurrence was defined as any distant metastasis, either pathologically proven or considered to be a lesion suspect for metastasis on imaging that showed growth on consecutive imaging. Local recurrence was defined as a tumor deposit located in the pelvic cavity, with pathologically proven adenocarcinoma or growth on consecutive imaging if histopathologic confirmation was absent. Multifocal local recurrence was defined as two or more separate deposits of recurrence in the pelvis. Location of local recurrence was classified according to the classification by Georgiou et al (28).

The baseline characteristics were age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, history of abdominal surgery, distance of the tumor from the anorectal junction (ARJ) on MRI, low defined rectal tumor according to the English National Low Rectal Cancer Development Programme (LOREC) (29), mesorectal fascia involvement (MRF) on preoperative MRI, neoadjuvant (chemo)radiation therapy, preoperative tumor-node-metastasis (TNM) classification, and type of procedure (low anterior resection [LAR] with end colostomy or LAR with primary anastomosis). Furthermore, pathologic TNM classification, histologic tumor type, positive circumferential resection margin (≤ 1 mm), quality of the TME specimen according to Quirke (30), 30-day postoperative mortality, 30-day surgical complications graded according to the Clavien-Dindo classification (31), and anastomotic leakage rate at the end of follow up according to the definition of the International Study Group of Rectal Cancer (32) were registered.

Data sources

All the hospitals provided their local DCRA data, including the unique patient number. After pseudonymisation, missing and incomplete data were added in the database by accessing the electronical medical record (EMR) of the local hospitals. In addition, local recurrence, systemic recurrence, survival data, and follow-up data were added using the EMR of the local hospitals. All preoperative MRI data were reviewed by trained researchers. Informed consent was deemed unnecessary according to the Dutch Medical Treatment Agreement Act. The regional medical ethical committee and local ethical committees of all the hospitals gave approval for the study (MEC-U, AW19.023 W18.100).

Statistical methods

Categorical data are presented as number and percentages. Continuous variables are presented as mean and standard deviation or median and interquartile range (IQR) depending on the distribution. Survival curves of the patients were plotted in Kaplan-Meier graphs. To control for confounding factors that might have influenced choice of the surgical technique, a Cox regression using a backward model was performed comparing the three techniques for 3-year overall-survival, 3-year DFS, 3-year local recurrence, and 3-year systemic recurrence. For the Cox regressions, missing data were imputed using multiple imputation if the type of the missing data was missing at random or missing completely at random.

The variables used in the Cox regression were age (continuous), sex, BMI (continuous), history of abdominal surgery, ASA classification (1/3 vs 3/4), distance of the tumor to the ARJ on MRI in centimeters (continuous), neoadjuvant (chemo)radiation therapy, and a variable combining clinical T stage and MRF involvement on preoperative MRI. This variable was graded as cT3 without MRF involvement, cT3 with MRF involvement, cT4a or cT4b. Whereas cT4a was defined as a tumor invading in the ventral peritoneum, cT4b was defined as a tumor invading the sphincter complex or an adjacent organ.

The regression models were evaluated for assumptions and adjusted if necessary. Hazard ratios (HRs) and p values were used to interpret the results. A confidence interval either below or above 1 was interpreted as significant. Analyses were performed with R (version 3.6.1) using the "survival" and "survminer" packages.

RESULTS

The study identified 1834 patients as eligible between 1 January 2015 and 31 December 2017. After excluding 764 patients, the study had 1070 candidate patients. Of these pa-

tients, 487 had surgery in a dedicated laparoscopy center, 340 had surgery in a dedicated robot-assisted center, and 243 had surgery in a dedicated TaTME center. Additionally, 153 patients had a resection performed by a technique that was not the standard technique of the dedicated center, and 300 patients underwent an abdominoperineal resection (APR) and were therefore excluded from the study.

Finally, 617 patients who underwent a low anterior resection (LAR) in a dedicated center were included in the analysis comprising 252 laparoscopic (L-LAR), 205 robot-assisted (R-LAR), and 160 TaTME procedures (Fig. 1). Abdominal perineal resection was performed for 202 patients (41.5%) in a laparoscopy center, for 106 patients (31.2%) in a robot-assisted center, and for 60 patients (24.7%) in a TaTME center. In the laparoscopy centers 56 (11.4%) patients did not undergo TME by the dedicated technique, and 27 (5.5%) of these patients underwent an open resection. In the robot-assisted and TaTME centers, respectively 34 (10.0%) and 62 (25.5%) patients did not undergo the dedicated technique, and respectively 5 (1.5%) and 8 (3.2%) of these patients underwent an open resection.

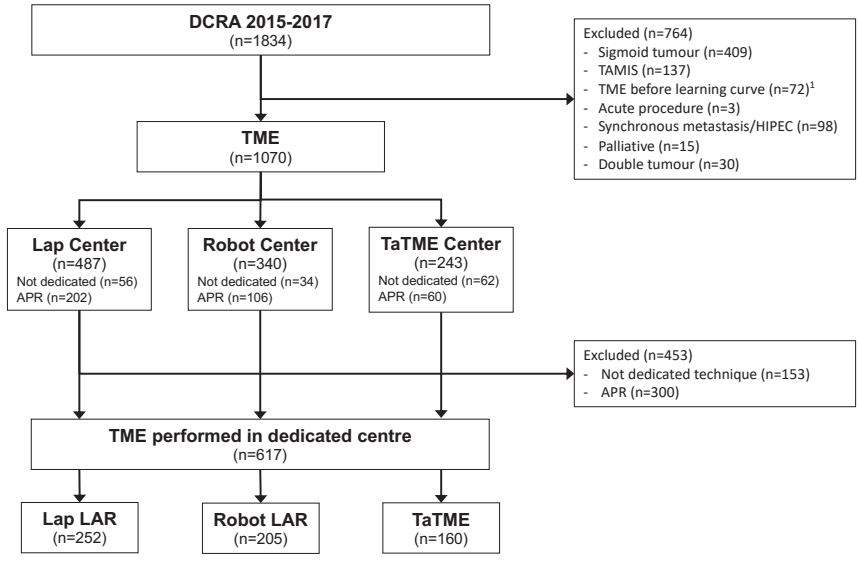

Fig. 1
Flow diagram of patients included in the study. *DCRA* Dutch Colorectal Audit, *TME* total mesorectal excision, *LAR* low anterior resection, *Lap* laparoscopic, *Robot* robot-assisted, *TaTME* transanal TME, *HIPEC* hyperthermal intraperitoneal chemotherapy, *IORT* intraoperative radiotherapy, *TEM* transanal endoscopic microsurgery, *APR* abdominoperineal resection. Patients who underwent surgery in 2015 at a TaTME or robot-assisted center that started performing TaTME or robot-assisted TME respectively in 2014

Patient characteristics

The mean patient age was higher in the laparoscopic L-LAR group than in the R-LAR and TaTME groups (68 ± 9.7 years vs. 66 ± 10.2 and 65 ± 10.9 years; p = 0.04). Data regarding race were not provided in the dataset. The median tumor distance from the ARJ on MRI was significantly greater in the L-LAR and R-LAR groups than in the TaTME group (7 ± 5.9 and 8 ± 6.9 cm vs. 4 ± 3.6 cm; p < 0.001). The L-LAR group had significantly less mesorectal fascia involvement than the R-LAR and TaTME groups (17.1% vs. 26.4% and 28.9%; p = 0.009). Furthermore, significantly fewer primary anastomoses were constructed in the L-LAR group than in the R- LAR and TaTME groups (68.3% vs. 91.2% and 82.5%; p < 0.001). Additionally, a significantly higher permanent stoma rate at the end of the follow-up period was observed in the L-TME group than in the R-TME and TaTME groups (42.1% vs. 22.0% and 31.2%) (Tables 1 and 2). Finally, the positive circumferential rate was 2.7% in the L-LAR group, 4.5% in the R-LAR group, and 3.2% in the TaTME group (p = 0.58).

Overall survival

The OS rate during the 3-year follow-up period was 90.0% in the L-LAR group, 90.4% in the R-LAR group, and 87.6% in the TaTME group (Table 2; Fig. 2). Cox regression did not show an association of the surgical technique with OS (Table 3). The factors associated with worse OS were age (HR 1.03; 95% confidence interval [CI], 1.00–1.06), ASA 3 and 4 (HR 6.63; 95% CI 3.66–12.0), cT3 MRF-tumor (HR, 2.05; 95% CI 1.01–4.16), and cT4b tumor (HR 6.77; 95% CI 2.04–22.4). Increased distance of the tumor to the ARJ was associated with improved OS (HR 0.88; 95% CI 0.79–0.98) (Table 3).

Disease-free survival

The DFS rate during the 3-year follow-up period was 77.8% in the L-LAR group, 75.8% in the R-LAR group, and 78.8% in the TaTME group (Table 2; Fig. 2). Cox regression did not show an association of the surgical technique with DFS. The factors associated with worse DFS were ASA 3 and 4 (HR 2.82; 95% CI 1.86–4.28), cT3 MRF-tumor (HR 1.76; 95% CI 1.07–2.90), cT4a tumor (HR 3.16; 95% CI 1.23–8.14), and cT4b tumor (HR 7.89; 95% CI 3.62–17.2) (Table 2).

Local recurrence

The local recurrence rate was 6.1% in the L-LAR group, 6.4% in the R-LAR group, and 5.7% in the TaTME group during the 3-year follow-up period. Multifocal recurrence was seen in 1 (7.1%) of 12 laparoscopic patients, 3 (18.8%) of 13 robot-assisted patients, and none of the TaTME patients (Table 2). Cox regression did not show an association of the surgical technique with local recurrence. The factors associated with local recurrence at 3 years were cT4a tumor (HR 11.58; 95% CI 2.40–55.8) and cT4b tumor (HR 12.94; 95% CI 2.64–64.0) (Table 4).

Table 1 Baseline characteristics

		L-LAR	R-LAR	TaTME	
		(*n* = 252) *n* (%)	(*n* = 205) *n* (%)	(*n* = 160) *n* (%)	*p* Value
Mean age (years)		68 ± 9.7	66 ± 10.2	65 ± 10.9	0.04
Mean BMI (kg/m^2)		26 ± 4.4	26 ± 3.8	26 ± 4.3	0.87
Sex	Male	155 (61.5)	128 (62.4)	111 (69.4)	0.24
	Female	97 (38.5)	77 (37.6)	49 (30.6)	
ASA classification	1	59 (23.4)	45 (22.0)	35 (21.9)	0.67
	2	137 (54.4)	123 (60.0)	95 (59.4)	
	3	53 (21.0)	37 (18.0)	29 (18.1)	
	4	3 (1.2)	0 (0.0)	1 (0.6)	
History of abdominal surgery		79 (31.3)	46 (22.4)	37 (23.1)	0.06
Median distance tumor to ARJ: cm (IQR)		7 (5–9)	8 (6–9)	4 [3, 6]	< 0.001
Low defined tumor[a]	Yes	110 (44.2)	69 (34.5)	80 (50.0)	0.01
	Missing	3 (1.2)	5 (2.4)	0 (0.0)	
Mesorectal fascia involvement on preoperative MRI	MRF+	43 (17.1)	53 (26.4)	46 (28.9)	0.009
	Missing	0 (0.0)	5 (2.4)	1 (0.6)	
cT	1	7 (2.8)	5 (2.4)	6 (3.8)	0.69
	2	80 (31.7)	66 (32.2)	42 (26.4)	
	3	156 (61.9)	117 (57.1)	104 (65.4)	
	4a	4 (1.6)	9 (4.3)	2 (1.3)	
	4b	5 (2.0)	7 (3.4)	5 (3.1)	
cN	0	108 (42.9)	87 (42.4)	86 (53.8)	0.04
	1	88 (34.9)	68 (33.2)	54 (33.8)	
	2	56 (22.2)	50 (24.4)	20 (12.5)	
	Missing	0 (0.0)	1 (0.5)	0 (0.0)	
Neoadjuvant therapy	None	109 (44.0)	82 (40.4)	64 (40.0)	0.46
	Radiotherapy	83 (33.5)	69 (34.0)	47 (29.4)	
	Chemoradiation	56 (22.6)	52 (25.6)	49 (30.6)	
	Missing	4 (1.6)	2 (1.0)	0 (0.0)	
Procedure	LAR + colostomy	80 (31.7)	18 (8.8)	28 (17.5)	< 0.001
	LAR + anastomosis	172 (68.3)	187 (91.2)	132 (82.5)	
Histologic type	Adenocarcinoma	240 (95.2)	196 (95.6)	155 (96.9)	0.38
	Mucinous	12 (4.8)	9 (4.4)	4 (2.5)	
	Other	0 (0.0)	0 (0.0)	1 (0.6)	
Differentiation	Well/moderate	233 (92.5)	184 (89.8)	146 (91.2)	0.90
	Poor	7 (2.8)	7 (3.4)	5 (3.1)	
	Unknown	12 (4.8)	14 (6.8)	9 (5.6)	

Table 1 Baseline characteristics (continued)

		L-LAR	R-LAR	TaTME	
		(*n* = 252) *n* (%)	(*n* = 205) *n* (%)	(*n* = 160) *n* (%)	*p* Value
pT	0	15 (6.0)	14 (6.9)	15 (9.4)	0.49
	1	28 (11.2)	25 (12.3)	22 (13.8)	
	2	99 (39.4)	66 (32.4)	55 (34.6)	
	3	107 (42.6)	93 (45.6)	64 (40.3)	
	4	2 (0.8)	6 (2.9)	3 (1.9)	
	Missing	1 (0.4)	2 (1.0)	1 (0.6)	
pN	0	166 (65.9)	136 (66.7)	114 (71.2)	0.60
	1	61 (24.2)	47 (23.0)	28 (17.5)	
	2	25 (9.9)	21 (10.3)	18 (11.2)	
	Missing	0 (0.0)	1 (0.5)	1 (0.6)	
CRM[b]	(≤ 1 mm)	4 (1.7)	9 (4.7)	4 (2.8)	0.18
	Missing	1 (0.4)	2 (1.0)	1 (0.6)	
Incomplete TME specimen		7 (2.9)	9 (4.4)	2 (1.3)	0.23
	Missing	8 (3.2)	1 (0.5)	5 (3.1)	
30-Day surgical complications		83 (32.9)	82 (40.0)	49 (30.6)	0.15
	CD ≥ 3	53 (21.0)	43 (21.0)	40 (25.0)	0.58
Anastomotic leakage[c]		30 (11.9)	33 (16.0)	26 (16.2)	0.85
30-Day mortality		4 (1.6)	3 (1.5)	0 (0.0)	0.29

L-LAR laparoscopic low anterior resection, *R-LAR* robot-assisted low anterior resection, *TaTME* transanal total mesorectal excision, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *ARJ* ano-rectal junction, *IQR* interquartile range, *MRI* magnetic resonance imaging, *MRF* mesorectal fascia involvement, *CRM* circumferential resection margin, *TME* total mesorectal excision, *CD* Clavien-Dindo classification grade

[1]Defined according to the English National Low Rectal Cancer Development Programme (LOREC)

[b]Positive CRM rate as percentage of patients with ypT1-4

[c]Anastomotic leakage as percentage of LAR with primary anastomosis

DISCUSSION

This study compared 3-year oncologic outcomes between L-LAR, R-LAR, and TaTME in dedicated centers while taking the learning curve into account. The results from this study showed equal oncologic outcomes for all three minimally invasive techniques. Comparable OS, DFS, local recurrence, and systemic recurrence were observed during the 3-year follow-up period. To our knowledge this is the first study to compare all three minimally invasive techniques performed by surgeons well beyond the learning curve of each specific technique, with the longest follow-up data presented to date.

Table 2 Oncologic results not corrected for preoperative characteristics

	L-LAR (*n* = 252) *n* (%)	R-LAR (*n* = 205) *n* (%)	TaTME (*n* = 160) *n* (%)	*p* Value
Median follow-up: months (IQR)	36 (25–46)	37 (26–45)	35 [25, 45]	0.83
3-Year overall survival	159 (90.0)	124 (90.4)	82 (87.6)	0.90
3-Year disease-free survival	121 (77.8)	97 (75.8)	73 (78.8)	0.76
3-Year local recurrence	12 (6.1)	12 (6.4)	7 (5.7)	0.82
Anterior	0 (0.0)	1 (0.5)	0 (0.0)	
Lateral	3 (1.1)	1 (0.5)	1 (0.6)	
Inferior	5 (2.0)	2 (1.0)	0 (0.0)	
Central anastomotic	2 (0.8)	5 (2.4)	3 (1.9)	
Central non-anastomic	6 (2.4)	6 (2.9)	0 (0.0)	
Peritoneal refletion	1 (0.4)	0 (0.0)	0 (0.0)	
Multifocal recurrence	1 (7.1)	3 (18.8)	0 (0.0)	0.47
3-Year systemic recurrence	32 (15.1)	28 (15.9)	15 (10.1)	0.43
Liver	21 (8.3)	13 (6.3)	8 (5.0)	
Lung	17 (6.7)	14 (6.8)	8 (5.0)	
Peritoneal	3 (1.2)	5 (2.4)	2 (1.2)	
Bone	1 (0.4)	2 (1.0)	2 (1.2)	
Ovary	1 (0.4)	0 (0.0)	0 (0.0)	
Brain	1 (0.4)	0 (0.0)	0 (0.0)	
Other	4 (1.6)	2 (1.0)	4 (2.5)	
Permanent stoma rate[a]	106 (42.1)	45 (22.0)	50 (31.2)	<0.001

L-LAR laparoscopic low anterior resection, *R-LAR* robot-assisted low anterior resection, *TaTME* transanal total mesorectal excision, *IQR* interquartile range
[a]Permanent stoma rate at the end of the follow-up period

The OS survival rates at 3 years in this study were 90.0% for the laparoscopic, 90.4% for the robot-assisted, and 87.6% for the TaTME technique. The corresponding DFS rates at 3 years were 77.8%, 75.8 and 78.8%. For both outcomes, no difference between the three techniques was observed in the multivariable Cox regression. First, these results showed the high quality of oncologic outcomes in the dedicated centers, underscoring our assumption that the included centers were dedicated and beyond the learning curve for the specific technique. The aforementioned rates are comparable with those of large trials comparing L-TME with open TME such as the AlaCaRT, ACOSOG Z6501, COREAN and COLOR II trials (2, 4, 5, 33). All these trials used strict inclusion criteria and excluded ASA 4 patients or cT4 tumors. In contrast, the current population-based cohort presents a more realistic image of clinical practice, with better external validity than the randomized clinical trials.

Second, these results show comparable oncologic outcomes among all three techniques. This is the first analysis to compare all three techniques. To date, no comparative oncolog-

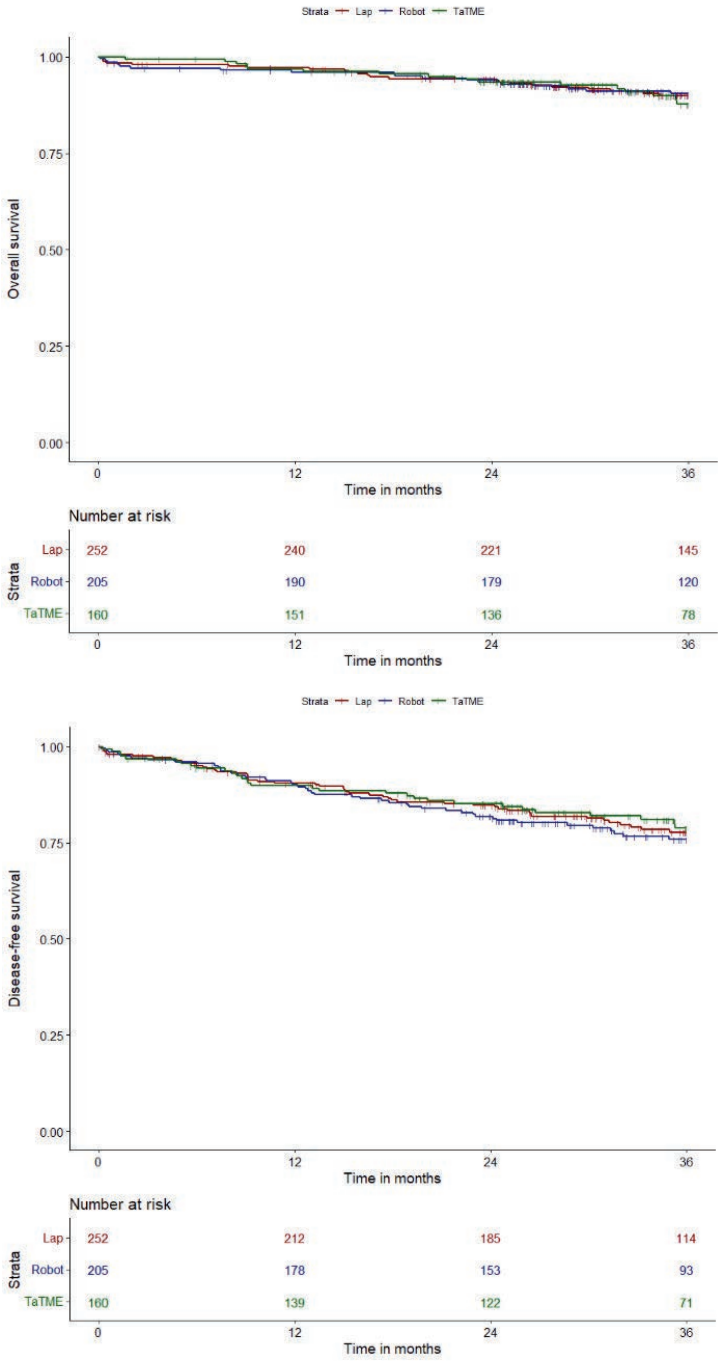

Fig. 2 Curves showing 3-year overall and disease-free survival. *Lap* laparoscopic low anterior resection, *Robot* robot-assisted low anterior resection, *TaTME* transanal total mesorectal excision

Table 3 Cox regression of 3-year overall survival (OS) and disease-free survival (DFS)

		3-Year OS			3-Year DFS		
		HR	**95% CI**	***p* Value**	**HR**	**95% CI**	***p* Value**
Approach	L-LAR	–	–	–	–	–	–
	R-LAR	1.31	(0.69–2.50)	0.42	1.18	(0.78–1.79)	0.44
	TaTME	0.78	(0.37–1.63)	0.50	0.75	(0.45–1.28)	0.29
Age		1.03	(1.00–1.06)	0.05	1.00	(0.99–1.02)	0.65
BMI (kg/m^2)		0.99	(0.94–1.05)	0.76	0.98	(0.94–1.02)	0.32
Sex	Male	1.10	(0.59–2.03)	0.75	1.33	(0.89–1.99)	0.16
ASA classification	3/4	6.62	(3.66–12.0)	< 0.001	2.82	(1.86–4.28)	<0.001
History of abdominal surgery	Yes	0.93	(0.51–1.72)	0.83	1.26	(0.83–1.91)	0.27
Distance tumor to ARJ		0.88	(0.79–0.98)	0.02	0.94	(0.88–1.02)	0.12
cT/MRF	cT3, MRF-	2.05	(1.01–4.16)	0.05	1.76	(1.07–2.90)	0.03
	cT3, MRF+	0.84	(0.31–2.32)	0.74	1.23	(0.64–2.35)	0.53
	cT4a	1.53	(0.31–7.42)	0.60	3.16	(1.23–8.14)	0.02
	cT4b	6.77	(2.04–22.4)	0.001	7.89	(3.62–17.2)	< 0.001
cN	cN+	0.91	(0.39–2.12)	0.83	0.84	(0.49–1.44)	0.53
Neoadjuvant therapy	Yes	1.11	(0.45–2.73)	0.83	1.25	(0.69–2.26)	0.46

HR hazard ratio, *CI* confidence interval, *L-LAR* laparoscopic low anterior resection, *R-LAR* robot-assisted low anterior resection, *TaTME* transanal total mesorectal excision, *BMI* body mass index, *OR* odds ratio, *BMI* body mass index, *ASA* American society of anesthesiologists, *ARJ* anorectal junction

Table 4 Cox regression of 3-year local recurrence and 3-year systemic recurrence

		3-year Local recurrence			3-year Systemic recurrence		
		HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Approach	L-LAR	–	–	–	–	–	–
	R-LAR	1.25	(0.54; 2.86)	0.60	1.03	(0.61; 1.73)	0.91
	TaTME	0.51	(0.17; 1.51)	0.23	0.74	(0.37; 1.49)	0.40
Age		1.00	(0.96; 1.03)	0.81	0.99	(0.97; 1.01)	0.34
BMI (kg/m2)		1.03	(0.95; 1.12)	0.46	1.02	(0.96; 1.08)	0.57
Sex	Male	1.74	(0.75; 4.06)	0.20	1.29	(0.78; 2.13)	0.32
ASA classification	3/4	1.98	(0.79; 4.95)	0.15	1.48	(0.81; 2.71)	0.20
History of abdominal surgery	Yes	1.04	(0.43; 2.53)	0.92	1.81	(1.08; 3.02)	0.02
Distance tumour to ARJ		0.88	(0.76; 1.02)	0.08	1.01	(0.93; 1.11)	0.76
cT/MRF	cT3, MRF-	2.24	(0.79; 6.33)	0.13	1.52	(0.78; 2.93)	0.22
	cT3, MRF+	2.24	(0.58; 8.57)	0.24	1.42	(0.62; 3.19)	0.40
	cT4a	11.58	(2.40; 55.8)	0.002	4.63	(1.55; 13.9)	0.006
	cT4b	12.94	(2.62; 64.0)	0.002	7.76	(2.82; 21.4)	< 0.001
cN	cN+	0.55	(0.20; 1.54)	0.26	0.98	(0.48; 2.00)	0.96
Neoadjuvant therapy	Yes	0.91	(0.30; 2.75)	0.87	1.56	(0.70; 3.48)	0.28

TaTME Transanal total mesorectal excision, *OR* odds ratio, *CI* confidence interval, *BMI* body mass index, *ASA* American society of anesthesiologists, *ARJ* anorectal junction

ic data regarding TaTME have been published. Retrospective cohort analyses regarding TaTME show a similar OS rate (19, 20). Studies comparing oncologic results after R-TME with L-TME are scarce, but mainly confirm our results. Although studies show comparable OS and DFS between R-TME and L-TME (16, 34-36), a recent propensity score-matched analysis showed significantly better OS and DFS in the R-TME group than in the L-TME group (37). However, this might have been caused by a relatively high rate of distant metastasis in the L-TME group, whereas the local recurrence rate was equal. Because systemic recurrence is suggested to be a mere result of the biologic behavior and tumor stage at presentation and a less relevant outcome regarding quality of surgery, the difference in OS and DFS might not be attributable to a difference in technique.

Local recurrence was present in 6.1% of L-LAR, 6.4% of R-LAR, and 5.7% of TaTME procedures. The multivariable Cox regression did not show any difference between the three techniques, indicating adequate surgical quality and safe surgery for all three minimally invasive techniques in the dedicated centers. These results are comparable with those of large randomized controlled trials comparing L-TME with open TME surgery. However, these trials did not include patients with T4 or T3 tumors that had mesorectal fascia involvement (2, 4, 5, 33). Furthermore, we used the rectal cancer definition as proposed by D'Souza et al (26). The exclusion of "rectosigmoid"' cancers could have led to the inclusion of relatively more low rectal cancers, and therefore to more difficult tumors because this is a known risk factor for local recurrence (38).

Recently, local recurrence rates after TaTME in Norway were reported to be 9.5%, and a significant proportion of multifocal recurrences were reported, leading to a nationwide halt of TaTME (14). Similar results were seen in the initial cases of centers learning the TaTME technique in the Netherlands (15). However, higher local recurrence rates also have been reported in the initial cases of R-TME and L-TME (16, 39). Although these studies suggest higher local recurrence rates during the learning curve, our results showed that adequate oncologic results can be obtained for L-LAR, R-LAR, and TaTME in experienced centers after fulfilment of the learning curve, in accordance with other series (19, 20, 40). Furthermore, no increased rate of multifocal recurrences was observed. Earlier reports on local recurrence after R-TME describe lower rates, but these retrospective cohorts had short follow-up times, with younger patients, lower BMI, and lower rates of neoadjuvant therapy than our cohort, which may suggest selection bias in these studies (18, 35, 37, 41-43).

Certain limitations of this study should be taken into account. First, this was a retrospective cohort study. Therefore, a certain degree of bias was present. However, we tried to overcome confounding by indication, using multivariable analysis to control for baseline characteristics that might have influenced the choice for a certain surgical

technique preoperatively. Our primary aim was to assess whether surgical technique would influence oncologic outcomes for TME. Therefore, we took into account only preoperative variables and did not control for postoperative variables such as pathologic TNM stage or positive circumferential resection margins because these postoperative variables are a result of the surgical technique.

Preferably, a prospective randomized controlled trial should be performed to evaluate the three minimally invasive procedures. In practice, however, randomization is hard to achieve because it can be doubted whether surgeons could be equally trained in each technique. Therefore, this population-based cohort was possibly a suitable alternative providing the current state of surgical practice with high external validity, in contrast to randomized controlled trials showing mostly low external validity due to strict inclusion and exclusion criteria. Nevertheless, because this was a retrospective cohort, the results should be replicated in a prospective study.

Second, because the surgical techniques were performed in dedicated centers, the institution itself could have influenced the outcomes as well. Adjustments could not be made for culture-, surgeon-, or team-related factors. However, by including more than one center per group, we tried to reduce this effect.

Third, we chose to select only patients who underwent a TME and excluded patients who underwent an APR. The patients who required an APR in a dedicated TaTME center underwent either a laparoscopic or an open APR because an APR is not an indication for the TaTME technique in the current Dutch clinical practice. Because we were interested in comparing the robot-assisted technique with the laparoscopic and TaTME techniques, in order to create homogeneous groups we decided to exclude patients who needed an APR. However, because APR is associated with worse oncologic outcomes, this might have influenced outcomes. Nevertheless, by excluding APR in all three groups, we tried to reduce confounding.

Finally, although we included only patients who underwent a minimally invasive TME at a dedicated center in which the learning curve had been fulfilled, the difference in experience could not be reduced to nil. The 10-year experience of the laparoscopic surgeons still exceeded the 3- to 5-year experience of the robot-assisted and TaTME surgeons.

Despite these limitations, this is the first study to show good and comparable oncologic results between R-LAR , L-LAR, and TaTME in centers with profound experience using the specific technique. All three techniques showed adequate OS and DFS rates. Moreover,

the recurrence rates are equal between the three minimally invasive techniques when performed by experienced surgeons, and multifocal recurrence rates are low. Therefore, oncologic safety can be achieved with all three minimally invasive techniques when performed by experienced surgeons. Prospective cohort studies comparing oncologic outcomes after fulfillment of the learning curve are needed to confirm our results.

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CHAPTER 8

THREE-YEAR ONCOLOGICAL RESULTS AFTER TOTAL MESORECTAL EXCISION FOR MRI-DEFINED LOW RECTAL CANCER

JC Hol*, TA Burghgraef *, MLW Rutgers, RMPH Crolla, AAW van Geloven, JWA Leijtens, F Polat, A Pronk, AB Smits, JB Tuynman, EGG Verdaasdonk, ECJ Consten, R Hompes, C Sietses
* Shared first authorship

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ABSTRACT

***Background*:** Total mesorectal excision (TME) is the standard for curative rectal cancer surgery. Distal rectal cancer remains more challenging. Long-term data regarding distal rectal cancer based on a strict anatomical definition are scarce. Although there is a trend towards more sphincter preserving low anterior resection (RLAR) instead of abdomino-perineal resection (APR) surgery, surgeons often choose to perform a non-restorative LAR (NRLAR). Little oncological outcome data are available for NRLAR.

***Objective*:** The aim of this study was to compare oncological outcomes depending on whether patients had a MRI-defined low rectal cancer (LOREC). The second aim was to assess the impact of each type of procedure (APR, NRLAR or RLAR) on oncological outcomes.

Design: Retrospective cohort study.

Settings: Data from eleven Dutch hospitals were included.

Patients: Patients undergoing TME between 2015 and 2017.

Intervention: A comparison was made depending on whether patients had a LOREC or non-LOREC tumour. A second comparison was made for each different type of surgery (APR, NRLAR or RLAR) and approach (laparoscopic, robot-assisted or transanal TME).

Main outcome measures: 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*:** In 998 patients 3-year oncological results did not differ between LOREC and non-LOREC or types of approach. NRLAR was associated with worse 3-year OS in all patients (HR: 1.74 (95%CI: 1.02-2.97), p=0.04) and in non-LOREC (HR: 2.25 (95%CI: 1.10-4.60), p=0.03). NRLAR was associated with worse 3-year DFS in all patients (HR: 1.99 (95%CI: 1.38-2.87), p<0.001), and in non-LOREC (HR: 2.20 (95%CI: 1.33-3.62), p=0.002). NRLAR was associated with worse 3-year LR rates in all patients (HR 2.87 (95%CI: 1.44-5.70), p=0.003), and in non-LOREC (HR 2.91 (95%CI: 1.17-7.21), p=0.02).

***Conclusions*:** NRLAR was associated with poorer oncological outcome than RLAR and APR. This might reflect technical difficulties during the procedure.

INTRODUCTION

The past decades there has been a shift from open surgery to minimally invasive techniques for total mesorectal excision (TME) for rectal cancer (1). Laparoscopic TME offers short-term benefits but it has not been proven superior in terms of long-term oncological outcomes (2-4). Robot-assisted TME and TaTME have been introduced to further improve results after laparoscopic TME and short-term results on these two new techniques looked promising (5-7). Although not proven in large randomized studies, long-term oncological results of these two techniques seem equal to those of conventional laparoscopic TME (8-11). Whereas most studies have examined the surgical techniques; few examined other factors that could influence long-term oncological outcomes after TME.

The LOREC MRI-based definition for low rectal cancer is based on anatomical landmarks where the tapering of the mesorectum starts, focussing on a patient group known to pose greater risk for positive resection margin by more difficult dissection (12). Most clinical studies have been using an arbitrary cut-off point from the anal verge as definition of the rectum. In the distal part of the rectum there is limited space to mobilize the rectum with intact mesorectum. This might lead to suboptimal oncological planes with involved margins and high conversion rates in distal tumours (13, 14). This is associated with worse oncological outcome (15, 16).

In contrast to daily practice, the proportion of non-restorative procedures in randomized trials is relatively small. Although there is a trend toward more sphincter preserving low anterior resection (LAR) rates of abdominoperineal resection (APR) and non-restorative LAR (NRLAR) are still high (17, 18). In particular for NRLAR little published data exists on oncological outcomes after NRLAR, compared to restorative LAR (RLAR) for primary rectal cancer. Moreover, previous studies have reported NRLAR might be associated with worse oncological outcome (19, 20).

The primary aim of this study was to explore 3-year oncological outcomes for rectal cancer, depending on whether there was a MRI defined low rectal (LOREC) cancer. Second, to explore whether the surgical treatment (APR, NRLAR or RLAR) and surgical approach has an impact on oncological outcome.

METHODS

Study design

A retrospective cohort study was performed in eleven dedicated rectal cancer centres in the Netherlands with large 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 technique the centre had most experience with (laparoscopic in 5 centres, robot-assisted in 3, TaTME in 3). All patients undergoing rectal resection for primary rectal cancer 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 (21). 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 because the learning curve had not yet fully run its course. Missing data was complemented using patients EMR and all preoperative MRI were reviewed by trained researchers. 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.

First, a comparison was made depending on whether patients had a low rectal tumour, according to the definition of the English National low rectal cancer development program (LOREC): "tumour with its lower border at or below the origin of the levators on the pelvic sidewall" based on sagittal MRI images (12). Second, a comparison was made for each different type of procedure (APR, NRLAR or RLAR) and most used type of surgical approach per centre (laparoscopic, robot-assisted or TaTME). Multivariate analyses were performed to compare 3-year oncological results.

Outcomes and definitions

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 and clinical TNM stage.

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 defied 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. Mucosectomy was scored as an APR. Quality of the TME specimens was defined according to Quirke et al (22). Positive circumferential margin (CRM) was defined as a margin of 1mm or less.

The primary outcome was overall survival (OS) at 3 years of follow-up. Overall survival was defined as the proportion of patients alive. Secondary outcomes were 3-year disease free survival (DFS), 3-year local recurrence (LR) rate and rate of multifocal recurrence. DFS 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. LR was defined as any tumour deposit in the pelvic cavity 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 (23). Multifocal recurrence was defined as presence of more than one pelvic lesion.

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 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, depending on whether patients had a LOREC tumour. Missing data was imputed using multiple imputations if the type of missing data was missing at random or completely at random. 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".

RESULTS

A total of 998 patients were included of which 596(59.7%) had a LOREC tumour. A flowchart can be seen in Figure 1.

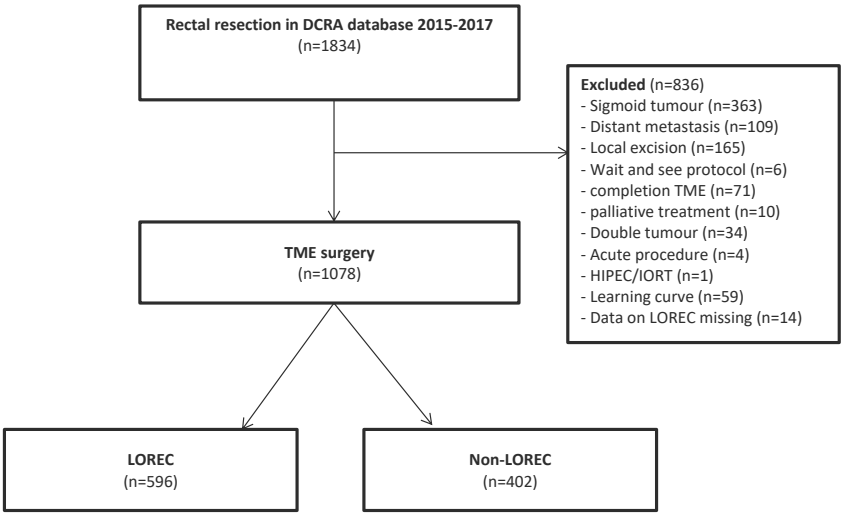

Figure 1 flowchart
Abbreviations: DCRA=Dutch ColoRectal Audit, HIPEC/IORT=hyperthermic intraperitoneal chemotherapy/intra-operative radiotherapy, LOREC=MRI-defined low rectal tumour

Baseline comparison for LOREC and non-LOREC

Comparing LOREC to non-LOREC, it can be seen that in the LOREC subset of patients median distance to ARJ in cm on MRI was lower, rate of MRF involvement on prestaging MRI was higher, rate of cT4 was higher, more neoadjuvant chemo radiation was administered and restorative rates were lower (33.2% vs 75.9%, p<0.001) (Table 1).

Baseline comparison per procedure

Table 1 gives a baseline comparison per type of procedure. In the LOREC subset of patients, in the NRLAR group, mean age was higher, rate of ASA III was higher (27.9% compared to 21.5% in APR and 11.1% in RLAR, p=0.006) and patients more frequently had a history of abdominal surgery (48.5% compared to 28.5% in APR and 25.3% in RLAR, p=0.001). The rate of MRF involvement on pre-operative MRI was highest in APR (44.0%), compared to NRLAR (22.4%) and RLAR (23.7%), p<0.001. The rate of cT4 tumours was higher in APR (15.5%), compared to NRLAR (6.0%) and RLAR (5.1%), p<0.001. Distance of the tumour to the ARJ was lowest in APR.

Of 402 that had a non-LOREC tumour, 33 underwent APR, 64 NRLAR and 305 RLAR. In the non-LOREC subset of patients the mean age and rate of ASA III was higher in the NRLAR group. History of abdominal surgery was more frequent in the APR group.

Table 1 Baseline comparison and restorative rates per type of procedure

		LOREC					Non- LOREC					
		Total	**APR**	**NRLAR**	**RLAR**	**p-value**	**Total**	**APR**	**NRLAR**	**RLAR**	**p-value**	**p-value (LOREC vs non-LOREC)**
N		596	330	68	198		402	33	64	305		
Age in years (mean(SD))		67.16 (10.67)	68.29 (10.52)	72.93 (9.32)	63.31 (10.04)	<0.001	66.81 (10.17)	68.94 (8.99)	75.69 (9.17)	64.72 (9.43)	<0.001	0.601
BMI (mean(SD))		26.11 (4.19)	26.36 (4.11)	26.62 (5.28)	25.54 (3.86)	0.053	26.22 (4.43)	27.78 (4.85)	26.43 (4.69)	26.01 (4.31)	0.086	0.698
Sex (%)	Male	373 (62.6)	215 (65.2)	38 (55.9)	120 (60.6)	0.277	268 (66.7)	24 (72.7)	43 (67.2)	201 (65.9)	0.728	0.210
	Female	223 (37.4)	115 (34.8)	30 (44.1)	78 (39.4)		134 (33.3)	9 (27.3)	21 (32.8)	104 (34.1)		
ASA (%)	I	121 (20.3)	62 (18.8)	7 (10.3)	52 (26.3)	0.006	78 (19.4)	1 (3.0)	5 (7.8)	72 (23.6)	<0.001	0.586
	II	357 (59.9)	194 (58.8)	41 (60.3)	122 (61.6)		235 (58.5)	20 (60.6)	32 (50.0)	183 (60.0)		
	III	112 (18.8)	71 (21.5)	19 (27.9)	22 (11.1)		87 (21.6)	12 (36.4)	26 (40.6)	49 (16.1)		
	IV	6 (1.0)	3 (0.9)	1 (1.5)	2 (1.0)		2 (0.5)	0 (0.0)	1 (1.6)	1 (0.3)		
History of abdominal surgery (%)		177 (29.7)	94 (28.5)	33 (48.5)	50 (25.3)	0.001	105 (26.1)	15 (45.5)	19 (29.7)	71 (23.3)	0.018	0.246
Distance of tumor to ARJ on MRI in centimeters (median[IQR])		3.00 [1.00, 5.00]	1.00 [0.00, 3.00]	5.00 [3.00, 6.00]	4.50 [3.00, 6.00]	<0.001	8.00 [6.00, 10.00]	7.00 [5.00, 8.00]	7.90 [6.00, 9.00]	8.00 [6.30, 10.00]	0.008	<0.001
MRF involvement on MRI (%)	MRF involved	206 (34.8)	144 (44.0)	15 (22.4)	47 (23.7)	<0.001	110 (27.8)	13 (40.6)	24 (38.7)	73 (24.2)	0.016	0.025

Table 1 Baseline comparison and restorative rates per type of procedure (continued)

		LOREC					Non- LOREC					
		Total	**APR**	**NRLAR**	**RLAR**	**p-value**	**Total**	**APR**	**NRLAR**	**RLAR**	**p-value**	**p-value (LOREC vs non-LOREC)**
cT (%)	1	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.5)	<0.001	8 (2.0)	0 (0.0)	0 (0.0)	8 (2.6)	0.588	0.004
	2	168 (28.3)	102 (31.0)	13 (19.4)	53 (26.8)		117 (29.2)	8 (24.2)	17 (27.0)	92 (30.2)		
	3	360 (60.6)	176 (53.5)	50 (74.6)	134 (67.7)		249 (62.1)	24 (72.7)	41 (65.1)	184 (60.3)		
	4	65 (10.9)	51 (15.5)	4 (6.0)	10 (5.1)		27 (6.7)	1 (3.0)	5 (7.9)	21 (6.9)		
cN (%)	0	257 (43.3)	147 (44.5)	29 (43.3)	81 (41.1)	0.760	179 (44.5)	12 (36.4)	25 (39.1)	142 (46.6)	0.267	0.173
	1	193 (32.5)	109 (33.0)	19 (28.4)	65 (33.0)		145 (36.1)	11 (33.3)	23 (35.9)	111 (36.4)		
	2	144 (24.2)	74 (22.4)	19 (28.4)	51 (25.9)		78 (19.4)	10 (30.3)	16 (25.0)	52 (17.0)		
Neoadjuvant therapy (%)	None	197 (33.6)	99 (30.7)	27 (40.9)	71 (35.9)	0.351	168 (42.4)	12 (37.5)	26 (41.9)	130 (43.0)	0.447	<0.001
	Radiotherapy	178 (30.3)	99 (30.7)	21 (31.8)	58 (29.3)		134 (33.8)	12 (37.5)	26 (41.9)	96 (31.8)		
	Chemoradiation	212 (36.1)	125 (38.7)	18 (27.3)	69 (34.8)		94 (23.7)	8 (25.0)	10 (16.1)	76 (25.2)		
Surgical procedure (%)	APR	330 (55.4)	330 (100.0)	0 (0.0)	0 (0.0)	<0.001	33 (8.2)	33 (100.0)	0 (0.0)	0 (0.0)	<0.001	<0.001
	NRLAR	68 (11.4)	0 (0.0)	68 (100.0)	0 (0.0)		64 (15.9)	0 (0.0)	64 (100.0)	0 (0.0)		
	RLAR	198 (33.2)	0 (0.0)	0 (0.0)	198 (100.0)		305 (75.9)	0 (0.0)	0 (0.0)	305 (100.0)		

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; LAR=low anterior resection;

Baseline comparison per approach

In the LOREC subset of patients, patients that underwent TME in a TaTME centre had lower distance to the ARJ and more cN0. In the non-LOREC subset of patients, patients that underwent TaTME had lower distance to ARJ on MRI and lower rate of MRF involvement. Patients in the robot-assisted group more frequently underwent RLAR (85.7%), compared to laparoscopic (65.2%) and TaTME (78.7%, p<0.001). NRLAR was most frequently observed in the laparoscopic group (24.8%), compared to robot-assisted (9.5%) and TaTME (10.6%, p<0.001). See supplementary Table 1 for a baseline comparison per technique.

Short-term outcome

Positive CRM rates were comparable between LOREC and non-LOREC (6.1% vs 3.8%, p=0.161). In the LOREC subset of patient, positive CRM rate was highest after APR (8.5%), compared to NRLAR (4.5%) and RLAR (4.7%) (p=0.04). See supplementary Table 2 for an overview of short-term outcomes.

Three-year oncological outcome

Table 2 gives a comparison of oncological outcome. There were no differences in oncological outcome comparing LOREC and non-LOREC (3-year OS 88.3% and 88.0% respectively, p=0.35). In the LOREC subset of patients worse 3-year DFS was seen after NRLAR (60.6%, compared to 71.0% in APR and 81.2% in RLAR, p=0.014). Three-year LR rate was 12.7% in NRLAR, 5.4% in RLAR and 5.7% in APR (p=0.17).

In the non-LOREC subset of patients worse 3-year OS, 3-year DFS and 3-year LR rate was seen after NRLAR compared to APR and RLAR. Three-year OS was 73.6% in NRLAR, 92.7% in RLAR and 75.0% in APR (p=<0.001). Three-year DFS was 59.2% in NRLAR, 79.5% in RLAR and 66.1 in APR (p=0.002). Three-year LR rate was 16.3% in NRLAR, 5.1% in RLAR and 0.0% in APR (p=0.01).

There were no differences in oncological outcome comparing laparoscopic, robot-assisted and TaTME centres (Supplementary Table 3).

The impact of different prognostic factors on 3-year OS is shown in Table 3. NRLAR was associated with worse OS in all patients (HR: 1.74 (95%CI: 1.02-2.97), p=0.04) and in non-LOREC (HR: 2.25 (95%CI: 1.10-4.60), p=0.03). In all patients, other factors associated with worse 3-year OS were: higher age, male sex, ASA III/IV and cT4.

The impact of different prognostic factors on 3-year DFS is shown in Table 4. NRLAR was associated with worse DFS in all patients (HR: 1.99 (95%CI: 1.38-2.87), p<0.001), and in

Table 2: Oncological outcome per type of procedure

		LOREC					Non- LOREC					
		Total	**APR**	**NRLAR**	**RLAR**	**p-value**	**Total**	**APR**	**NRLAR**	**RLAR**	**p-value**	**p-value (LOREC vs Non-LOREC)**
N		596	330	68	198		402	33	64	305		
Follow up in months (median[IQR])		35.31 [24.87, 45.75]	34.77 [24.15, 47.74]	30.23 [23.52, 41.84]	36.28 [25.93, 44.45]	0.184	36.26 [25.48, 46.43]	37.61 [24.52, 48.13]	32.23 [14.70, 41.38]	36.95 [26.30, 47.61]	0.015	0.276
3-year overall survival (%)		534 (88.3)	294 (87.5)	57 (82.9)	183 (91.5)	0.2	359 (88.0)	25 (75.0)	49 (73.6)	285 (92.7)	< 0.001	0.83
3-year disease free survival (%)		455 (73.3)	245 (71.0)	46 (60.6)	164 (81.2)	0.014	313 (75.3)	22 (66.1)	42 (59.2)	249 (79.5)	0.002	0.49
3-year local recurrence (%)		29 (5.9)	15 (5.7)	6 (12.7)	8 (5.4)	0.17	20 (6.2)	0 (0.0)	7 (16.3)	13 (5.1)	0.01	1.000
Location of local recurrence	Anterior	2 (0.3)	2 (0.6)	0 (0.0)	0 (0.0)		3 (0.7)	0 (0.0)	1 (1.6)	2 (0.7)		
	Lateral	8 (1.3)	6 (1.8)	0 (0.0)	2 (1.0)		4 (1.0)	0 (0.0)	1 (1.6)	3 (1.0)		
	Inferior	8 (1.3)	4 (1.2)	2 (3.0)	2 (1.0)		5 (1.2)	0 (0.0)	3 (4.8)	2 (0.7)		
	Central, anastomotic	7 (1.2)	2 (0.6)	0 (0.0)	5 (2.5)		3 (0.7)	0 (0.0)	0 (0.0)	3 (1.0)		
	Central, non-anastomotic	14 (2.4)	6 (1.8)	6 (9.0)	2 (1.0)		8 (2.0)	0 (0.0)	5 (7.9)	3 (1.0)		
Location of local recurrence	Peritoneal reflection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		1 (0.2)	0 (0.0)	1 (1.6)	0 (0.0)		
	Multifocal local recurrence	3 (8.3)	2 (11.8)	0 (0.0)	1 (8.3)		4 (16.7)	0 (0.0)	2 (22.2)	2 (14.3)	0.796	0.566

Table 2: Oncological outcome per type of procedure (continued)

		LOREC					Non- LOREC					
		Total	**APR**	**NRLAR**	**RLAR**	**p-value**	**Total**	**APR**	**NRLAR**	**RLAR**	**p-value**	**p-value (LOREC vs Non-LOREC)**
3-year systemic recurrence (%)		96 (18.8)	61 (21.6)	10 (19.1)	25 (14.3)	0.16	53 (15.2)	8 (26.0)	14 (28.5)	31 (11.7)	0.001	0.18
	Liver	44 (7.4)	26 (7.9)	7 (10.4)	11 (5.6)		30 (7.5)	6 (18.2)	7 (11.1)	17 (5.6)		
	Lung	63 (10.6)	41 (12.4)	7 (10.4)	15 (7.6)		27 (6.7)	5 (15.2)	8 (12.7)	14 (4.6)		
	Peritoneal	17 (2.9)	10 (3.0)	2 (3.0)	5 (2.5)		8 (2.0)	1 (3.0)	4 (6.3)	3 (1.0)		
	Bone	4 (0.7)	1 (0.3)	1 (1.5)	2 (1.0)		2 (0.5)	1 (3.0)	0 (0.0)	1 (0.3)		
	Ovary	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		1 (0.2)	0 (0.0)	0 (0.0)	1 (0.3)		
	Brain	4 (0.7)	3 (0.9)	0 (0.0)	1 (0.5)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
	Other	13 (2.2)	6 (1.8)	2 (3.0)	5 (2.5)		5 (1.2)	0 (0.0)	2 (3.2)	3 (1.0)		

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

Table 3 Multivariable Cox-regression analysis for Overall Survival *

		All patients		LOREC		Non-LOREC	
		HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age	70-80	1.88 (1.19, 2.98)	0.01	1.79 (0.99, 3.20)	0.051	2.25 (1.09, 4.70)	0.03
	>80	2.11 (1.19, 3.74)	0.007	2.13 (1.03, 4.39)	0.04	3.10 (1.18, 8.14)	0.02
Sex	Male	1.81 (1.16, 2.80)	0.008	2.05 (1.14, 3.68)	0.02		
ASA	III/IV	2.83 (1.89, 4.24)	<0.001	2.78 (1.62, 4.78)	<0.001	2.62 (1.38, 4.99)	0.003
cT4		2.33 (1.40, 3.87)	0.001	2.38 (1.29, 4.39)	0.006	2.67 (1.08, 6.61)	0.03
cN+						0.55 (0.30, 1.02)	0.06
Distance from ARJ on MRI	0-4cm					2.32 (0.67, 8.02)	0.19
	4-8cm					0.55 (0.29, 1.03)	0.06
	>8cm					Reference	
Procedure	APR	1.21 (0.77, 1.89)	0.41			3.11 (1.32, 7.32)	0.01
	NRLAR	1.74 (1.02, 2.97)	0.04			2.25 (1.10, 4,60)	0.03

Abbreviations: OR=odds ratio; ASA= American Society of Anesthesiologists; APR=abdominoperineal resection; NRLAR=non-restorative low anterior resection
*Variables included: surgical technique, age category, sex, ASA 1-2/3-4, distance form ARJ on MRI, MRF involvement, cT4, cN+, intraoperative change of plan, type of procedure (APR, NRLAR or RLAR)

Table 4 Multivariable Cox-regression analysis for Disease Free Survival *

		All patients		LOREC		Non-LOREC	
		HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age	70-80			1.52 (1.04, 2.20)	0.03		
	>80			1.70 (1.02, 2.83)	0.04		
Sex	Male	1.26 (0.96, 1.67)	0.10				
ASA	III/IV	1.95 (1.47, 2.58)	<0.001	1.82 (1.24, 2.66)	0.002	1.77 (1.13, 2.77)	0.013
cT4		2.77 (1.96, 3.91)	<0.001	2.18 (1.44, 3.32)	<0.001	3.77 (2.12, 6.73)	<0.001
cN+				1.38 (0.97, 1.95)	0.07		
Procedure	APR	1.30 (0.97, 1.74)	0.07			1.83 (0.95, 3.52)	0.07
	NRLAR	1.99 (1.38, 2.87)	<0.001			2.20 (1.33, 3.62)	0.002

Abbreviations: OR=odds ratio; ASA= American Society of Anesthesiologists; APR=abdominoperineal resection; NRLAR=non-restorative low anterior resection
*Variables included: surgical technique, age category, sex, ASA 1-2/3-4, distance form ARJ on MRI, MRF involvement, cT4, cN+, neoadjuvant therapy, intraoperative change of plan, type of procedure (APR, NRLAR or RLAR)

Table 5 Multivariable Cox-regression analysis for Local Recurrence *

		All patients		LOREC		Non-LOREC	
		HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Sex	Male	1.77 (0.93, 3.34)	0.08				
Distance from ARJ on MRI in centimeters	<6cm						
cT4		4.81 (2.42, 9.57)	<0.001	2.91 (1.24, 6.82)	0.02	5.07 (1.85, 13.94)	0.001
cN+		0.66 (0.37, 1.16)	0.15				
Procedure	APR	0.82 (0.42, 1.61)	0.57			NA	NA
	NRLAR	2.87 (1.44, 5.70)	0.003			2.91 (1.17, 7.21)	0.02

Abbreviations: OR=odds ratio; ASA= American Society of Anesthesiologists; APR=abdominoperineal resection; NRLAR=non-restorative low anterior resection
*Variables included: surgical technique, age category, sex, ASA 1-2/3-4, distance form ARJ on MRI, MRF involvement, cT4, cN+, neoadjuvant therapy, intraoperative change of plan, type of procedure (APR, NRLAR or RLAR)

non-LOREC (HR: 2.20 (95%CI: 1.33-3.62), p=0.002). In all patients, other factors associated with worse 3-year DFS were: male sex, ASA III/IV and cT4.

The impact of different prognostic factors on 3-year LR rate is shown in Table 5. NRLAR was associated with worse LR rate in all patients (HR 2.87 (95%CI: 1.44-5.70), p=0.003), and in non-LOREC (HR 2.91 (95%CI: 1.17-7.21), p=0.02). In all patients and in both the LOREC and non-LOREC subset of patients, cT4 was associated with worse 3-year LR rates.

DISCUSSION

In this retrospective multicentre cohort study from 11 Dutch hospitals, 998 patients undergoing elective primary rectal cancer resections were included. Oncological results did not differ between MRI-defined low rectal tumours and higher rectal tumours or for surgical approach. Non-restorative LAR (NRLAR) was associated with worse 3-year oncological results, compared to RLAR and APR. Before and after correction for confounding variables 3-year DFS, OS and LR were significantly worse after NRLAR.

Before and after correction for confounding variables NRLAR was associated with worse 3-year DFS and OS and higher LR rates, compared to RLAR and APR. This finding is consistent with that of Roodbeen et al who also found that NRLAR is associated with a higher risk of LR and worse OS (19). The observed 3-year OS, DFS and LR rates are consistent with large randomized trials comparing laparoscopic with open TME, such as COLOR II, ALaCART and ACOSOG Z6051 trial (2-4). The mesorectum tapers towards the distal rectum and becomes thinner. This leads to a more difficult dissection and many studies suggested that positive CRM rates increases as the distance to the anal verge increases (24). However, in the COLOR II trial laparoscopy was associated with lower positive CRM rates and lower LR rates in patients with distal rectal cancer (2). 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 (25). So far only short-term results of LOREC tumours have been reported (25, 26). The results of the present study did not show any difference in oncological results after laparoscopic, robot-assisted or TaTME for LOREC tumours. The main difference between the present study and previous studies on low-rectal cancer is this compared MRI defined low rectal tumours based on strict anatomical definition with other MRI-defined rectal tumours.

One of the most crucial factors for survival is whether a radical resection can be achieved (16). The number of positive CRM in this study was higher in NRLAR in the non-LOREC subset of patients (8.5%), while it was comparable for the LOREC subset of patients. These

results of the non-LOREC subset of patients reflect those of Andarin et al. who also found higher positive CRM rates in a study comparing RLAR and NRLAR (27). Margins of 5% in RLAR and 14% in NRLAR led to 5% and 10% 5-year LR rates. These results reflect those of Ortiz et al. who also found higher positive CRM rates and higher LR rates after NRLAR compared to RLAR (28). However, Roodbeen et al. also found higher LR rates after NRLAR, but found comparable positive CRM rates. Tapered specimens in distal tumours might be another explanation for the higher LR rates. The poorer oncological outcome after NRLAR might also be a reflection of technical difficulties during low pelvic dissection in a subset of patients. A long and difficult TME dissection might lead to the choice of construction of and end colostomy.

Pelvic sepsis is also linked to higher LR rates and especially anastomotic leakage could comprise oncological outcome (29, 30). Leaving a rectal stump after NRLAR may lead to formation of pelvic abscess by leakage or blow-out of the rectal stump (31). Jonker et al. showed fewer 30-day infective complications after low-Hartmann compared to LAR with anastomosis (32). 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 (31). In the present study, intra-abdominal abscess rates were similar after APR, NRLAR and RLAR in LOREC, but in non-LOREC higher abscess rates was seen after NRLAR, compared to APR and RLAR (own data). This higher rate of abscess formation might have contributed to the observed difference in oncological outcome.

A factor that might have influenced survival was radiotherapy. But radiotherapy was given equally to 30% in 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 higher cT and cN stage in NRLAR for LOREC. Intra-operative difficulties due to difficult dissection might also play a role in the decision to formation of and end colostomy. In this study, we tried to correct for such potential confounders using a multivariate analysis. Selection bias might be apparent because of the retrospective collection of the data. Moreover, there was no correction for EMVI or anterior location of the tumour, which are prognostic unfavourable factors (33).

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.

An APR should lead to equal risk of abscess formation (31). There is a currently ongoing randomized trial comparing APR with NRLAR with regard to postoperative surgical morbidity (34). Furthermore, within laparoscopic the highest percentage of NRLAR was present. Since both robot-assisted and TaTME were associated with low NRLAR rates, this finding favours both approaches for low rectal cancer in term of oncological outcomes.

Conclusion

This study identified that NRLAR for primary rectal cancer is associated with worse 3-year OS, DFS and higher LR rates than RLAR or APR. Three-year oncological results did not differ between MRI defined low rectal cancer (LOREC) and non-LOREC and 3-year oncological results did not differ between laparoscopic, robot-assisted or TaTME centres.

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Supplementary Table 1 Baseline comparison and restorative rates per approach

		LOREC					Non- LOREC					
		Total	Laparoscopy	Robot	TaTME	p-value	Total	Laparoscopy	Robot	TaTME	p-value	p-value (LOREC vs non-LOREC)
N		596	301	165	130		402	161	147	94		
Age in years (mean(SD))		67.16(10.67)	67.54(9.91)	68.02(10.71)	65.22(12.06)	0.056	66.81(10.17)	67.94(9.64)	65.89(10.79)	66.31(9.95)	0.180	0.601
BMI (mean(SD))		26.11(4.19)	26.30(4.40)	25.91(3.99)	25.94(3.96)	0.543	26.22 (4.43)	26.51 (4.53)	25.97 (4.03)	26.12(4.86)	0.547	0.698
Sex (%)	Male	373 (62.6)	185 (61.5)	104 (63.0)	84 (64.6)	0.817	268 (66.7)	106 (65.8)	96 (65.3)	66 (70.2)	0.703	0.210
	Female	223 (37.4)	116 (38.5)	61 (37.0)	46 (35.4)		134 (33.3)	55 (34.2)	51 (34.7)	28 (29.8)		
ASA (%)	I	121 (20.3)	51 (16.9)	40 (24.2)	30 (23.1)	0.118	78 (19.4)	33 (20.5)	31 (21.1)	14 (14.9)	0.555	0.586
	II	357 (59.9)	190 (63.1)	88 (53.3)	79 (60.8)		235 (58.5)	91 (56.5)	84 (57.1)	60 (63.8)		
	III	112 (18.8)	55 (18.3)	37 (22.4)	20 (15.4)		87 (21.6)	35 (21.7)	32 (21.8)	20 (21.3)		
	IV	6 (1.0)	5 (1.7)	0 (0.0)	1 (0.8)		2 (0.5)	2 (1.2)	0 (0.0)	0 (0.0)		
History of abdominal surgery (%)		177 (29.7)	94 (31.2)	45 (27.3)	38 (29.2)	0.665	105 (26.1)	50 (31.1)	31 (21.1)	24 (25.5)	0.137	0.246
Distance of tumor to ARJ on MRI in centimeters (median[IQR])		3.00 [1.00, 5.00]	3.00 [1.00, 5.00]	3.00 [1.00, 5.00]	1.50 [0.00, 3.00]	<0.001	8.00 [6.00, 10.00]	8.00 [6.00, 10.00]	8.25 [7.30, 10.00]	6.00 [5.00, 7.50]	<0.001	<0.001
MRF involvement on MRI (%)	MRF involved	206 (34.8)	92 (30.9)	64 (39.0)	50 (38.5)	0.130	110 (27.8)	36 (22.5)	39 (27.3)	35 (37.6)	0.034	0.025
cT (%)	1	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.8)	0.178	8 (2.0)	5 (3.1)	2 (1.4)	1 (1.1)	0.542	0.004
	2	168 (28.3)	84 (28.0)	48 (29.3)	36 (27.7)		117 (29.2)	51 (31.7)	44 (29.9)	22 (23.7)		
	3	360 (60.6)	190 (63.3)	91 (55.5)	79 (60.8)		249 (62.1)	95 (59.0)	89 (60.5)	65 (69.9)		

Supplementary Table 1 Baseline comparison and restorative rates per approach (continued)

		LOREC					Non- LOREC					
		Total	**Laparoscopy**	**Robot**	**TaTME**	**p-value**	**Total**	**Laparoscopy**	**Robot**	**TaTME**	**p-value**	**p-value (LOREC vs non-LOREC)**
	4	65 (10.9)	26 (8.7)	25 (15.2)	14 (10.8)		27 (6.7)	10 (6.2)	12 (8.2)	5 (5.4)		
cN (%)	0	257 (43.3)	127 (42.2)	59 (36.0)	71 (55.0)	0.002	179 (44.5)	70 (43.5)	67 (45.6)	42 (44.7)	0.674	0.173
	1	193 (32.5)	89 (29.6)	63 (38.4)	41 (31.8)		145 (36.1)	63 (39.1)	47 (32.0)	35 (37.2)		
	2	144 (24.2)	85 (28.2)	42 (25.6)	17 (13.2)		78 (19.4)	28 (17.4)	33 (22.4)	17 (18.1)		
Neoadjuvant therapy (%)	None	197 (33.6)	105 (36.0)	46 (27.9)	46 (35.4)	0.012	168 (42.4)	71 (45.5)	61 (41.8)	36 (38.3)	0.397	<0.001
	Radiotherapy	178 (30.3)	81 (27.7)	67 (40.6)	30 (23.1)		134 (33.8)	54 (34.6)	51 (34.9)	29 (30.9)		
	Chemoradiation	212 (36.1)	106 (36.3)	52 (31.5)	54 (41.5)		94 (23.7)	31 (19.9)	34 (23.3)	29 (30.9)		
Surgical procedure (%)	APR	330 (55.4)	178 (59.1)	93 (56.4)	59 (45.4)	<0.001	33 (8.2)	16 (9.9)	7 (4.8)	10 (10.6)	<0.001	<0.001
	NRLAR	68 (11.4)	53 (17.6)	9 (5.5)	6 (4.6)		64 (15.9)	40 (24.8)	14 (9.5)	10 (10.6)		
	RLAR	198 (33.2)	70 (23.3)	63 (38.2)	65 (50.0)		305 (75.9)	105 (65.2)	126 (85.7)	74 (78.7)		

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; LAR=low anterior resection;

Supplementary Table 2 Short-term outcome per type of procedure

		LOREC					Non- LOREC					
		Total	**APR**	**NRLAR**	**RLAR**	**p-value**	**Total**	**APR**	**NRLAR**	**RLAR**	**p-value**	**p-value (LOREC vs non-LOREC)**
N		596	330	68	198		402	33	64	305		
pT	0	51 (8.6)	34 (10.3)	0 (0.0)	17 (8.6)	0.039	29 (7.2)	1 (3.0)	5 (7.8)	7 (2.3)	0.250	0.114
	1	55 (9.3)	27 (8.2)	5 (7.6)	23 (11.6)		39 (9.8)	1 (3.0)	4 (6.2)	34 (11.2)		
	2	226 (38.1)	123 (37.4)	25 (37.9)	78 (39.4)		129 (32.2)	11 (33.3)	23 (35.9)	95 (31.4)		
	3	251 (42.3)	136 (41.3)	35 (53.0)	80 (40.4)		189 (47.2)	18 (54.5)	27 (42.2)	144 (47.5)		
	4	10 (1.7)	9 (2.7)	1 (1.5)	0 (0.0)		14 (3.5)	2 (6.1)	5 (7.8)	7 (2.3)		
pN	0	409 (68.7)	232 (70.3)	36 (52.9)	141 (71.6)	0.02	268 (66.7)	24 (72.7)	46 (71.9)	198 (64.9)	0.664	0.063
	1	142 (23.9)	79 (23.9)	25 (36.8)	38 (19.3)		87 (21.6)	5 (15.2)	13 (20.3)	69 (22.6)		
	2	44 (7.4)	19 (5.8)	7 (10.3)	18 (9.1)		47 (11.7)	4 (12.1)	5 (7.8)	38 (12.5)		
CRM positive		33 (6.1)	25 (8.5)	3 (4.5)	5 (2.8)	0.04	14 (3.8)	1 (3.1)	5 (8.5)	8 (2.9)	0.118	0.161
Incomplete TME		46 (7.9)	34 (10.4)	3 (4.5)	9 (4.7)	0.04	12 (3.0)	2 (6.1)	1 (1.6)	9 (3.0)	0.490	0.003
Histological type	Adenocarcinoma	560 (94.0)	310 (93.9)	63 (92.6)	187 (94.4)	0.74	387 (96.3)	31 (93.9)	62 (96.9)	294 (96.4)	0.905	0.265
	Mucinous	34 (5.7)	18 (5.5)	5 (7.4)	11 (5.6)		14 (3.5)	2 (6.1)	2 (3.1)	10 (3.3)		
	Other	2 (0.3)	2 (0.6)	0 (0.0)	0 (0.0)		1 (0.2)	0 (0.0)	0 (0.0)	1 (0.3)		
Differentiation type	Well/moderate	523 (87.8)	281 (85.2)	63 (92.6)	179 (90.4)	0.27	366 (91.0)	29 (87.9)	56 (87.5)	281 (92.1)	0.582	0.249
	Poor	22 (3.7)	15 (4.5)	2 (2.9)	5 (2.5)		12 (3.0)	2 (6.1)	2 (3.1)	8 (2.6)		
	Unknown	51 (8.6)	34 (10.3)	3 (4.4)	14 (7.1)		24 (6.0)	2 (6.1)	6 (9.4)	16 (5.2)		

Abbreviations: APR=abdominoperineal resection; NRLAR=non restorative low anterior resection; RLAR=restorative low anterior resection; LAR=low anterior resection; CD=-Clavien-Dindo classification;

Supplementary Table 3 Oncological outcome per approach

		LOREC					Non-LOREC					
		Total	**Laparoscopy**	**Robot**	**TaTME**	**p-value**	**Total**	**Laparoscopy**	**Robot**	**TaTME**	**p-value**	**p-value (LOREC vs non-LOREC)**
N		596	301	165	130		402	161	147	94		
Follow up in months (median[IQR])		35.31 [24.87, 45.75]	36.03 [25.38, 47.54]	34.61 [24.53, 43.53]	34.66 [24.49, 44.87]	0.367	36.26 [25.48, 46.43]	35.93 [25.34, 47.84]	37.36 [25.71, 47.59]	35.59 [25.97, 43.86]	0.823	0.276
3-year overall survival (%)		534 (88.3)	274 (90.0)	143 (85.5)	117 (87.5)	0.42	359 (88.0)	144 (88.5)	133 (89.4)	82 (84.6)	0.72	0.83
3-year disease free survival (%)		455 (73.3)	234 (74.6)	119 (69.3)	102 (75.6)	0.35	313 (75.3)	128 (77.1)	114 (74.9)	71 (72.8)	0.79	0.49
3-year local recurrence (%)		29 (5.9)	15 (6.1)	9 (6.7)	5 (4.2)	0.81	20 (6.2)	7 (5.8)	8 (6.1)	5 (7.4)	0.91	1.000
Location of local recurrence	Anterior	2 (0.3)	2 (0.7)	0 (0.0)	0 (0.0)		3 (0.7)	1 (0.6)	1 (0.7)	1 (1.1)		
	Lateral	8 (1.3)	5 (1.7)	1 (0.6)	2 (1.5)		4 (1.0)	3 (1.9)	1 (0.7)	0 (0.0)		
	Inferior	8 (1.3)	7 (2.3)	0 (0.0)	1 (0.8)		5 (1.2)	3 (1.9)	2 (1.4)	0 (0.0)		
	Central, anastomotic	7 (1.2)	2 (0.7)	3 (1.8)	2 (1.5)		3 (0.7)	0 (0.0)	2 (1.4)	1 (1.1)		
	Central, non-anastomotic	14 (2.4)	8 (2.7)	6 (3.7)	0 (0.0)		8 (2.0)	4 (2.5)	4 (2.7)	0 (0.0)		
	Peritoneal reflection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		1 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)		
	Multifocal local recurrence	3 (8.3)	2 (11.1)	1 (7.7)	0 (0.0)		4 (16.7)	2 (22.2)	2 (22.2)	0 (0.0)	0.449	0.566

Supplementary Table 3 Oncological outcome per approach (continued)

		LOREC					Non-LOREC					
		Total	**Laparoscopy**	**Robot**	**TaTME**	**p-value**	**Total**	**Laparoscopy**	**Robot**	**TaTME**	**p-value**	**p-value (LOREC vs non-LOREC)**
3-year systemic recurrence (%)		96 (18.8)	51 (19.8)	29 (20.4)	16 (14.6)	0.37	53 (15.2)	22 (15.9)	20 (16.3)	11 (12.4)	0.89	0.18
	Liver	44 (7.4)	30 (10.0)	9 (5.5)	5 (3.8)		30 (7.5)	14 (8.7)	10 (6.8)	6 (6.4)		
	Lung	63 (10.6)	29 (9.6)	23 (14.0)	11 (8.5)		27 (6.7)	11 (6.8)	8 (5.5)	8 (8.5)		
	Peritoneal	17 (2.9)	11 (3.7)	3 (1.8)	3 (2.3)		8 (2.0)	1 (0.6)	6 (4.1)	1 (1.1)		
	Bone	4 (0.7)	1 (0.3)	2 (1.2)	1 (0.8)		2 (0.5)	0 (0.0)	1 (0.7)	1 (1.1)		
	Ovary	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		1 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)		
	Brain	4 (0.7)	2 (0.7)	1 (0.6)	1 (0.8)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
	Other	13 (2.2)	7 (2.3)	3 (1.8)	3 (2.3)		5 (1.2)	1 (0.6)	3 (2.1)	1 (1.1)		

Abbreviations: LOREC= low rectal cancer definition; IQR=interquartile range

CHAPTER 9

IMPLICATIONS OF THE NEW MRI-BASED RECTUM DEFINITION ACCORDING TO THE SIGMOID TAKE-OFF: A MULTI-CENTER COHORT STUDY

TA Burghgraef, **JC Hol**, ML Rutgers, G Brown, R Hompes, C Sietses, N D'Souza, ECJ Consten

Submitted

ABSTRACT

Objective: To determine the effect of implementing the sigmoid take-off definition on the amount of rectal cancer diagnosis and its effect on clinical outcomes.

Summary background data: The introduction of the sigmoid take-off definition, will lead to a shift in rectal cancer patients. As an effect, a proportion of patients will be treated differently.

Methods: This is a multicenter retrospective cohort study in eleven large Dutch rectal cancer centers with profound experience with minimal invasive total mesorectal excision. Patients were included if they underwent a total mesorectal excision between January 1st 2015 and December 31st 2017, were registered in the Dutch Colorectal Audit as having a rectal carcinoma according to the former definition, underwent an elective procedure with curative intent, and if pre-operative MRI or CT imaging was available. MRI imaging of all patients was re-assessed for the sigmoid take-off definition. The primary outcome was the amount of patients having a rectal carcinoma according to the sigmoid take-off definition. Secondary outcomes included differences in clinical outcomes between rectal and sigmoid cancer patients according to the sigmoid take-off.

Results: In total 1436 patients with rectal carcinoma according to the former definition were included. Of these, 192 (13.4%) patients were diagnosed with a sigmoid carcinoma. Out of the 163 sigmoid cancer patients without synchronous metastasis, 92 (56.4%) would have been offered other (neo-) adjuvant therapy if the sigmoid take-off had been used. Sigmoid cancer patients had significantly fewer surgical complications, less anastomotic leakages and less major morbidity.

Conclusions: 13.4% of the current rectal cancer patients are diagnosed with sigmoid carcinoma according to the sigmoid take-off. 56.4% of these patients would have received other (neo-) adjuvant treatment due to use of the new definition. Additionally, sigmoid patients have a significantly lower risk on postoperative complications.

MINI ABSTRACT

The implementation of the sigmoid take-of definition for rectal carcinoma leads to a decrease in rectal cancer patients of 13.6%. 56.4% of these patients would have received other (neo-) adjuvant treatment due to the use of the new definition.

INTRODUCTION

Colorectal cancer is the second cause of cancer-related deaths in Western countries. Rectal cancer is estimated to account for over 30% of the overall incidence of colorectal cancer (1, 2). Although colorectal cancer is often reported as a single entity, colon carcinoma and rectal carcinoma differ significantly regarding pathology, anatomy, treatment and subsequent complications (3-5). The curative treatment of rectal carcinoma consists of total mesorectal excision (TME), preceded by neoadjuvant therapy depending on tumor characteristics. The curative treatment of colon carcinoma consists of resection of the colonic segment including its lymph nodes, followed by adjuvant chemotherapy for patients with stage III disease (6).

Due to the difference in therapy between colon and rectum carcinoma, it is essential to accurately classify these tumours. However, until recently no clear consensus existed regarding the definition of the rectum, with a subsequent unclear definition of rectum carcinoma (7). While the variation in used definitions has its effect on the use of (neo-) adjuvant therapies for patients with a recto-sigmoid tumour, it might also influence research outcomes since various arbitrary cut-off points have been used for published articles (8-13). To overcome these problems, a new definition has been proposed, defining the rectum as the part below the sigmoid take-off (STO) (14). This anatomical landmark can be assessed using magnetic resonance imaging (MRI) or computer tomography (CT) imaging.

Since its introduction, several studies have embraced the STO, and some clinical guidelines started using the definition as well (6, 15). It is suggested that its implementation would lead to a decrease in rectal carcinoma compared with formerly used definitions. In addition, patients diagnosed with rectal carcinoma according to former definitions, and a sigmoid carcinoma according to the STO definition, would now be treated differently with regard to (neo-)adjuvant therapy and might benefit from adjuvant chemotherapy. Especially since proximal rectum tumors according to former definitions do not seem to respond to neo-adjuvant radiotherapy, and are suggested to benefit from adjuvant therapy (9, 16). Therefore, the aim of this multicenter cohort is to describe the shift in rectal carcinoma diagnoses and its clinical implications as an effect of the STO definition.

MATERIALS AND METHODS

A retrospective multicenter cohort study was performed in eleven dedicated colorectal centers in the Netherlands. A protocol, regarding the design, methods and statistical

analysis was composed prior to initiation of the study. The study was reported in accordance with the STROBE guidelines (17). Informed consent was deemed unnecessary according to the Dutch Medical Treatment Agreement Act. The medical ethical committee and local ethical committees of all hospitals gave approval for the study (MEC-U, AW19.023 W18.100).

Aims

The primary aim was to describe the number of patients with rectal carcinoma according to the STO, compared to patients with rectal carcinoma according to the former definition. Secondary aims included comparison of intra-operative, postoperative, pathological and oncological outcomes. Additionally, we aimed to evaluate the effects on survival and recurrence in patients that would have been treated differently with regard to (neo-)adjuvant therapy due to use of the STO. For this analysis patients with a sigmoid tumor according to the STO were matched to patients registered in the Dutch Cancer Registry (NKR) that underwent surgery for sigmoid cancer in 2015.

Patients

Patients were included if they (1) were older than 18 years, (2) were registered as rectal carcinoma in the Dutch Colorectal Audit (DCRA) database between 2015 January 1st and 2017 December 31st, (3) were treated using total mesorectal excision (TME) or partial mesorectal excision (PME), (4) with curative intent. Patients were excluded in they (1) were operated in an emergency setting, or (2) if no pre-operative imaging was accessible. As the former definitions used in the different hospitals participating in this multicenter cohort are heterogenous, we used registration in the national obligatory DCRA database as rectal carcinoma as an inclusion criterium. For evaluating the effects on survival and recurrence, patients with synchronous metastasis were excluded.

Data and outcomes

Data was pseudonymised, and missing data was added in the electronic case report form using the local hospitals' electronical medical record. Baseline characteristics included age, body mass index (BMI), sex, American Society of Anesthesiology (ASA) classification, distance from the tumor to the anorectal junction (ARJ) on MRI, mesorectal fascia involvement on preoperative MRI, clinical TNM stage and administration of (neo-) adjuvant therapy. Registered outcomes were: type of surgical procedure, stoma constructed during initial surgical procedure, skin-skin time, conversion, intra-operative complications, post-operative complications up until 30 days, major morbidity, mortality, anastomotic leakage, reintervention, readmission, length of stay, pathological TNM stage, quality of TME specimen according to Quirke (18) and positive circumferential margin, defined as ≤ 1 mm. Morbidity was classified according to the Clavien-Dindo

classification, with major morbidity being class three or higher (19). Anastomotic leakage was defined according to the definition of the International Study Group of Rectal Cancer, and was registered until the end of follow up (20, 21).

Radiological assessment

MRI or CT imaging was assessed by six researchers. They all received training of a senior researcher with extensive experience in assessing STO. The training was given under supervision of a senior radiologist. Before being allowed to enter data in the electronic case report form, they would need to adequately asses 10 MRIs. Researchers were retrained and MRIs were re-assessed until 10 MRIs in a row were adequately reported. A tumor was defined as a rectal tumor if the lower border of the tumor was below the STO (14). Furthermore, a low rectal tumor was defined according to the LOREC definition: "a tumor with its lower border at or below the origin of the musculus levator on the pelvic sidewall" (22).

Statistical analysis

Descriptive statistics were given using a barplot for type of tumor relative to the distance from the ARJ. Categorical data was presented as number and percentages. Continuous data was presented as mean and standard deviation or median and interquartile range (IQR) depending on the distribution. Univariate analysis of was done using the Chi-square test for categorical data. The independent sample T-test or the Wilcoxon-rank sum test, were used for continuous data, depending on the distribution. A p-value of < 0.05 was considered significant.

For the analyses of survival and recurrence in patients that had been treated differently with regard to (neo-) adjuvant therapy due to the use of the STO definition the following patients were matched: Patients that were treated as rectal cancer patients due to the use of former definitions, but should have been treated as sigmoid cancer patients according to the STO definition, were matched to patients from the national Dutch Cancer Registry that underwent surgery in 2015 for sigmoid cancer. First, patients that received neo-adjuvant therapy, but would not be offered adjuvant therapy according to the STO (postoperative pTxN0 tumor), were classified as 'overtreated pN0'. Second, patients that received neo-adjuvant therapy, and would be offered adjuvant therapy according to the STO (postoperative pTxN$^+$ tumor), were classified as 'overtreated pN$^+$'. Third, patients that did not receive neo-adjuvant therapy, but would be offered adjuvant therapy according to the STO (postoperative pTxN$^+$ tumor), were classified as 'undertreated'. Patients classified as 'overtreated pN0' were matched to sigmoid cancer patients that did not receive adjuvant therapy, to evaluate the effect of neo-adjuvant therapy in sigmoid cancer patients. Patients classified as 'overtreated pN$^+$' and 'undertreated'

were matched to sigmoid cancer patients that received adjuvant therapy to evaluate the effect of adjuvant therapy in sigmoid cancer patients. Matching was done on a 1:2 ratio, based on age, sex, ASA, BMI, and clinical TN stage. Outcomes of interest were overall survival and disease free survival at 3 years of follow up. Analyses were conducted using R (version 3.6.1), with the packages "survival", "Matching", "Mice" and "survminer".

RESULTS

In total, 1742 patients were identified as eligible, of whom 304 were excluded, resulting in 1436 patients included in the analysis. (Figure 1) Of these patients, 192 (13.4%) had a sigmoidal tumor, whilst 1244 patients had a rectal tumor according to the STO. Of the 192 patients with a sigmoid tumor, after excluding 21 patients with a synchronous metastasis, 163 patients were included for analysis assessing survival and recurrence in patients who should have been treated differently with regard to (neo-) adjuvant therapy.

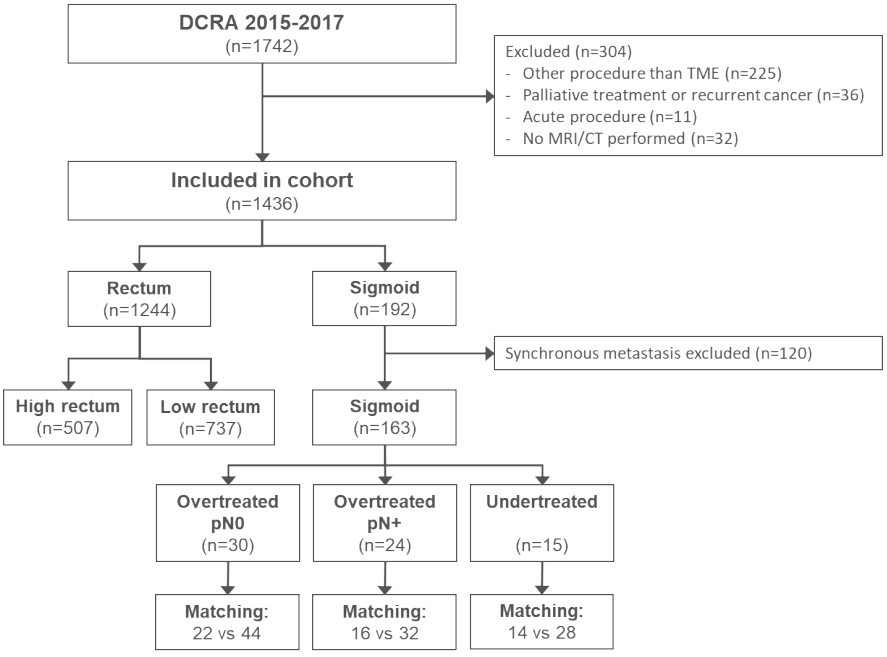

Figure 1. Patient flow diagram
DCRA: Dutch Colorectal Audit, TME: total mesorectal excision, MRI: magnetic resonance imaging, CT: computer tomography, high rectum: patients with a MRI defined rectal tumor but not a LOREC defined rectal tumor, low rectum: patients with a LOREC defined rectal tumor.

Baseline characteristics

Compared to STO defined rectal cancer patients, sigmoid cancer patients had less cT4 tumors, and more cN0 tumors, with a lower rate of patients receiving neoadjuvant therapy. Furthermore, tumors were located further from the ARJ. (Table 1) Significantly more patients did not receive a stoma (61.5% versus 23.6%, p<0.001), significantly more patients received an anastomosis (84.9% versus 52.3%, p<0.001), and less patients underwent an abdominoperineal resection (3.1% versus 34.4%, p<0.001). Furthermore, 59.9% of the rectal tumors were low rectal tumors according to the LOREC criteria, with the majority having a distance to the ARJ of 0-5 cm on MRI. Rectal tumors that were not classified as low rectal tumors were predominantly situated between 6-10 cm from the ARJ. Sigmoid tumors had a distance from the ARJ of 9-15 cm on MRI. When distance was measured using colonoscopy, five peaks of measurements were seen at 5, 8, 10, 12 and 15 cm (Figure 2).

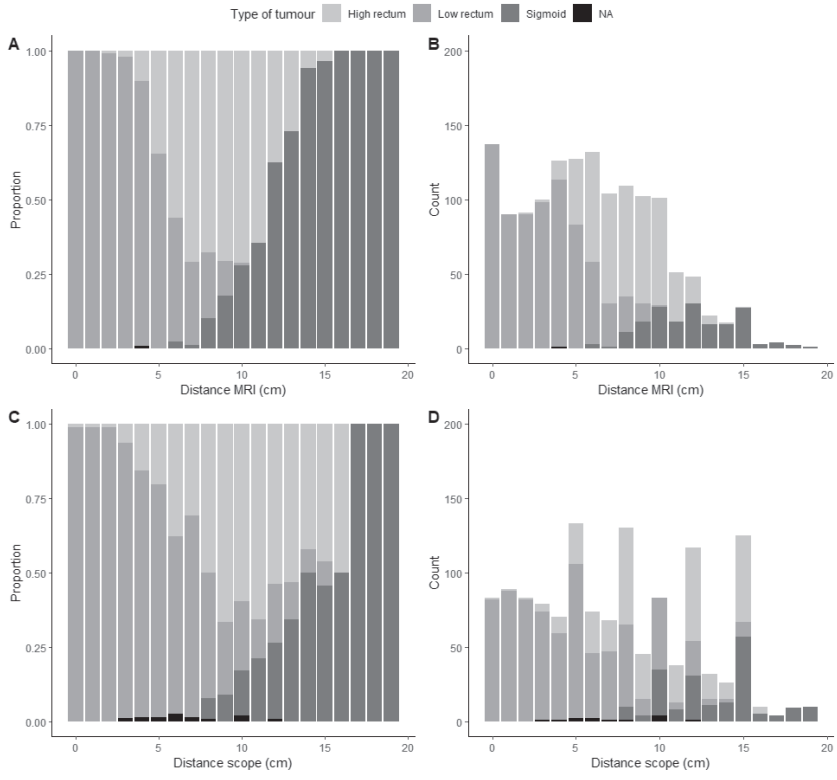

Figure 2 Distribution of types of tumours relative to distance to anorectal junction.
Low rectum: rectal tumour according to LOREC criteria, High rectum: rectal tumour according to sigmoidal take-off, Sigmoid: sigmoidal tumour according to sigmoidal take-off. **A**: proportion of tumours relative to distance using MRI. **B:** absolute number of tumours relative to distance using MRI. **C:** proportion of tumours relative to distance using colonscopy. **D:** absolute number of tumours relative to distance using colonoscopy.

Table 1 Baseline characteristics

n		Total	Sigmoid	Rectum	p
		1436	192	1244	
Age (mean (SD))		67 (10.3)	67 (10.6)	67 (10.3)	0.60
BMI (mean (SD))		26 (4.2)	26 (4.7)	26 (4.1)	0.14
Sex (n, %)	Male	923 (64.3)	122 (63.5)	801 (64.4)	0.88
	Female	513 (35.7)	70 (36.5)	443 (35.6)	
ASA (n, %)	1	274 (19.1)	33 (17.2)	241 (19.4)	0.63
	2	874 (60.9)	121 (63.0)	753 (60.5)	
	3	275 (19.2)	35 (18.2)	240 (19.3)	
	4	13 (0.9)	3 (1.6)	10 (0.8)	
Distance scopy (median [IQR])		8 [4-11]	14 [11-15]	7 [3-10]	<0.001
Distance MRI (median [IQR])		6 [3-9]	12 [10-14]	5 [2-7]	<0.001
LOREC (n, %)		737 (51.8)	0 (0.0)	737 (59.9)	<0.001
MRF+ (n, %)		428 (30.7)	40 (24.1)	388 (31.6)	0.06
cT (n, %)	1	36 (2.5)	9 (5.0)	27 (2.2)	0.01
	2	410 (28.9)	58 (32.4)	352 (28.4)	
	3	841 (59.3)	104 (58.1)	737 (59.4)	
	4	132 (9.3)	8 (4.5)	124 (10.0)	
cN (n, %)	0	642 (44.9)	101 (53.4)	541 (43.6)	0.04
	1	458 (32.0)	51 (27.0)	407 (32.8)	
	2	331 (21.1)	37 (19.6)	294 (23.7)	
cM (n, %)	0	1316 (93.2)	163 (94.2)	1153 (93.1)	0.68
	1	96 (6.7)	10 (5.8)	86 (6.9)	
Neoadjuvant (n, %)	None	578 (40.9)	116 (60.7)	462 (37.8)	<0.001
	Radiotherapy	444 (31.4)	50 (26.2)	394 (32.2)	
	Chemoradiation	392 (27.7)	25 (13.1)	367 (30.0)	
Technique (n, %)	Open	59 (4.1)	5 (2.6)	52 (4.2)	<0.001
	Laparoscopic	706 (49.2)	114 (59.4)	592 (47.7)	
	Transanal TME	264 (18.4)	12 (6.2)	252 (20.3)	
	Robot-assisted	407 (28.3)	61 (31.8)	346 (27.9)	
Procedure (n, %)	APR	434 (30.2)	6 (3.1)	428 (34.4)	<0.001
	LAR + colostomy	189 (13.2)	23 (12.0)	166 (13.3)	
	LAR + anastomosis	813 (56.6)	163 (84.9)	650 (52.3)	
Stoma (n, %)	No stoma	411 (28.6)	118 (61.5)	293 (23.6)	<0.001
	Deviating ileostomy	402 (28.0)	43 (22.4)	359 (28.9)	
	Ending ileostomy	8 (0.6)	1 (0.5)	7 (0.6)	
	Deviating colostomy	35 (2.4)	5 (2.6)	30 (2.4)	
	Ending colostomy	578 (40.3)	25 (13.0)	553 (44.5)	
	Unknown	2 (0.1)	0 (0.0)	2 (0.2)	
Conversion (n, %)		71 (4.9)	10 (5.2)	61 (4.9)	0.99
Peroperative complication (n, %)		93 (6.5)	7 (3.6)	86 (6.9)	0.12

SD: standard deviation, ASA: American Society Anesthesiologists class, IQR: interquartile range, LOREC: low rectal tumor, MRF+: mesorectal fascia involvement on pre-operative MRI, cT: clinical tumor stage cN: clinical nodal stage, cM: clinical metastatic stage, Intra-operative outcomes. TME: total mesorectal excision, APR: abdominoperineal resection, LAR: low anterior resection.

Postoperative outcomes

Overall complication rate (33.9% versus 48.6%, p<0.001), surgical complication rate (20.3% versus 34.0%, p<0.001) and major morbidity rates (10.4% versus 20.7%, p<0.001) were significantly lower in the sigmoid group compared to the rectum group. Reintervention rate, readmission rate an length of stay were also significantly lower in the sigmoid group. Regarding pathological and oncological outcomes only limited differences were observed. More ypT0 and less ypT3-4 tumors were seen in the sigmoidal group. Radicality was not statistically different (4.3% versus 6.4%, p=0.36). In addition, 3-year overall survival (89.9% versus 88.7%, p=0.73), 3-year disease-free survival (73.2% versus 73.7%, p=0.95) and 3-year local recurrence rate (4.2% versus 4.7%, p=0.90) were not different either. Permanent stoma rate at the end of follow up was significantly lower in the sigmoid group (18.2% versus 56.2%, p<0.001) (Table 2).

Matched analysis

Out of the 163 patients with a sigmoid tumor as defined by the STO, 92 patients (56.4%) would have been treated otherwise due to implementation of the definition, as they had an indication for neo-adjuvant therapy or for adjuvant therapy if the STO was used. 30 patientswere classified as 'overtreated pN0', 24 patients as 'overtreated pN+' and 15 patients as 'undertreated'. For the sub-analysis, 26 'overtreated pN0' were case-matched to 52 patients that did not receive adjuvant therapy, 16 'overtreated pN^{+}' patients were matched to 32 patients that received adjuvant therapy, and 14 'undertreated' patients were case-matched to 28 patients that received adjuvant therapy. After matching, no significant baseline differences existed for all three groups (Supplemental table 2, 3 and 4).

No difference regarding 3-year overall survival or 3-year disease free survival was observed in the 'overtreated pN0' and 'overtreated pN+' patients. In the ´undertreated´ patients 3-year overall survival (96.4% versus 84.4%, p=0.39) was not different. However, 3-year disease free survival was significantly better in the group of patients receiving adjuvant therapy (85.7% versus 50.0%, p=0.01).

DISCUSSION

This study aimed to evaluate the shift in rectal cancer diagnosis and its clinical implication, as an effect of the implementation of the STO definition. In this study 13.6% of the patients classified as having a rectal tumor based on the former definition had a sigmoidal tumor according to the STO definition. More postoperative complications were

Table 2 Postoperative outcomes.

n		Total	Sigmoid	Rectum	p
		1436	**192**	**1244**	
Postoperative complications (n,%)		669 (46.6)	65 (33.9)	604 (48.6)	<0.001
Surgical complications (n,%)		462 (32.2)	39 (20.3)	423 (34.0)	<0.001
	Abcess	91 (6.3)	7 (3.6)	84 (6.8)	0.14
	Ileus	211 (14.7)	21 (10.9)	190 (15.3)	0.14
	Wound infection	63 (4.4)	2 (1.0)	61 (4.9)	0.03
	Anastomotic leakage	131 (16.1)	12 (7.4)	119 (18.3)	0.001
Major morbidity (n,%)	CD =>3	278 (19.4)	20 (10.4)	258 (20.7)	<0.001
Mortality (n,%)		15 (1.1)	3 (1.6)	12 (1.0)	0.69
Reintervention (n,%)		236 (16.4)	19 (7.6)	217 (17.3)	<0.001
Readmission (n,%)		210 (14.6)	25 (10.0)	188 (15.0)	0.003
LOS (median [IQR])		6 [5-9]	5 [4-7]	6 [5-9]	<0.001
pT (n,%)	0	102 (7.1)	7 (3.6)	95 (7.7) [#]	<0.001
	1	140 (9.8)	20 (10.4)	120 (9.7)	
	2	476 (33.3)	50 (26.0)	426 (34.4) [#]	
	3	664 (46.4)	101 (52.6)	563 (45.4) [#]	
	4	49 (3.4)	14 (7.3)	35 (2.8) [#]	
pN (n,%)	0	941 (65.7)	123 (64.0)	818 (65.9)	0.89
	1	339 (23.7)	46 (24.1)	293 (23.6)	
	2	152 (10.6)	22 (11.5)	130 (10.5)	
pM (n,%)	0	1316 (93.8)	178 (94.2)	1138 (93.9)	0.84
	1	86 (6.2)	11 (5.8)	75 (6.2)	
Incomplete TME (n,%)		78 (5.6)	8 (4.6)	70 (5.7)	0.76
R1/R2 (n,%)		67 (5.0)	8 (4.3)	73 (6.4)	0.36
Follow up time (median, IQR)		36 [25-47]	36 [26-45]	36 [25-47]	0.62
Permanent stoma rate (n,%)		732 (51.1)	35 (18.2)	697 (56.2)	<0.001
3-year OS (n,%)		1271 (88.9)	169 (89.9)	1102 (88.7)	0.73
3-year DFS (n,%)		1054 (73.6)	139 (73.2)	915 (73.7)	0.95
3-year LR (n,%)		66 (4.6)	8 (4.2)	58 (4.7)	0.90
	Multifocal (n,%)	10 (12.7)	1 (12.5)	9 (12.7)	1.00
3-year SR (n,%)		268 (18.7)	40 (20.9)	228 (18.2)	0.54

CD: clavien-dindo classification, LOS: length of stay, IQR: interquartile range. pT: pathological tumour stage, pN: pathological node stage, pM: pathological metastasis stage, TME: total mesorectal excision, R1/R2: irradical surgery, IQR: interquartile range, OS: overall survival, DFS: disease-free survival, LR: local recurrence, SR: systemic recurrence.

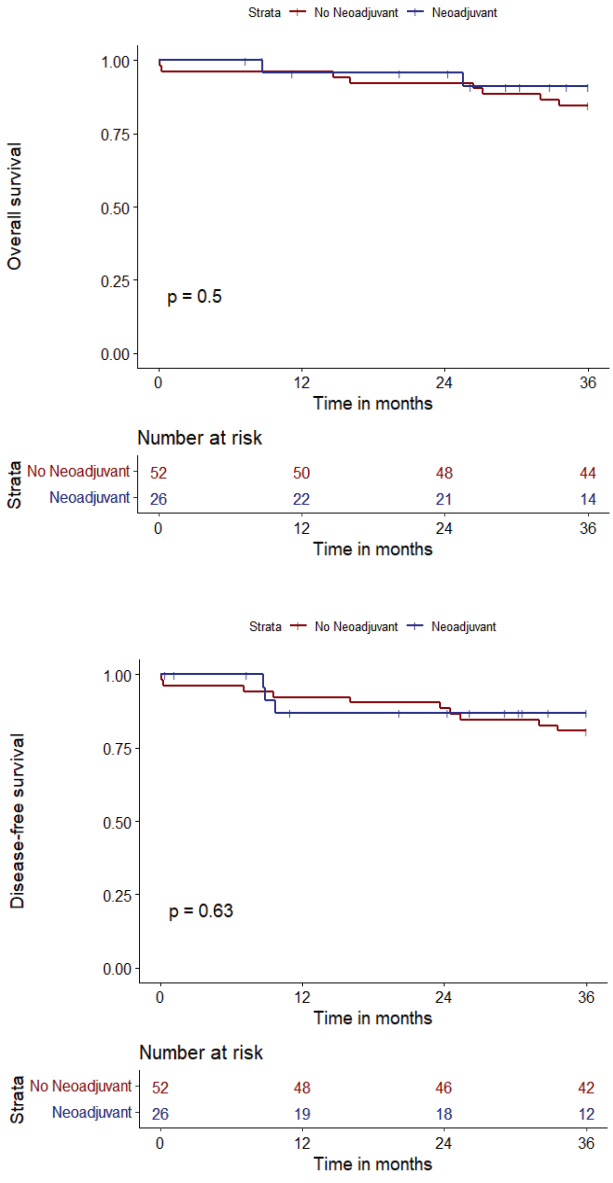

Figure 3A: Log-rank survival curve of overtreated pN0 sigmoid patients compared to matched sigmoid patients from the Dutch Cancer registration with respectively overall survival and disease-free survival.

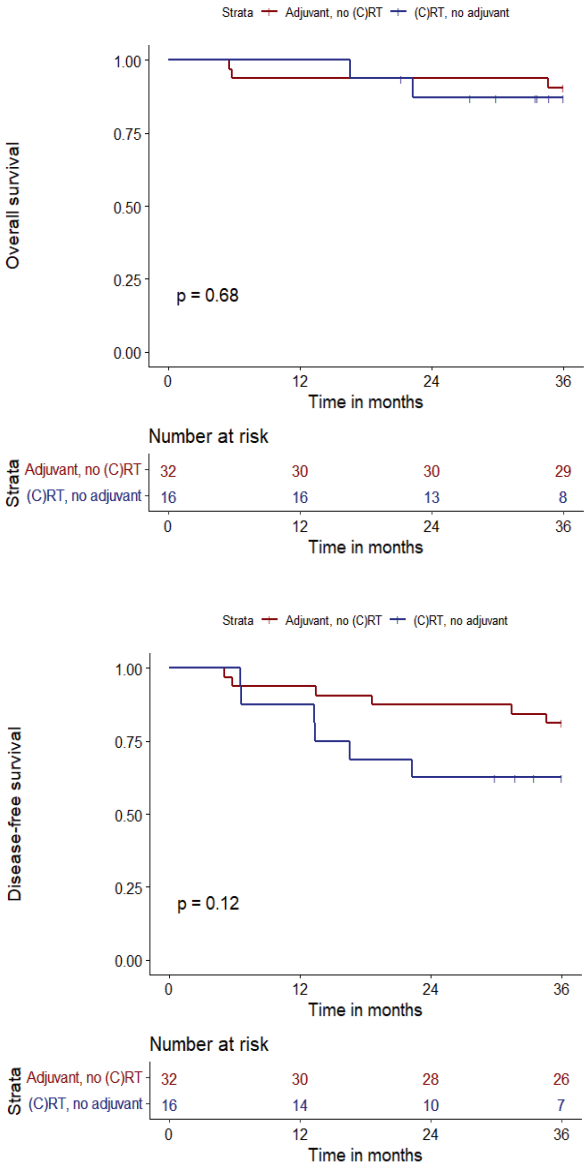

Figure 3B: Log-rank survival curve of overtreated pN+ sigmoid patients compared to matched sigmoid patients from the Dutch Cancer registration with respectively overall survival and disease-free survival.

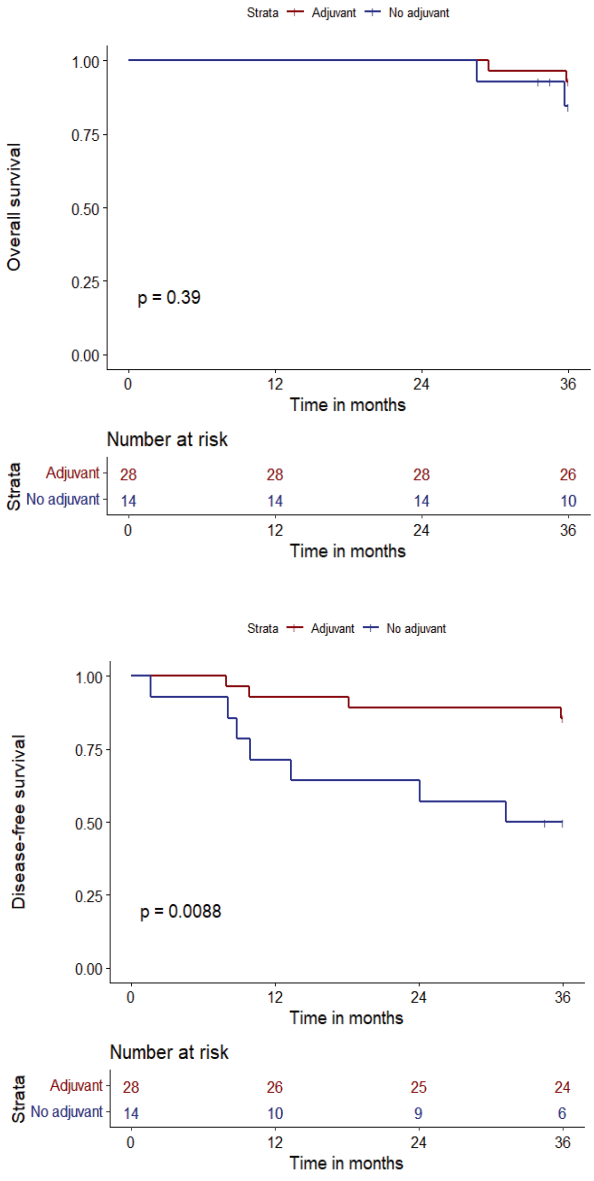

Figure 3C: Log-rank survival curve of undertreated sigmoid patients compared to matched sigmoid patients from the Dutch Cancer registration with respectively overall survival and disease-free survival.

seen in patients with rectal tumors. Additionally, 56.4% of the patients in the sigmoid group would be treated differently if the STO definition would have been used.

This study showed that 13.6% of the patients with a rectal tumor according to the former definition, are diagnosed with a sigmoid tumor according to the STO definition. Additionally, 59.1% of the patients with a rectal tumor according to the STO have a low rectal tumor, according to the LOREC definition (22). By our knowledge this is the first study, to show the effect on rectal cancer cases due to the implementation of the STO definition. This study suggests a shift from rectal cancer patients to colon cancer patients. Our data suggests that the majority of STO tumors are between 0 and 10 cm distance from the ARJ, while the majority of sigmoid tumors are situated between 10-15 cm. In addition, the data clearly describes the discrepancy between distance of the tumor based on MRI and distance based on colonoscopy. Prevalence peaks were seen at 8, 12, 10 and 15 cm based on colonoscopy measurements, suggesting that distance is mostly estimated rather than measured. This is confirmed in other studies, showing that MRI distance is more accurate than colonoscopy distance (23). However, distance from the ARJ measured on MRI, varied widely within sigmoid tumors and rectal tumors, suggesting that distance is an arbitrary criterion that does not take into account individual characteristics of the patient. The STO is however an anatomical landmark that is affected by individual characteristics such as the size of the sacral promontory and peritoneal reflection as shown by Li et al (24). These are arguments are in favor of the STO definition compared to the formerly used distance-based definitions.

Significant differences exist in perioperative outcomes between rectal tumors and sigmoid tumors according to the STO. As expected, more primary anastomoses were constructed in the sigmoid group, and more APR were performed in the rectum group. Clearly, this is related to tumor height, as tumor height is one of the key factors in the decision to construct an anastomosis. Additionally, complication rates were significantly higher in the rectum group, with subsequently higher reintervention and readmission rates, and longer length of hospital stay. This is in concordance with other studies comparing colon cancer surgery with rectal cancer surgery (3). Anastomotic leakage is more prevalent in the rectal cancer group, which could explain the higher proportion of morbidity in this group. This is most likely also related to tumors height, as this is an independent risk factor for anastomotic leakage (21). These results underline the suggestion that sigmoid and rectal tumors differ significantly with regard to clinical outcomes. Additionally, the introduction of STO definition may have consequences for existing scientific literature. As tumors between 10-15 cm from the ARJ on MRI are mostly sigmoid tumors, these tumors will be excluded in new studies embracing the STO definition. Older studies might have included more distal sigmoid tumors which

are associated with more favorable clinical outcomes. This reduces the external validity of such studies, and emphasizes the need for a more uniform definition of the rectum (12, 25, 26).

Regarding patients that were diagnosed with a sigmoid tumor according to the STO, a significant amount of 92 patients (56.4%) would be treated differently if clinical guidelines would be applied. 15 patients were undertreated, as they should have been treated with adjuvant treatment since they were diagnosed with sigmoid carcinoma according to the STO, and 54 patients were overtreated, as they were diagnosed with sigmoid carcinoma according to the STO and were given neo-adjuvant therapy. The undertreated patients had a significant decrease in 3-year DFS in the matched analysis, while 3-year OS was equal. This underlines the importance of adjuvant therapy for patients with sigmoidal tumors, as is known from several large trials and is used in most (inter)national guidelines (6, 27). This is supported by previous findings suggesting that patients with a rectal tumor between 10-15 cm might benefit from adjuvant chemotherapy, as they experienced significantly better overall survival and disease-free survival (16). Additionally, it is suggested that neo-adjuvant radiotherapy was not as effective in patients with a rectal tumor between 10-15 cm as in patients with lower rectal tumors (9).

Some limitations should be taken into account. First, this is a retrospective cohort of patients, which comes with bias. However, selection bias is not an issue since there is no comparison of different types of interventions. Additionally this is a large dataset, thereby the effects of the new definition reflects clinical practice. Second, the STO and LOREC definitions were not assessed by radiologists, this might have affected the quality of radiological assessment. However, the researchers were trained under supervision of a radiologist, and as stated previously, the STO can be used by non-radiologists as well, without having a large effect on outcomes (28). Finally, numbers were low in the analyses regarding survival and recurrence of patients with a sigmoid tumor according to the STO and a rectal tumor according to the former definitions. This limits the generalizability of these results.

Concluding, 13.6% of the patients formerly diagnosed with rectal carcinoma are diagnosed with sigmoid carcinoma according to the STO-based definition. Additionally, these patients had a significantly lower risk of peri-operative complications than rectal carcinoma patients, with reduced risk of readmission, reintervention and permanent stoma rate. Finally, 56.4% of the sigmoid patients according to the STO would have received receive other (neo-) adjuvant treatment, due to the change of the definition.

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Supplemental table 1: Baseline characteristics of matched overtreated pN0 sigmoid with sigmoid from the Dutch Cancer Registration.

		Sigmoid	Overtreated pN0	p	SMD
		52	26		
Age (median [IQR])		68 [63, 74]	66 [60, 71]	0.34	0.24
BMI (median [IQR])		27 [25, 30]	26 [23, 29]	0.11	0.38
Sex (n, %)	Female	16 (30.8)	8 (30.8)	1.00	<0.001
	Male	36 (69.2)	18 (69.2)		
ASA (n, %)	1	11 (21.2)	8 (30.8)	0.29	0.54
	2	32 (61.5)	16 (61.5)		
	3	3 (5.8)	2 (7.7)		
	4	0 (0.0)	0 (0.0)		
	Missing	6 (11.5)	0 (0.0)		
Distance MRI (median [IQR])		NA	11 [10, 12]		
MRF+ (n, %)		NA	11 (42.3)		
cT (n, %)	1	7 (13.5)	0 (0.0)	0.07	0.74
	2	12 (23.1)	3 (11.5)		
	3	32 (61.5)	23 (88.5)		
	4	0 (0.0)	0 (0.0)		
cN (n, %)	0	3 (5.8)	2 (7.7)	0.44	0.36
	1/2	46 (88.5)	24 (92.3)		
	Missing	5 (9.6)	0 (0.0)		
Neoadjuvant therapy (n, %)	None	NA	0 (0.0)		
	Radiotherapy	NA	15 (57.7)		
	Chemoradiation	NA	11 (42.3)		
Adjuvant therapy (n, %)	Adjuvant therapy	0 (0.0)	0 (0.0)		

BMI: body mass index, ASA: American Society of Anesthesiologists classification, MRI: magnetic resonance imaging, MRF+: mesorectal fascia involvement on pre-operative MRI, cT: clinical tumour class, cN: clinical node class, pT: pathological tumour class, pN: pathological node class, R1/R2: irradical surgery, IQR: interquartile range, NA: not applicable.

Supplemental table 2: Baseline characteristics of matched overtreated pN+ sigmoid with sigmoid from the Dutch Cancer Registration.

		Sigmoid	Overtreated pN+	p	SMD
		32	16		
Age (median [IQR])		68 [60, 70]	69 [60, 73]	0.48	0.19
BMI (median [IQR])		25 [24, 28]	27 [25, 29]	0.37	0.13
Sex (n, %)	Female	8 (25.0)	4 (25.0)	1.00	<0.001
	Male	24 (75.0)	12 (75.0)		
ASA (n, %)	1	8 (25.0)	2 (12.5)	0.38	0.61
	2	19 (59.4)	13 (81.2)		
	3	2 (6.2)	1 (6.2)		
	4	0 (0.0)	0 (0.0)		
	Missing	3 (9.4)	0 (0.0)		
Distance MRI (median [IQR])		NA	12 [9, 13]		
MRF+ (n, %)		NA	7 (43.8)		
	Missing		6.2		
cT (n, %)	1	1 (3.1)	0 (0.0)	0.13	0.73
	2	2 (6.2)	5 (31.2)		
	3	27 (84.4)	10 (62.5)		
	4	2 (6.2)	1 (6.2)		
cN (n, %)	0	2 (6.2)	1 (6.2)	0.59	0.37
	1/2	28 (87.5)	15 (93.8)		
	Missing	2 (6.2)	0 (0.0)		
Neoadjuvant therapy (n, %)	None	NA	0 (0.0)		
	Radiotherapy	NA	12 (75.0)		
	Chemoradiation	NA	4 (25.0)		
Adjuvant therapy (n, %)	Adjuvant therapy	32 (100.0)	0 (0.0)		

BMI: body mass index, ASA: American Society of Anesthesiologists classification, MRI: magnetic resonance imaging, MRF+: mesorectal fascia involvement on pre-operative MRI, cT: clinical tumour class, cN: clinical node class, pT: pathological tumour class, pN: pathological node class, R1/R2: irradical surgery, IQR: interquartile range.

Supplemental table 3: Baseline characteristics of matched undertreated sigmoid with sigmoid from the Dutch Cancer Registration.

		Sigmoid	Undertreated	p	SMD
		28	14		
Age (median [IQR])		63 [60, 69]	63 [60, 68]	0.90	0.01
BMI (median [IQR])		28 [26, 28]	27 [26, 28]	0.79	0.004
Sex (n, %)	Female	10 (35.7)	5 (35.7)	1.00	<0.001
	Male	18 (64.3)	9 (64.3)		
ASA (n, %)	1	10 (35.7)	5 (35.7)	0.353	0.577
	2	14 (50.0)	9 (64.3)		
	3	0 (0.0)	0 (0.0)		
	4	0 (0.0)	0 (0.0)		
	Missing	4 (14.3)	0 (0.0)		
Distance MRI (median [IQR])		NA	12 [12, 14]		
MRF+ (n, %)		NA	0 (0.0)		
	Missing		1 (7.1)		
cT (n, %)	1	6 (21.4)	1 (7.1)	0.464	0.417
	2	6 (21.4)	8 (57.1)		
	3	16 (57.1)	5 (35.7)		
	4	0 (0.0)	0 (0.0)		
cN (n, %)	0	27 (96.4)	14 (100.0)	1.00	0.27
	1/2	0 (0.0)	0 (0.0)		
	Missing	1 (3.6)	0 (0.0)		
Neoadjuvant therapy (n, %)	None	NA	14 (100.0)		
	Radiotherapy	NA	0 (0.0)		
	Chemoradiation	NA	0 (0.0)		
Adjuvant thearpy (n, %)	Adjuvant therapy	28 (100.0)	0 (0.0)		

BMI: body mass index, ASA: American Society of Anesthesiologists classification, MRI: magnetic resonance imaging, MRF+: mesorectal fascia involvement on pre-operative MRI, cT: clinical tumour class, cN: clinical node class, pT: pathological tumour class, pN: pathological node class, R1/R2: irradical surgery, IQR: interquartile range.

PART 3

STOMA RELATED MORBIDITY IN TOTAL MESORECTAL EXCISION

CHAPTER 10

MORBIDITY AND COSTS OF DIVERTING ILEOSTOMY IN TRANSANAL TOTAL MESORECTAL EXCISION WITH PRIMARY ANASTOMOSIS FOR RECTAL CANCER

JC Hol, F Bakker, NT van Heek, GM de Jong, FM Kruyt, C Sietses

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ABSTRACT

Background: The role of diverting ileostomy is debated in rectal cancer surgery with primary anastomosis. The aim of this study was to evaluate the associated morbidity and hospital costs of diversion after sphincter saving TaTME surgery.

Methods: All patients undergoing TaTME with primary anastomosis for rectal cancer between January 2012 and December 2019 in a single centre were included. Patients with diverting ileostomy creation during primary surgery were compared with those without ileostomy. Outcomes included length of hospital stay, anastomotic leakage rates and total hospital costs at one year.

Results: One hundred patients were included in the ileostomy group, 46 patients were in the non-ileostomy group. The number of female patients was 31 (30.7%) in the ileostomy group and 21 (45.7%) in the non-ileostomy group. Mean age was 64.5 ± 11.1 years in the ileostomy group and 62.6 ± 10.7 years in the non-ileostomy group. The anastomotic leakage rate was 21.7% in the non- ileostomy group and 15.8% in the ileostomy group ($p = 0.385$). The grade of leakage and number of anastomotic takedowns did not differ between groups. Mean costs at 1 year after surgery was €26,500.13 in the ileostomy group and €16,852.61 in the non-ileostomy group. The main cost driver was longer total length of hospital stay at 1 year (mean 12.4 ± 13.3 days vs 20.6 ± 12.6 days, $p = 0.000$).

Conclusion: Morbidity and associated costs after diverting ileostomy are high. The incidence and morbidity of anastomotic leakage was not reduced by creation of an ileostomy. Omission of a diverting ileostomy could possibly result in a reduction in treatment associated morbidity and costs.

INTRODUCTION

Anastomotic leakage is a severe complication of sphincter saving rectal cancer surgery and occurs in up to 20% of patients (1). It is associated with high morbidity rates, ICU admissions, extended hospital stay, need for reinterventions and readmissions and increased mortality rates (1, 2). It is associated with worse long-term oncological outcome (3). Treatment of anastomotic leakage can result in anastomotic take-down with permanent stoma rates of around 20%, associated with a significant impact on quality of life (4).

It is suggested that the anastomosis could be protected by the use of a diverting ileostomy (5). Even though there seems to be a large practice variation, construction of a diverting ileostomy is common practice these days (6). On the other hand, evidence emerges that a diverting ileostomy does not reduce the incidence of anastomotic leakage, but might reduce the impact (7). However, a diverting ileostomy itself is associated with significant morbidity (8). Stoma-related complication occur in more than half of patients with a diverting stoma and result in more hospital admissions (9). Stoma reversal requires another planned readmission and operation associated with morbidity (9). Therefore, it is associated with a considerable amount of cost beyond the initial cancer treatment (10).

Routine diversion is increasingly debated and there seems to be a large variation between different hospitals in decision making for creation of a diverting ileostomy (6). The disadvantages of ileostomy creation are often not fully taken into account. Because of the associated morbidity and extra costs of an ileostomy, the cost-effectiveness should be taken into consideration in the decision making. However, carefully executed cost-analyses are scarce (11). The aim of this study is to evaluate the associated morbidity and costs of treatment, dependent on whether a diverting ileostomy was constructed during transanal total mesorectal excision (TaTME) with primary anastomosis for rectal cancer.

MATERIALS AND METHODS

Patients

All consecutive patients that underwent TaTME with primary anastomosis between January 2012 and December 2019 for histologically proven rectal cancer were retrospectively included. TaTME was the preferred procedure for rectal resections and surgical technique was performed as described previously by Veltcamp et al (12). Data was collected in January 2021 and each patient had at least 1-year follow-up. The study was approved by the ethics committee of the hospital.

All patients were discussed in a multidisciplinary board, preoperative radiotherapy was administered according to the Dutch guidelines (13). The anastomosis was preferably made side to end using a 31 EEA or 33 EEA hemorrhoid stapler (Medtronic, Dublin, Ireland). Construction of a diverting ileostomy was the attending surgeons' choice, based on multiple criteria: patient characteristics (e.g. male, age, obesity, administration of neoadjuvant radiotherapy) and intra-operative criteria (e.g. difficulty of the operation, height of the anastomosis, incomplete or missing donuts). All patients were subjected to the same postoperative protocol. C-reactive protein (CRP) was measured routinely on each first four postoperative days in all patients. In case of elevated CRP (>150mgl/L) or clinical suspicion of anastomotic leakage, an abdominal computed tomography (CT) scan was performed with rectal contrast. Abdominal imaging was not performed routinely. If CT scan showed signs of anastomotic leakage, laparoscopy with drainage and inspection of the anastomosis and transanal inspection of the anastomosis was performed within 24 h. If an ileostomy was not created during primary surgery, an ileostomy was created during reoperation. When suitable, endoscopic treatment with vacuum-assisted drainage (EVAC) was started to close the abscess cavity. In case of a temporary ileostomy a sigmoidoscopy was performed 6 weeks after primary surgery during outpatient visit before considering planned ileostomy reversal within 3 months after primary surgery.

Outcomes

Patient characteristics documented included sex, BMI, age, American Society of Anesthesiologists (ASA) score. Tumour characteristics documented included rectal cancer height on magnetic resonance imaging (MRI) in cm from anal verge, MRI defined low rectal cancer (14), clinical TNM stage based on MRI, and if neoadjuvant (chemo)radiation was administered. Data was collected on morbidity (complications, reoperations and readmissions, length of postoperative hospital stay in days) at 30 days and one year postoperatively. Stoma reversal and readmissions for treatment of recurrent disease were not scored as readmissions. Anastomotic leakage was defined as anastomotic dehiscence or intra-abdominal abscess adjacent to the anastomotic site, requiring radiologic or surgical intervention during follow-up, including leakages beyond 30 days. Grade of leakage was classified depending on treatment, according to Rahbari et al (15). Stoma-related morbidity included any stoma-related readmission and associated complications and was classified according to Clavien-Dindo classification (16). Parastomal hernias and incisional hernias requiring intervention after stoma reversal were scored. Stoma reversal related morbidity within 30 days was scored according to Clavien-Dindo. Total days of admission at 1 year were the sum of length of stay of initial admission, total days of readmissions and length of stay after stoma reversal (in case of stoma reversal). Presence and type of stoma at 1-year follow-up was scored.

Cost evaluation

Costs of the resources used were derived from the patient registry provided by the financial department of the Gelderse Vallei hospital, Ede, the Netherlands. In the Netherlands, the hospitals reimbursement for diagnostic and therapeutic procedures is standardized using Diagnostic Treatment Combination codes (DBC). Costs concerned any resource use related to the DBC related to the primary operation, starting at the day of primary surgery until 1 year after primary surgery. DBC codes used were rectal cancer (335), recto sigmoid cancer (334) and ICU (000). Costs were divided in 15 resource categories: outpatient visits, daycare visits, admission days, diagnostics, operation, paramedic care during admission, radiology, laboratory, microbiology, pathology, other laboratory costs, paramedics during outpatients visits, blood products, ICU admission and other unspecified costs. The price for primary surgery, relaparotomy and relaparoscopy was €4,916.69, €1,917.49 and €1,574.64, respectively. The price for ileostomy reversal surgery was €1,989.26. Costs for admission to the surgical ward and ICU were €498.99 and € 2,294.25 per day, respectively.

Statistical analysis

Patients were divided into two groups: the ileostomy group consisted of the patients with creation of an ileostomy during primary surgery. The non-ileostomy group consisted of patients without creation of an ileostomy during primary surgery. Student's t test or the Mann Whitney U test was used for comparison of continuous parameters, depending on distribution. A Chi-square test was used for categorical variables. Categorical data were displayed as number (%), continuous variables were displayed as mean (standard deviation) or median (range) in case of non-normal distribution. Differences in costs were compared using Student's t test and ANOVA test, correcting for baseline differences. Due to skewed data and to assess robustness, a non-parametric bootstrap analysis was performed. Costs are presented as mean (standard deviation) in euros. Differences in the distribution of variables were considered significant for p values lower than 0.05. SPSS version 24 (IBM, Chicago, IL, USA) was used for statistical analysis.

RESULTS

A total of 217 patients underwent TaTME for rectal cancer during the inclusion period. A total of 148 patients underwent a sphincter preserving procedure and were eligible for inclusion. One patient was excluded, because cost administration was incomplete for an unknown reason. Of 147 patients, 101 had an ileostomy creation during primary surgery and 46 did not. The number of female patients was 31 (30.7%) in the ileostomy

group and 21 (45.7%) in the non-ileostomy group (p = 0.079). Mean age was 64.5 ± 11.1 years in the ileostomy group and 62.6 ± 10.7 years in the non-ileostomy group (p = 0.328).

Characteristics

Significantly more patients received neoadjuvant radiation therapy in the ileostomy group (73.3% vs 47.8%, p = 0.003). In addition, more patients received neoadjuvant chemoradiotherapy in the ileostomy group (32.7% vs 15.6%, p = 0.003). No differences were seen for other baseline characteristics (Table 1).

Table 1 Patient characteristics

		Non-ileostomy group		**Ileostomy group**		**Total**		
		N=46	**%**	**N=101**	**%**	**N=147**	**%**	**p-value**
Sex	Male	25	54.3	70	69.3	95	64.6	0.079
	Female	21	45.7	31	30.7	52	35.4	
BMI	Mean (SD)	25.9 (3.3)		26.4(4.1)		26.3(3.9)		0.462
Age	Mean (SD)	62.6(10.7)		64.5 (11.1)		63.8 (11.0)		0.328
ASA	I	12	26.1	26	25.7	38	25.9	0.749
	II	26	56.5	62	61.4	88	59.9	
	III	8	17.4	13	12.9	21	14.3	
Height from AV (cm)	Mean (SD)	7.2(2.9)		7.8(3.4)		7.7(3.3)		0.309
MRI defined low rectal cancer	Yes	17	37.0	37	36.6	54	36.7	0.486
Clinical Tumour stage	T1	1	2.2	2	2.0	3	2.0	0.080
	T2	9	19.6	18	17.8	27	18.4	
	T3	29	28.4	73	72.3	102	69.4	
	T4	2	4.3	7	6.9	9	6.1	
	Unknown	5	10.9	1	1.0	6	4.1	
Clinical Nodal stage	N0	22	47.8	45	44.6	67	45.6	0.091
	N1	16	34.8	31	30.7	47	32.0	
	N2	5	10.9	24	23.8	29	19.7	
	Unknown	3	6.5	1	1.0	4	2.7	
Synchronous Metastasis	M+	2	4.3	5	5.0	7	4.8	0.864
Preoperative therapy	RT	22	47.8	74	73,3	96	65.3	0.003
	CRT	7	15.6	33	32.7	40	27.4	0.003

Numbers in parentheses are percentages, unless mentioned otherwise
BMI body mass Index (kg/m^2), SD standard deviation, ASA American Society of Anesthesiologists, cm centimeters, AV anal verge, RT radiotherapy, CRT radiotherapy with additional chemotherapy; MRI magnetic resonance imaging

Postoperative morbidity

An overview of the postoperative morbidity can be seen in Table 2. The incidence of anastomotic leakage was comparable between the two groups: 21.7% in the non-ileostomy group and 15.8% in the ileostomy group (p = 0.385). The grade of leakage, time of diagnosis and rate of anastomotic take-down did not differ between the two groups. Nine out of 10 patients with leakage in the non-ileostomy group required a laparoscopy with creation of an ileostomy. In one patient the anastomosis was directly taken down. In another patient the anastomosis was taken down after ileostomy creation (Table 2).

At 30 days, the overall morbidity rates were higher in the ileostomy group: 29.7% of the patients had minor complications compared to 13% in the non-ileostomy group and 29.7% had major complications compared to 26.1% in the non-ileostomy group (p = 0.039). At 1 year, the overall morbidity rates were higher in the ileostomy group: 26.7% had minor complications compared to 8.7% in the non-ileostomy group and 38.6% had major complications compared to 26.1% in non-ileostomy group (p = 0.002).

At 30 days, 20.8% of the patients had minor stoma-related complications and 8.9% major stoma-related complications in the ileostomy group. Of patients with a secondary ileostomy in the non-ileostomy group 1 (11.1%) had minor stoma-related complications and 1 (11.1) major stoma-related complications (p = 0.780), see Table 3.

At 1 year, 20.8% of the patients had minor stoma-related complications and 14.9% major stoma-related complications in the ileostomy group. Of patients with secondary ileostomy in the non-ileostomy group 1 (11.1%) had minor stoma-related complications and 1 (11.1) major stoma-related complications (p = 0.792).

In the ileostomy group 11.9% had a stoma-related readmission within a year. Of patients with secondary ileostomy in the non-ileostomy group 1 (11.1%) had stoma-related readmission (p = 0.945). Dehydration was the most common reason for stoma-related readmission (7.3%).

Planned stoma reversal took place in 8 out of 9 patients (88.9%) with secondary ileostomy in the non-ileostomy group. Reversal took place in 91 (90.1%) in the ileostomy group (p = 0.908). Of patients undergoing reversal, 2 (25.0%) had minor morbidity after reversal in the non-ileostomy group. In the ileostomy group 26.4% had minor morbidity and 7.7% had major morbidity after reversal (p = 0.881). The stoma rate at 1 year was 22.2% in the non-ileostomy group and 18.8% in the ileostomy group (p = 0.911).

Table 2 Postoperative morbidity

		Non-ileostomy group		Ileostomy group		Total		
		N=46	%	N=101	%	N=147	%	P-value
Anastomotic leak (any)	Yes	10	21.7	16	15.8	26	17.7	0.385
Type of leak (ABC)	A	0	0	0	0	0	0	0.081
	B	0	0	5	5.0	5	3.4	
	C	10	21.7	11	10.9	21	14.3	
Leak requiring reintervention	Relaparoscopy	10	21.7	11	10.9	21	14.3	0.081
	Drainage only	0	0	5	5.0	5	3.4	
Unintended ileostomy	Yes	9	19.6	0	0	9	6.1	0.000
	Already had ileostomy	0	0	16	15.8	16	10.9	
Anastomotic take-down	Yes	2	4.3	8	7.9	10	6.8	0.425
Late/early leakage	Within 30 days	10	21.7	14	13.9	24	16.3	0.325
	After 30 days	0	0	2	2.0	2	1.4	
Length of initial postoperative hospital stay (days)	Mean(SD)	7.9 (7.8)		12.4(14.0)		11.0(12.6)		0.045
30-day Postoperative morbidity	No complications	28	60.9	41	40,6	69	46.9	0.039
	Minor Clavien-Dindo 1-2	6	13.0	30	29.7	36	24.5	
	Severe Clavien-Dindo ≥3	12	26.1	30	29.7	42	28.6	
30-day reoperation	Yes	12	26.1	25	24.8	37	25.2	0.863
30-day readmission	Yes	5	10.9	13	12.9	18	12.2	0.731
1-year morbidity	No complications	30	65.2	35	34.7	65	44.2	0.002
	Minor Clavien-Dindo 1-2	4	8.7	27	26.7	31	21.1	
	Severe Clavien-Dindo ≥3	12	26.1	39	38.6	51	34.7	
Non-stoma related readmission	Yes	5	10.9	23	22.8	28	19.0	0.088
Total days of non-stoma related readmissions	Mean(SD)	12.8 (9.8)		10.6 (15.3)		10.9 (14.4)		0.758
Total days of admission within 1 year	Mean(SD)	12.4 (13.3)		20.6 (10.6)		18.1 (12.1)		0.000
Stoma at 1 year	Yes	4	8.7	19	18.8	23	15.6	0.117
Type of stoma at 1 year	No stoma	42	91.3	82	81.2	124	84.4	0.235
	Loop ileostomy	1	2.2	11	10.9	12	8.2	
	End ileostomy	0	0	2	2.0	2	1.4	
	End colostomy	3	6.5	6	5.9	9	6.1	

Numbers in parentheses are percentages, unless mentioned otherwise

Table 3 Stoma related morbidity

		Non-ileostomy group		Ileostomy group		Total		
		N=9*	%	N=101	%	N=147	%	p-value
30-day stoma related morbidity	No complications	7	77.8	71	70.3	78	70.9	0.780
	Minor Clavien Dindo 1-2	1	11.1	21	20.8	22	20.0	
	Severe Clavien Dindo ≥3	1	11.1	9	8.9	10	6.8	
1 year stoma related morbidity	No complications	7	77.8	65	64.4	72	65.5	0.792
	Minor Clavien Dindo 1-2	1	11.1	21	20.8	22	20.0	
	Severe Clavien Dindo ≥3	1	11.1	15	14.9	16	14.5	
Parastomal hernia	Yes	0	0	5	5.3	5	4.9	0.506
Stoma related readmissions	Yes	1	11.1	12	11.9	13	11.8	0.945
Total days of stoma related readmission	Mean(SD)	2**			8.8(8.7)	7.6(8.5)		0.513
Reason for stoma related readmission	High output/ dehydration	1	11.1	7	6.9	8	7.3	0.958
	Non-functioning stoma/ileus	0	0	3	3.0	3	2.7	
	Dermatitis	0	0	1	1.0	1	0.9	
	Herniation	0	0	1	1.0	1	0.9	
Stoma related reoperations	Yes	0	0	6	5.9	6	5.5	0.452
Stoma reversal	No	1	11.1	10	9.9	12	8.2	0.908
	Yes	8	88.9	91	90.1	100	68.0	
Reversal related morbidity***	No complications	0	0	60	65.9	66	66.7	0.881
	Minor Clavien-Dindo 1-2	2	25.0	24	26.4	26	26.3	
	Severe Clavien-Dindo ≥3	0	0	7	7.7	7	7.1	
Total days of stay after reversal	Mean(SD)	7.1(7.5)		7.3(7.3)		7.3(7.3)		*0.949*
Reason non reversal	Palliative treatment	1	11.1	4	4.0	5	4.5	0.627
	Expected poor functional outcome	0	0	3	3.0	3	2.7	
	Secondary colostomy	0	0	2	2.0	2	1.8	
	High risk patient	0	0	1	1.0	1	0.9	
Incisional hernia after reversal	Yes	0	0	11	12.0	11	109	0.592
Stoma at 1 year	Yes	2	22.2	19	18.8	21	19.1	0.803
Type of stoma at 1 year	No stoma	7	77.8	82	81.2	89	80.9	0.911
	Loop ileostomy	1	11.1	11	10.9	12	10.9	
	End ileostomy	0	0	2	2.0	2	1.8	
	End colostomy	1	11.1	6	5.9	7	6.4	

Numbers in parentheses are percentages, unless mentioned otherwise * Patients with a secondary ileostomy ** No SD because only one patient *** Of patients undergoing reversal

The initial length of hospital stay was 12.4 ± 14.3 days in the ileostomy and 7.9 ± 7.8 days in the non-ileostomy group (p = 0.045). Mean total admission days of hospital admissions within 1 year was 12.4 ± 13.3 in the non-ileostomy group and 20.6 ± 10.6 in the ileostomy group (p = 0.000).

Cost analysis

Costs of the different resource categories are shown in Table 4. Hospital admission days and operations were the largest source of costs at 1 year in both groups. The mean cost for total days of hospital admissions within 1 year was €10,291.05 ± €5,276.97 in the ileostomy group and €6.200.02 ± €6,649.54 in the non-ileostomy group (p = 0.000). The mean cost for operations was €7.952.35 ± €2,359.44 in the ileostomy group and €6,322.16 ± €2,710.09

Table 4 Mean cost per patient and difference in mean cost per resource in euros

	Non-ileostomy group		**Ileostomy group**		**Difference between groups**	
	N=46	**SD**	**N=101**	**SD**		**p-value**
Outpatient visits	642.50	374.62	798.61	330.54	156.11	0.012
Day care visits	26.28	129.38	120.31	370.83	94.03	0.097
Admission days	6,200.02	6,649.54	10,291.05	5,276.97	4,091.02	0.000
Diagnostics (including endoscopy)	396.60	536.34	671.82	662.78	275.21	0.015
Operation	6,322.16	2,710.09	7,952.35	2,359.44	1,630.19	0.000
Paramedic during admissions	81.78	188.63	197.40	346.45	115.61	0.036
Radiology	500.17	501.98	653.26	581.28	153.09	0.125
Laboratory	392.43	619.04	740.70	1,240.25	348.26	0.074
Microbiology	55.81	135.58	134.35	350.05	78.54	0.144
Pathology laboratory	437.48	247.74	386.51	346.00	50.98	0.370
Other laboratory costs	3.12	14.15	7.25	€ 29.98	4.13	0.375
Paramedic during outpatient	580.74	646.81	1,076.64	1,029.30	495.90	0.003
Blood products	10.09	€ 68.41	37.77	237.52	27.68	0.440
ICU admission	549.32	1,888.03	2,695.49	16,808.00	2,146.17	0.390
Other not specified	654.05	731,13	736.62	637.13	82.56	0.488
Total costs at 1 year	16,852.61	11,490.54	26,500.13	20,279.07	9.647,52	0.003

ICU: intensive care unit

in the non-ileostomy (p = 0.000). Significantly higher mean costs were seen in the ileostomy group for outpatients visits (€798.61 ± €330.54 vs €642.50 ± €374.62, p = 0.012), diagnostics (€671.82 ± €662.78 vs €396.60 ± €536.34, p = 0.015), paramedic care during admissions (€197.40 ± €346.45 vs €81.78 ± €188.63, p = 0.036) and paramedic care during outpatient visits (€1,076.64 ± €1,029.30 vs €580.74 ± €646.81, p = 0.003).

Table 5 Mean total cost and difference in mean total cost per patient in euros

	Non-ileostomy group	Ileostomy group					
	N=46	N=101	Difference between groups	SE	95%CI lower	95%CI upper	p-value
Total costs at 1 year	16,852.61	26,500.13	9,647.52	3,204.69	3,313.57	15,981.47	0.003
Adjusted analysis*	16,483.16	26,500.13	10,430.31	3,324.30	3,858.81	17,001.82	0.002
Non-parametric test (median(range))	11,349.41 (10,045.28-18,724.81)	21,733.75 (17,383.19-29,347.87)					0.000

*ANCOVA test with neoadjuvant chemotherapy and neoadjuvant radiation therapy as covariates

Mean total costs were €16,852.61 in the non-ileostomy group and €26,500.13 in the ileostomy group, resulting in a mean difference of €9,647.52 (p = 0.003; CI 95% €3,313.57–€15,981.47). Adjusted analysis and non-parametric testing showed similar results (Table 5).

DISCUSSION

Routine diversion after rectal cancer surgery has been debated in the recent years. Surgeons favouring diversion suggested the creation of an ileostomy might be beneficial in terms of reducing the impact of anastomotic leakages (5, 17). Surgeons omitting a diverting ileostomy stress the significant morbidity and costs associated with the ileostomy itself (6). In this single centre study, 101 patients with ileostomy were compared to 46 without ileostomy creation during primary rectal cancer surgery. Significantly more morbidity and higher costs were seen at one year in the group with ileostomy creation during primary surgery. Anastomotic leakage rates and permanent stoma rates did not differ 1 year after surgery.

The encountered anastomotic leakage rate of 17.7% was comparable to that seen in the international TaTME registry and a large snapshot study (1, 2). This number might seem relatively high, but there is a wide range in reported leak rates in literature, depending on definition, setting and length of follow up. It should be noted that our definition of anastomotic leakage comprised any type of leakage, therefore including chronic fistula and delayed leakages (beyond 30 days) as well.

Previous research indicates that a diverting ileostomy may not reduce the incidence of anastomotic leakage; however, it might reduce the impact of anastomotic leakage (7),

ensuring that the consequences of anastomotic leakage are diminished and the anastomosis has better chance to heal. The results from our current study do not show this. The takedown rates and permanent stoma rates were comparable between the two groups. This is in line with the results from previous studies showing comparable anastomotic takedown rates (18). Furthermore, some studies suggest the risk of permanent stoma after leakage might even be higher in the ileostomy group (4).

Prior studies have noted that morbidity related to the construction and presence of the stoma during several months can be considerable (9). We observed stoma-related morbidity in 35.7% at 1 year in patients who received an ileostomy during primary surgery, which is comparable to that encountered in previous studies (9, 18). Moreover, stoma reversal is known to be associated with significant morbidity as well (9). Several studies have shown the stoma is not reversed at all in up to 20% of all patients (19, 20). The same rate of non-reversal was seen in our study and the 1-year stoma-related morbidity in our study resulted in almost twice as many days of hospital sin the ileostomy group. This was an important cost driver, resulting in significantly higher costs in the ileostomy group. The main reason for readmissions was dehydration/high-output ileostomy. Another important cost driver in the ileostomy group was reoperation. Although the number of relaparoscopies for anastomotic leakage was obviously higher in the group without ileostomy, patients with an ileostomy generally required more reoperations, including a planned stoma reversal. This has also been underlined by other authors (8).

The negative impact of diverting ileostomy on costs has been pointed out in other studies as well. Koperna et al. showed 1.5 times higher costs in the ileostomy group (21). However, this study was performed in the era of open surgery with relatively small numbers, and therefore, its results cannot be generalized. Floodeen et al. used data derived from a randomized trial and the total number of days of hospital stay were comparable between groups and the observed difference in cost of €5,741 per patient was relatively small (11). Comparable results were seen in a more recent study by Chapman et al. with shorter follow-up time (22). Our study gives an overview of the exact costs in both groups from the hospital perspective based on local hospital costs, whereas most other studies use an estimation of costs. Beside costs for operations and hospital admissions, we included other resources used for rectal cancer treatment. We included ICU admission costs to give a unique and honest depiction of the hospital costs, because severe complications requiring ICU admissions could have been more apparent in one of the groups. Most other cost analyses do not take ICU admissions into account as this can be a disproportionate cost driver in a relatively small amount of patients and has the potential to skew the outcome in one of both groups.

An ileostomy might be omitted during TME surgery in a subgroup of patients. The results from our study do not suggest omission is safe in all patients. Risk factors for anastomotic leakage need to be taken into consideration. Risk factors include: smoking, obesity, age, ASA classification, distant tumour location and neoadjuvant therapy (23). Interestingly, neoadjuvant therapy is an independent risk factor for anastomotic leakage and non-reversal of a secondary stoma (1, 19). In our study the leakage rate was expected to be higher in the ileostomy group with more neoadjuvant treatment; however, the anastomotic leakage rate was comparable between groups. Moreover, there was no significant difference in stoma rate at 1 year. This suggests that an ileostomy could have been omitted in some of these patients. Additional research is needed for selection of subgroups of patients in whom an ileostomy can be safely omitted (24).

An ileostomy might be omitted during TME surgery in a subgroup of patients. The results from our study do not suggest omission is safe in all patients. Risk factors for anastomotic leakage need to be taken into consideration. Risk factors include: smoking, obesity, age, ASA-classification, distant tumour location and neoadjuvant therapy (23). Interestingly, neoadjuvant therapy is an independent risk factor for anastomotic leakage and non-reversal of a secondary stoma (1, 19). In our study the leakage rate was expected to be higher in the ileostomy group with more neoadjuvant treatment, however the anastomotic leakage rate was comparable between groups. Moreover, there was no significant difference in stoma rate at one year. This suggests an ileostomy might be omitted in some of these patients. Additional research is needed for selection of subgroups of patients in whom an ileostomy can be safely omitted.

Some limitations of our study should be mentioned. First, selection bias is apparent as more patients received neoadjuvant therapy in the ileostomy group, which is one of the criteria for the choice to create an ileostomy. The study had low power to assess the impact of factors, such as neoadjuvant therapy on costs because of the relative small sample size and retrospective nature of the study. The relatively small sample size could have decreased the chance for type II errors. A larger sample size would be ideal to identify a significant difference in anastomotic leakage rate. However, the anastomotic leakage rates were comparable to that in other studies. The rate of anastomotic take-down an rate of permanent stoma did not differ, suggesting no significant difference in leakage despite of lack of power. The primary goal of the study was not to show any difference in anastomotic leakage, but to focus on costs associated with morbidity after ileostomy creation. Furthermore, we created a homogenous cohort using a single centre, single surgeon cohort with the same TaTME technique. The morbidity and the potential learning curve effect of our cohort have been described extensively in previous studies (24). Second, minor morbidity was not investigated, such as skin irritation and

plaque leakage. However, our goal was to create a robust cost comparison between the two groups and to describe the most important complications, cost drivers and to estimate the costs of stoma-related complications, rather than an actual cost-reduction analysis. Therefore, no formal quality of life assessment and no quality adjusted life years calculation have been performed. The cost analysis is an estimation of the actual cost reduction. Omission of stomas, and therefore, reduction of stoma-related morbidity and associated costs could ultimately benefit in reduced number of nurses or staff in hospital.

CONCLUSIONS

Morbidity and associated costs after diverting ileostomy are high. The incidence and morbidity of anastomotic leakage was not reduced by creation of an ileostomy. The rate of permanent stoma was lower in the group without ileostomy. Omission of a diverting ileostomy could result in a reduction in treatment associated morbidity and costs. Close attention should be paid to signals of anastomotic leakage to allow for urgent reintervention to assure early treatment of the leakage. Further effort should be put in research defining patients in whom an ileostomy can safely be omitted.

ETHICS APPROVAL

The study was approved by the local Ethics Committee of the hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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CHAPTER 11

IMPACT OF A DIVERTING ILEOSTOMY IN TOTAL MESORECTAL EXCISION WITH PRIMARY ANASTOMOSIS FOR RECTAL CANCER

JC Hol, TA Burghgraef, MLW Rutgers, RMPH Crolla, AAW van Geloven, R Hompes, JWA Leijtens, F Polat, A Pronk, AB Smits, JB Tuynman, EGG Verdaasdonk, ECJ Consten, C Sietses

Submitted

ABSTRACT

Aim: The aim of this study is to gain insight in the risk of permanent stoma and morbidity depending on whether a diverting ileostomy is constructed during total mesorectal excision (TME) with primary anastomosis for rectal cancer.

Method*:* Patients undergoing TME with primary anastomosis for rectal cancer between 2015 and 2017 in eleven participating centres were included. A comparison was made depending on whether a diverting ileostomy was constructed during primary surgery. Primary endpoint was stoma rate at one year. Secondary endpoints were severity and rate of anastomotic leakage, overall complication rate within 30 days and stoma reversal related morbidity.

Results: In 353 out of 595 patients (59.3%) a diverting ileostomy was created during primary surgery. Stoma rate at one year was 9.9% in the non-ileostomy group and 18.7% in the ileostomy group (p=0.003). After correction for confounders, multivariate analysis showed that diverting ileostomy was an independent risk factor for stoma at one year (OR 2.563 (95%CI 1.424-4.611), p=0.002). Anastomotic leakage rate was 17.8% in the non-ileostomy group and 17.2% in the ileostomy group (p=0.913). Overall 30 days complication rate was 37.6% in the non-ileostomy group and 56.1% in the ileostomy group (p<0.001). Stoma reversal related morbidity rate was 17.9%.

Conclusions: The stoma rate at one year was higher in patients with ileostomy construction during primary surgery. The incidence and severity of anastomotic leakage were not reduced by creation of an ileostomy. The morbidity after diverting ileostomy creation was significant.

WHAT DOES THIS PAPER ADD TO THE LITERATURE?

After correction for potential confounders this study showed diverting ileostomy was an independent risk factor for higher stoma rate one year after surgery. Diverting ileostomy is associated with significant morbidity and does not lead to lower anastomotic leakage rates. These findings have important implications for developing future studies on selective diversion.

INTRODUCTION

Total mesorectal excision (TME), often combined with neoadjuvant treatment is standard of care for curative rectal cancer treatment (1, 2). The introduction of minimally invasive techniques reduced morbidity, infection rates and length of postoperative hospital stay (3, 4). When possible, a sphincter-saving procedure is performed with an anastomosis to regain bowel continuity after resection.

Anastomotic leakage after a sphincter-saving procedure is a common and serious complication associated with severe morbidity and mortality (5). The incidence of anastomotic leakage is up to 20% (5, 6). It predisposes rectal cancer patients to worse oncological outcomes (7). Treatment of anastomotic leakage can result in anastomotic take-down with permanent stoma rates of 20%, associated with a significant impact on quality of life (8).

Creation of a temporary loop ileostomy during sphincter-saving TME surgery might decrease the consequences of an anastomotic leakage (9, 10). On the other hand, a diverting ileostomy itself can induce significant discomfort, morbidity, and mortality (11, 12). Stoma related complications occur in more than half of the cases and result in more hospital admission (11). This is associated with increased treatment costs (13). Patients have to go through a second surgery for stoma closure, which is associated with significant risks and morbidity (11). Furthermore, a significant proportion of the diverting stomas are never closed (14).

Even when a diverting stoma is constructed there is still a risk of anastomotic leakage (9). Therefore, routine diversion is increasingly debated. There seems to be a large variation in selecting patients for stoma construction. In 76% of the patients a stoma is created, which varies from 0 to 100% between centres (15). Several studies have assessed the efficacy of high selective diversion only, instead of routine diversion (16). However, most previous studies focussed on the impact of diversion on anastomotic leakage, while only few concentrated on the high numbers of stoma related complications and the risk of permanent stoma after loop ileostomy construction. Therefore, the aim of this study is to gain insight in the risk of permanent stoma and morbidity depending on whether a diverting ileostomy is constructed during TME with primary anastomosis for rectal cancer.

METHOD

Study design and patients

A retrospective multicentre cohort study was performed in eleven hospitals in the Netherlands. All patients 18 years or older, diagnosed with histologically proven rectal cancer and operated between January 2015 and December 2017 with construction of a primary anastomosis were included. Excluded from analysis were patients with sigmoidal tumours according to the sigmoidal take-off definition (17), presence of multiple colonic tumours, acute procedures and non-TME surgery including local excision, transanal endoscopic microsurgery (TEM) or transanal minimally invasive surgery (TAMIS). Neoadjuvant treatment was administered, when deemed necessary according to the Dutch national guidelines (18). Each of the eleven participating centres performed at least 40 procedures per year, using either laparoscopic, robot-assisted TME or TaTME. Construction of a diverting ileostomy was the attending surgeon's choice. For analysis patients were dived into two groups: depending on the construction of a diverting ileostomy during primary surgery.

Data was derived from the Dutch Colo Rectal Audit (DCRA) (19). Data not captured in this nationwide audit was completed using the local electronic medical record (EMR). Patients were pseudo anonymised before consulting the EMR for data collection. All data was collected between January and April 2020 and stored in the data management system CASTOR. A protocol study protocol was composed prior to initiation of the study and approved by the MEC-U medical ethics committee (AW 9.023/W18.100) and by the local boards of all participating centres.

Outcomes and definitions

Baseline characteristics included: age, sex, body mass index (BMI), ASA classification (American Society of Anesthesiologists), tumour height from anorectal junction (ARJ) in centimetres based on pre-treatment MRI, tumour height based on pre-treatment MRI according to LOREC criteria (20), clinical TNM staging based on MRI, mesorectal fascia (MRF) involvement on MRI, administration of pre-operative (chemo)radiation therapy, type of surgery, intra-operative details on stapled or hand sewn anastomosis, presence of intra-operative complications, conversion to laparotomy and operating time in minutes. Length of initial hospital stay was the number of postoperative days during initial admission. Complications related to primary surgery were categorised according to Clavien-Dindo (21). All reinterventions and readmissions within 30 days related to primary surgery were scored. Anastomotic leakage was defined as dehiscence or intra- abdominal abscess near the anastomosis, requiring any type of intervention. Anastomotic leakage was graded according to the need for intervention, based on

the definition of the International Study Group of Rectal Cancer (ISGRC) (22). Date of diagnosis of leakage was the date of detection on radiological imaging or reoperation.

Primary endpoint was the overall stoma rate at one year, including any type of stoma. Secondary endpoints were rate of anastomotic leakage, overall complication rate within 30 days and stoma reversal related morbidity.

Statistical analysis

Data of categorical variables were presented as numbers (%), data of continuous variables were presented as mean (standard deviation) or median [interquartile range] depending on type of distribution. Comparison of categorical data was done using Chi-square analysis, or fisher exact test when appropriate. Comparison of continuous data between groups was done using T-test in case of normal distribution or Mann-Whitney-U test in case of non-normal distribution. After univariate logistic regression, multivariate logistic regression was performed using backward selection. For one variable propensity score adjusted multivariate regression was performed because of low incidence of the primary outcome, and subsequent suspected problems with overfitting. All statistical analyses were carried out using SPSS Statistics version 24 (IBM, Chicago, IL, USA).

RESULTS

A total of 1834 patients were registered in DCRA between 2015 and 2017 in the participating hospitals. A total of 595 underwent sphincter saving TME surgery for rectal cancer and have met the inclusion criteria. In 353 patients (59.3%) a diverting ileostomy was created at primary surgery. An overview can be seen in the flow diagram (Figure 1). The hospitals unadjusted proportion of diverting ileostomy creation varied from 7.1% to 83.0% (supplementary Figure 1).

Characteristics

Table 1 shows an overview of all characteristics of both groups. There were more male patients in the ileostomy group (68.3% vs 56.2%, p=0.003), more MRI defined low rectal cancers in the ileostomy group (43.9% vs 36.8%, p=0.010), more cT3-4 tumours in the ileostomy group (p<0.001), while there was less cN0 stage in the ileostomy group (34.3% vs 61.6%, p<0.001). More (chemo)radiation therapy was administered in the ileostomy group (75.6% vs 38.4%, p<0.001).

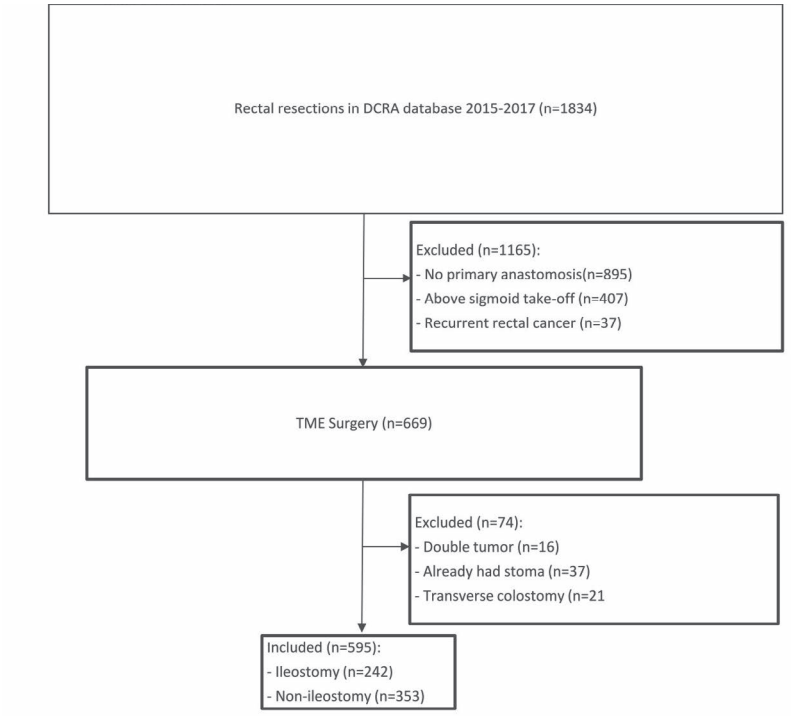

Figure 1 Flowchart

30 day morbidity

Table 2 shows an overview of the morbidity in both groups. 30-day morbidity rates were significantly higher in the ileostomy group (56.1% vs 37.6%, p<0.001). This was confirmed in a multivariate logistic regression analysis (OR 2.037(95%CI1.434-2.892), p<0.001), see Supplementary Table 1. The surgical complication rate was higher in the ileostomy group (42.8% vs 27.7%, p<0.001) and the presence of ileus was also higher in the ileostomy group (24.1% vs 8.3%). Severe complications (Clavien-Dindo grade III or higher) were less frequently seen in the ileostomy group (39.7 vs 61.5%, p=0.001) and median days of ICU admission was shorter in the ileostomy group (1[1-2] vs 1[1-1], p=0.046). More readmissions within 30 days occurred in the ileostomy group (20.1% vs 11.2%, p=0.003) and median length of hospital stay in days was longer in the ileostomy group (7[5-15] vs 5 [4-7], p<0.001).

Stoma related morbidity

Table 3 shows an overview of the stoma-related morbidity in both groups. In the non-ileostomy group, 43(17.8%) had secondary ileostomy construction. The rate of stoma related complications within 30 days was 45.5% in the ileostomy group and 6.6% in the non-ileostomy group (p<0.001). Stoma related complications occurring after 30

Table 1 Characteristics

		Non-ileostomy		Ileostomy		Total		
		N=242	%	N=353	%	N=595	%	p-value
Sex	Male	136	56.2	241	68.3	377	63.4	0.003
	Female	106	43.8	112	31.7	218	36.6	
Age (years)	Mean(SD)	64.5(10.0)		63.8(9.3)		64.0(9.6)		0.397
BMI	Mean(SD)	25.7	4.2	26.1	3.8	25.9	3.98	0.287
ASA	I	62	25.6	85	24.1	147	24.7	0.377
	II	139	57.4	223	63.2	362	60.8	
	III	39	16.1	44	12.5	83	13.9	
	IV	2	0.8	1	0.3	3	0.5	
Height from ARJ on MRI (cm)	Median[IQR]	7[5-9]		6[4.5-8]		6.5	[4.5-9.0]	0.002
MRI defined LOREC low rectal cancer		89	36.8	155	43.9	244	41.0	0.010
Clinical Tumour stage	T1	12	5.0	10	2.8	22	3.7	<0.001
	T2	104	43.0	63	17.8	167	28.1	*
	T3	119	49.2	255	72.2	374	62.9	*
	T4	7	2.9	25	7.1	32	5.4	*
Clinical Nodal stage	N0	149	61.6	121	34.3	270	45.4	0.000*
	N1	74	30.6	125	35.4	199	33.4	
	N2	18	7.4	107	30.3	125	21.0	*
	Unknown	1	0.4	0	0,0	1	0.2	
Synchronous Metastasis	Yes	12	5.0	34	9.6	46	7.7	0.111
Preoperative therapy	No	149	61.6	86	24.4	235	39.5	<0.001
	(chemo)radiation	93	38.4	267	75.6	360	60.5	

Table 1 Characteristics (continued)

		Non-ileostomy		Ileostomy		Total		
		N=242	%	N=353	%	N=595	%	p-value
Type of surgery	Open	5	2.1	7	2.0	12	2.0	0.027
	Laparoscopic	98	40.5	122	34.6	220	37.0	
	TaTME	77	31.8	92	26.1	169	28.4	
	Robotic	62	25.6	132	37.4	194	32.6	*
Technique of anastomosis	Handsewn	7	2.9	14	4.0	21	3.5	0.753
	Stapled	234	96.7	336	95.5	570	96.0	
	Robotic stapler	1	0.4	2	0.6	3	0.5	
Type of anastomosis	Side to Side	59	24.4	82	23.3	141	23.7	0.456
	End to Side	134	55.4	215	61.1	349	58.8	
	End to End	41	16.9	46	13.1	87	14.6	
	Other configuration	8	3.3	9	2.6	17	2.9	
Intra-operative complications	Yes	13	5.4	18	5.1	31	5.2	1.000
Duration of operation minutes	Mean(SD)	184.3(83.2)		194.9(67.3)		190.5(74.3)		0.086
Conversion to laparotomy	Yes	6	2.5	15	4.2	21	3.5	0.270

Numbers in parentheses are percentages, unless mentioned otherwise
Abbreviations: BMI = Body Mass Index (kg/m2), SD = standard deviation, ASA = American Society of Anesthesiologists, cm = centimeters, ARJ = anorectal junction. LOREC = MRI defined low rectal cancer below insertion of levator muscle
*=post-hoc test significant for this category

Table 2 Morbidity

		Non-ileostomy		Ileostomy		Total		
		N=242	%	N=353	%	N=595	%	p-value
Complications within 30 days		91	37.6	198	56.1	289	48.6	<0.01
	Pulmonary complications	9	3.7	21	5.9	30	5.0	0.256
	Cardiac complications	8	3.3	13	3.7	21	3.5	0.827
	Thrombotic event	2	0.8	8	2.3	10	1.7	0.213
	Infection not pulmonary or surgical	16	6.6	34	9.6	50	8.4	0.229
	Neurological	6	2.5	10	2.8	16	2.7	0.806
	Urological	19	7.9	20	5.7	39	6.6	0.314
	Other	10	4.1	41	11.6	51	8.6	0.001
Surgical complications within 30days		67	27.7	151	42.8	218	36.6	<0.001
	Abscess	10	4.1	7	2.0	17	2.9	0.138
	Bleeding	8	3.3	5	1.4	13	2.2	0.155
	Ileus	20	8.3	85	24.1	105	17.6	<0.001
	Fascia dehiscence	1	0.4	3	0.8	4	0.7	0.650
	Bowel perforation	3	1.2	2	0.6	5	0.8	0.653
	Ureter/bladder leak	1	0.4	1	0.3	2	0.3	0.788
	Wound infection	7	2.9	10	2.8	17	2.9	0.966
	Other	9	3.7	26	7.4	35	5.9	0.076
Anastomotic leak (any)	Yes	43	17.8	61	17.3	104	17.5	0.913
Most severe complication (Clavien Dindo)**	Mild Grade 1-2	35	38.5	120	60.3	155	53.4	0.001
	Severe Grade 3 or higher	56	61.5	79	39.7	13.5	46.6	

Table 2 Morbidity (continued)

		Non-ileostomy		Ileostomy		Total		
		N=242	%	N=353	%	N=595	%	p-value
Reinterventions within 30 days	yes	52	21.5	71	20.1	123	20.7	0.757
Readmission within 30 days	yes	27	11.2	71	20.1	98	16.5	0.003
Number of readmissions	1	23	85.2	58	81.7	81	82.7	0.896
	2	3	11.1	10	14.1	13	13.3	
	3	1	3.7	3	4.2	4	4.1	
Reason for readmission	Anastomotic leakage or abscess	14	51.9	25	35.2	39	39.8	0.014
	ileus	0	0.0	15	21.1	15	15.3	*
	obstipation	1	3.7	1	1.4	2	2.0	
	Stoma related	1	3.7	13	18.3	14	14.3	
	Infection not pulmonary or surgical	2	7.4	1	1.4	3	3.1	
	Other type	9	33.3	16	22.5	25	25.5	
Total days of readmission within 30 days	Median [IQR]	11[3-35.5]		5.5[2.25-14.0]		5.5[3.0-13.0]		0.744
Length of hospital stay (days)	Median[IQR]	5[4-7]		7[5-15]		6[4-12]		<0.001
Days of ICU admission	Median[IQR]	1[1-2]		1[1-1]		1[1-1]		0.046

Numbers in parentheses are percentages. unless mentioned otherwise
Abbreviations: IQR = interquartile range
*=post-hoc test significant for this category
** of 290 patients with complications

Table 3 Stoma related morbidity

		Non-ileostomy		Ileostomy		Total		
		N=242	%	N=353	%	N=595	%	p-value
Stoma related morbidity within 30 days		6	6.6	90	45.5	96	33.2	<0.001
	High output/ dehydration	3	1.2	67	19.0	70	11.8	<0.001
	Prolapse	1	0.4	1	0.3	2	0.3	1.000
	Parastomal hernia	0	0.0	3	0.8	3	0.5	0.275
	Other	4	1.7	25	7.1	29	4.9	0.003
Had stoma during first year	Constructed at primary resection	0	0.0	333	94.3	333	56.0	<0.001*
	After primary resection because of complication	40	16.5	7	2.0	47	7.9	*
	After reversal new stoma	0	0.0	9	2.5	9	2.5	*
	Other	3	1.2	4	1.1	7	1.2	
	Never had a stoma	199	82.2	0	0.0	199	33.4	*
Presence of a stoma at one year	Yes	24	9.9	66	18.7	90	15.1	0.003
Type of stoma one year	Stoma free	218	90.1	287	81.3	505	84.9	0.013*
	Loop ileostomy	12	5.0	48	13.6	60	10.1	*
	End ileostomy	0	0.0	1	0.3	1	0.2	
	Loop colostomy	1	0.4	2	0.6	3	0.5	
	End colostomy	11	4.5	15	4.2	26	4.4	

Table 3 Stoma related morbidity (continued)

		Non-ileostomy		Ileostomy		Total		
		N=242	%	N=353	%	N=595	%	p-value
Stoma related complications after 30 days	yes	16		72	20.5	88	21.9	0.101
	Ileus	0	0.0	5	1.4	5	0.8	0.084
	Prolapse	3	1.2	6	1.7	9	1.5	0.745
	Parastomal hernia	5	2.1	7	2.0	12	2.0	1.000
	Stricture	1	0.4	2	0.6	3	0.5	1.000
	Dehiscence	0	0.0	1	0.3	1	0.2	1.000
	Necrosis	1	0.4	1	0.3	2	0.3	1.000
	Skin issues	6	2.5	45	12.7	51	8.6	<0.001
	High output/ dehydration	4	1.7	14	4.0	18	3.0	0.144
	Other	1	0.4	3	0.8	4	0.7	0.650
Stoma related reinterventions during follow-up	yes	5	2.1	12	3.4	17	2.8	0.044
Number of stoma related reinverventions	Median[IQR]	1[1-1]		1[1-1]		1[1-1]		0.799
Stoma related readmissions after 30 days**	Yes	0	0.0	8	2.3	8.0	1.3	
Number of stoma related readmissions	1	0	0.0	7	87.5	7.0	87.5	
	3	0	0.0	1	12.5	1.0	12.5	
Total days of stoma related readmissions after 30 days	Median [IQR]	NA		6[2.25-10.5]		6[2.25-10.5]		

Table 3 Stoma related morbidity (continued)

		Non-ileostomy		Ileostomy		Total		
		N=242	%	N=353	%	N=595	%	p-value
Reason non reversal	Patient preference	1	4.8	3	10.3	4	8.0	0.415
	Palliative treatment	3	14.3	7	24.1	10	20.0	
	Expected poor functional outcome	3	14.3	3	10.3	6	12.0	
	Underwent APR	4	19.0	1	3.4	5	10.0	
	Other	10	47.6	15	51.7	25	50.0	

Numbers in parentheses are percentages. unless mentioned otherwise
Abbreviations: IQR = interquartile range, APR = abdominoperineal resection
*=post-hoc test significant for this category
** 5 had high output ileostomy, 1 had parastomal hernia, 2 had ileus

Table 4 Subgroup analysis of anastomotic leakage

		Non-ileostomy		Ileostomy		Total		
		N=43	%	N=61	%	N=104	%	p-value
Grade of leakage (ABC)	A	4	9.3	13	21.3	17	16.3	<0.001
	B	6	14.0	30	49.2	36	34.6	*
	C	33	76.7	18	29.5	51	49.0	*
Type of leakage	Dehiscence	27	62.8	18	29.5	45	43.3	0.002*
	Abcess	11	25.6	32	52.5	43	41.3	*
	Sinus	0	0.0	4	6.6	4	3.8	
	Fistula	3	7.0	2	3.3	5	4.8	
	Other	2	4.7	5	8.2	7	6.7	
Days until detection of leakage	Median[IQR]	5[3-11]		12[7-32]		8[4-20.5]		<0.001
Early or late leakage	Diagnosis within 4 weeks	41	95.3	46	75.4	87	83.7	0.007
	Diagnosis after 4 weeks	2	4.7	15	24.6	17	16.3	
Reintervention within 30 days	Yes	39	90.7	41	67.2	80	76.9	0.008
Most severe complication within 30 days (Clavien Dindo)	Mild Grade 1-2	3	7.1	13	24.1	16	16.7	0.027
	Severe Grade 3 or higher	39	92.9	41	75.9	80	83.3	
ICU admission in days	Median[IQR]	2[1-3.5]		1[1-3]		2[1-3.25]		0.205
Admission time in days	Median[IQR]	11[5.5-19.25]		7.5[5-17.25]		8[5-17.25]		0.384
Presence of a stoma at one year	No	21	48.8	30	49.2	51	49.0	0.676
	Loop ileostomy	12	27.9	19	31.1	31	29.8	
	Loop colostomy	1	2.3	0	0.0	1	1.0	
	End colostomy	9	20.9	12	19.7	21	20.2	

Numbers in parentheses are percentages, unless mentioned otherwise.
Abbreviations: ICU=intensive care unit
*=post-hoc test significant for this category

days, during follow up were 20.5% in the ileostomy group and 3.4% had stoma related interventions**.** At 4 weeks postoperatively 96.6% had a stoma in the ileostomy group and 15.3% of patients had a stoma in the non-ileostomy group (p<0.001). During the first year, 82.2% never had a stoma in the non-ileostomy group. At one year postoperatively 18.7% had a stoma in the ileostomy group and 9.9% had a stoma in the non-ileostomy group (p=0.003). This difference in stoma rate at one year was confirmed in a multivariate logistic regression analysis (OR 2.563 (95%CI 1.424-4.611), p=0.002), see supplementary Table 1. Figure 2 shows the presence of stoma during one year follow-up in both groups.

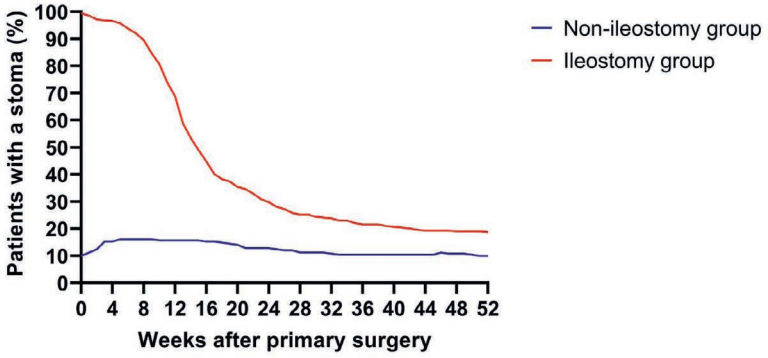

Figure 2 Presence of a stoma after primary surgery

Anastomotic leakage

The overall rate of anastomotic leakage did not differ between groups (17.3% in the ileostomy group and 17.8% in the non-ileostomy group, p=0.913), see Table 2. Table 4 gives an overview of a subgroup analysis of morbidity after anastomotic leakage in 104 patients. Rate of grade C leakage was lower in the ileostomy group (29.5% of all leakages, compared to 76.7% in the non-ileostomy group, p<0.001). This was confirmed by a multivariate analysis (OR 0.263(95%CI 0.138-0.505), p<0.001), see supplementary Table 1. Rate of grade B leakage was higher in the ileostomy group (49.2% vs 14%). In the non-ileostomy group in all grade C leakages a stoma was created during reoperation. In 25 out of 33 (75.8%) grade C leakages an ileostomy was created, the others required direct take-down of the anastomosis.

The median duration between primary surgery and diagnosis of anastomotic leakage was 5[3-11] days in the non-ileostomy group and 12[7-32] days in the ileostomy group (p<0.001). More late leakages after 4 weeks were seen in the ileostomy group (24.6% vs 4.7%, p=0.007). Leakage rate at 4 weeks was 13.0% in the ileostomy group and 16.9% in the non-ileostomy group (p=0.185). Leakage rate at one year was 15.9% in the ileostomy

Table 5 Stoma reversal related morbidity

		Non-ileostomy		Ileostomy		Total		P-value
		N=25	54.3%	N=322	91.7%	N=347	87.4%	<0.001
Reversal related morbidity within 30 days	Yes	4	16.0	58	18.0	62	17.9	1.000
	No complications	21	84.0	264	82.0	285	82.1	
	Surgical complication	2	8.0	42	13.0	44	12.7	0.557
	Ileus	1	4.0	26	8.1	27	7.8	0.707
	Anastomotic leakage	0	0.0	6	1.9	6	1.7	1.000
	Fascia dehiscence	0	0.0	0	0.0	0	0.0	
	Bleeding	0	0.0	7	2.2	7	2.0	0.673
	Abscess	0	0.0	1	0.3	1	0.3	1.000
	Perforation	0	0.0	0	0.0	0	0.0	
	Wound infection	0	0.0	5	1.6	5	1.4	1.000
	Other surgical*	1	4.0	4	1.2	5	1.4	0.313
	General complications	1	4.0	15	4.7	16	4.6	1.000
	Pulmonary	0	0.0	1	0.3	1	0.3	1.000
	Cardiac	0	0.0	3	0.9	3	0.9	1.000
	Thrombotic	0	0.0	0	0.0	0	0.0	
	Neurological	0	0.0	4	1.2	4	1.2	1.000
	Infectious	0	0.0	3	0.9	3	0.9	1.000
	urological	0	0.0	1	0.3	1	0.3	1.000
	other	1	4.0	7	2.2	8	2.3	1.000
	Other complications not specified	1	4.0	5	1.6	6	1.7	0.364

Table 5 Stoma reversal related morbidity

		Non-ileostomy		Ileostomy		Total		P-value
		N=25	54.3%	N=322	91.7%	N=347	87.4%	<0.001
Reversal related morbidity within 30 days	Yes	4	16.0	58	18.0	62	17.9	1.000
	No complications	21	84.0	264	82.0	285	82.1	
	Surgical complication	2	8.0	42	13.0	44	12.7	0.557
	Ileus	1	4.0	26	8.1	27	7.8	0.707
	Anastomotic leakage	0	0.0	6	1.9	6	1.7	1.000
	Fascia dehiscence	0	0.0	0	0.0	0	0.0	
	Bleeding	0	0.0	7	2.2	7	2.0	0.673
	Abscess	0	0.0	1	0.3	1	0.3	1.000
	Perforation	0	0.0	0	0.0	0	0.0	
	Wound infection	0	0.0	5	1.6	5	1.4	1.000
	Other surgical*	1	4.0	4	1.2	5	1.4	0.313
	General complications	1	4.0	15	4.7	16	4.6	1.000
	Pulmonary	0	0.0	1	0.3	1	0.3	1.000
	Cardiac	0	0.0	3	0.9	3	0.9	1.000
	Thrombotic	0	0.0	0	0.0	0	0.0	
	Neurological	0	0.0	4	1.2	4	1.2	1.000
	Infectious	0	0.0	3	0.9	3	0.9	1.000
	urological	0	0.0	1	0.3	1	0.3	1.000
	other	1	4.0	7	2.2	8	2.3	1.000
	Other complications not specified	1	4.0	5	1.6	6	1.7	0.364

Table 5 Stoma reversal related morbidity (continued)

		Non-ileostomy		Ileostomy		Total		P-value
		N=25	54.3%	N=322	91.7%	N=347	87.4%	<0.001
Incisional hernia at previous stoma site	No	21	84.0	283	88.7	304	88.4	0.523
	Yes	4	16.0	30	9.4	34	9.9	
	Unknown	0	0.0	6	1.9	6	1.7	
Surgical treatment of incisional hernia**	no	1	25.0	19	63.3	20	58.8	0.231
	yes	3	75.0	11	36.7	14	41.2	
New stoma after reversal	yes	1	4.0	34	10.6	35	10.1	0.438
Type of new stoma after reversal	Loop ileostomy	1	100.0	2	5.9	3	8.6	0.143
	End ileostomy	0	0.0	1	2.9	1	2.9	
	Loop colostomy	0	0.0	9	26.5	9	25.7	
	End colostomy	0	0.0	21	61.8	21	60.0	
	Unknown	0	0.0	1	2.9	1	2.9	
Reason for new stoma after reversal	Leakage after reversal	0	0.0	11	32.4	11	31.4	0.779
	Poor functional outcome	0	0.0	5	14.7	5	14.3	
	Palliative treatment	0	0.0	2	5.9	2	5.7	
	Other	1	100.0	16	47.1	17	48.6	

Numbers in parentheses are percentages, unless mentioned otherwise

* Others included reoperations for: 1 ileus, 1 serosa defects, 1 ileus requiring bowel resection, 1 laparoscopic lavage, 1 abscess at anastomotic site

** % of patients with Incisional hernia

group and 16.8% in the non-ileostomy group (p=0.540). The rate and type of stoma at one year did not differ between groups after anastomotic leakage. At one year 20.9% in the non-ileostomy group and 19.7% in the ileostomy group had an end-colostomy (p=0.676). Univariate and multivariate analysis showed no impact of ileostomy on the anastomotic leakage rate (OR 0.737(95%CI 0.460-1.180), p=0.204), see supplementary Table 1.

Morbidity after stoma reversal

A total of 347 patients (87.4%) had undergone stoma reversal: 322 (91.7%) in the ileostomy group and 25 out of 46 patients (54.3%) who had a secondary ileostomy in the non-ileostomy group. After stoma reversal, 62(17.9%) had postoperative complications of which ileus was the most common complication (7.8%). Wound infection rate was 1.4%. 34 patients (9.9%) developed an incisional hernia at the previous stoma site for which 41.2% underwent surgical treatment of this incisional hernia. A new stoma was constructed after reversal in 35 cases (10.1%). The most common type of new stoma after reversal was end colostomy in 21(60%). The most common reason for new stoma after reversal was anastomotic leakage at the colorectal anastomosis in 11 (31.4%). Table 5 shows an overview of morbidity after stoma reversal.

DISCUSSION

In this multicentre retrospective study, 353 patients with diverting ileostomy were compared to 242 without diverting ileostomy creation during primary rectal cancer surgery. In the ileostomy group, 18.7% had presence of a stoma at one year, while this was 9.9% in the non-ileostomy group. The higher rate of stoma at one year was confirmed in a multivariate analysis. Significantly more postoperative and stoma related morbidity was seen in the group with ileostomy creation during primary surgery. The incidence and mortality of anastomotic leakage was comparable between both groups, although more grade C leakages were seen in the non-ileostomy group. In all grade C leakages in the non-ileostomy group a secondary stoma was constructed.

The observed anastomotic leakage rate of around 17% in both groups match those observed in previous studies which include late leakages as well (6, 23). These results are similar to those reported for the minimally invasive techniques used in this study (23, 24). More late leakages were seen in the ileostomy group and this was associated with higher rates of permanent stomas. These results are in agreement with Borstlap et al, who showed that the diagnosis of leakage is delayed if a diverting stoma is present (6). A previous randomized trial on the role of diverting stoma reported higher symptomatic

leakage rates in the group without ileostomy, but long-term stoma rates were comparable between groups (10). Surgeons in favour of routine diversion stress that patients who develop anastomotic leakage and do not have their anastomosis defunctioned might be at risk of more severe complications. The current study showed a higher reintervention rate in patients with anastomotic leakage in the group without ileostomy. Although the number of severe complications was higher in the non-ileostomy group due to more reoperations, the number of days of ICU admission did not differ. Emmanuel et al showed the number of relaparoscopies for anastomotic leakage was higher in the group without ileostomy, but patients with an ileostomy generally require more reoperations when including planned stoma reversal surgery (25).

It is also stressed that patients who develop anastomotic leakage might be at risk of losing the anastomosis in case of anastomotic leakage. The present study did not show a higher anastomotic takedown rate after anastomotic leakage in the group without ileostomy. In fact, the rate of stoma at one year was higher in the ileostomy group, even after correction for confounders. The rate of end colostomy was comparable between groups. This supports the opinion that routine diversion might be omitted in a subgroup of patients. There are other studies suggesting that a diverting stoma can be safely omitted without loss of continuity in case of leakage (16, 26). It should be noted that these studies used a setting of close anastomotic leakage surveillance with an aggressive management protocol. Early detection and intervention for anastomotic leakage is important to optimize outcome. Anastomotic leakage is associated with poorer oncological outcomes. Long-term results from the GRECCAR 5 trial showed that oncological outcomes were not worse in patients with early biochemical diagnosis of anastomotic leakage (27). Early diagnosis of anastomotic leakage is more likely to succeed in absence of an ileostomy.

Although a diverting stoma is intended to be restored, up to 20% of all patients end up with a permanent stoma (28). This can be either a new secondary stoma of any kind or the existing defunctioning stoma. This is a clinically important problem as it exposes patients to long-term morbidity of an ileostomy and the associated impact on quality of life (8). The ileostomy group reflects a cohort that has more risk factors for anastomotic leakage. Neoadjuvant therapy is an independent risk factor for non-reversal of a secondary stoma (6, 14). Although the anastomotic leakage rate was expected to be higher in the ileostomy group because of more neoadjuvant treatment, the anastomotic leakage rate was comparable. Stoma rate at one year was higher in the ileostomy group, even after correction for risk factors using a multivariate analysis. Stoma rate at one year was not higher in the subgroup of patients with anastomotic leakage. This finding is contrary to previous studies which have suggested the risk of permanent stoma after

anastomotic leakage might be higher in ileostomy patients (8). We saw a diverting stoma formed at the primary procedure is not related to final outcome of a permanent stoma among patients with anastomotic leakage. This suggests an ileostomy might be omitted in a group of patients.

The results from the present study however do not suggest omission is safe in all patients. Further research should be conducted to identify patients at risk of anastomotic leakage and a permanent stoma. Also, future effort should be put in better understanding and modification of risk factors which might decrease anastomotic leakage rates in the future. Prevention, early diagnosis and early management of anastomotic leakage might improve the anastomotic healing rate (6, 16). Early diagnosis should be achieved by paying close attention to signals of anastomotic leakage, to ensure early reintervention to provide optimal control of sepsis and anastomotic healing. This should be done in a comparable matter, however to date there is no international guideline on the treatment of anastomotic leakage.

There are many studies focusing on the impact of diversion on anastomotic leakage. However, only few focus on the disadvantages of ileostomy construction. Postoperative morbidity within 30 days was significantly higher patients with a diverting ileostomy and stoma related complications were present in almost half of all patients with a diverting ileostomy. These results support previous research which emphasizes a diverting ileostomy itself is associated with significant morbidity (11, 25). Moreover, stoma reversal surgery related morbidity was 17.9%. These results match those observed in earlier studies stating that stoma reversal can come at a high risk (11, 29). All of these disadvantages can lead to increased treatment cost beyond the initial cancer treatment, suggesting the possible benefits might not outweigh the costs of a diverting ileostomy (13).

The present study gives a comprehensive overview of stoma related morbidity and is one of the largest studies on this topic so far. Most studies were underpowered and diversion is often not used as parameter in studies on anastomotic leakage. Morbidity during the entire stoma period was included, instead of a 30-year period only and stoma closure related morbidity was included as well. All defunctioning stomas were ileostomies and colostomies were excluded from analysis to create a more homogeneous cohort. Ileostomies are associated with a higher number of readmission rates, mostly due to dehydration (11). Selection bias might be apparent as there was more neoadjuvant radiation therapy in the ileostomy group. This was corrected for using a multivariate analysis. Minor morbidity was not investigated, such as skin irritation and plaque leakage. Obviously multiple centres participated in this study, therefore different indications for ileostomy creation and different treatment protocols for anastomotic leakage were

used. Length of hospital stay after the initial operation was calculated. But it would be interesting to know the total length of hospital stay for the entire treatment to perform an economic evaluation. Ultimately, quality of life and functional outcome data might be useful in discussing the topic with patients and shared decision making.

Conclusion

In summary, the stoma rate at one year is higher in patients with ileostomy construction during primary surgery. The incidence and morbidity of anastomotic leakage were not reduced by creation of an ileostomy. The morbidity after diverting ileostomy creation is significant. Omission of a diverting ileostomy could result in a reduction in treatment associated morbidity. Further research should focus on safe omission of a diverting ileostomy.

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Supplementary Table 1 Outcomes of univariate logistic regression and multivariate logistic regression for all factors

Stoma at 1 year follow-up								
Univariate analysis					**Multivariate analysis**			
	RR	**95%CI Lower**	**95% CI Upper**	**P-value**	**RR**	**95%CI Lower**	**95% CI Upper**	**P-value**
Ileostomy	2.089	1.268	3.441	0.004	2.563	1.424	4.611	0.002
Sex	0.411	0.241	0.704	0.001	0.501	0.273	0.921	0.026
Age	1.027	1.002	1.053	0.034	1.044	1.012	1.076	0.006
BMI	1.041	0.986	1.100	0.142				
ASA	1.208	0.848	1.721	0.295				
Distance ARJ on MRI	0.907	0.837	0.983	0.018				
Neoadjuvant	1.538	0.952	2.486	0.079				
Conversion	0.552	0.156	1.960	0.358				
Intra-operative complication	0.729	0.290	1.831	0.501				
cT	1.232	0.852	1.782	0.267				
cN	1.122	0.874	1.440	0.366				
cM	1.112	0.858	1.443	0.422				
Leakage	12.723	7.640	21.188	<0.001	15.366	8.802	26.826	<0.001
Overall anastomotic failure rate								
Univariate analysis					**Multivariate analysis**			
	RR	**95%CI Lower**	**95% CI Upper**	**P-value**	**RR**	**95%CI Lower**	**95% CI Upper**	**P-value**
Ileostomy	0.962	0.626	1.479	0.860	0.737	0.460	1.180	0.204
Sex	0.616	0.387	0.981	0.041	0.625	0.389	1.003	0.052
Age	0.995	0.974	1.017	1.017				
BMI	1.007	0.955	1.062	0.789				
ASA	1.124	0.804	1.571	0.495				
Distance ARJ on MRI	0.906	0.841	0.977	0.011	0.915	0.848	0.988	0.023
Neoadjuvant	1.578	1.003	2.484	0.049	1.598	0.976	2.615	0.062
Conversion	0.679	0.241	1.919	0.466				
Intra-operative complication	1.109	0.416	2.960	0.836				

Complications within 30 days								
Univariate analysis					**Multivariate analysis**			
	RR	**95%CI Lower**	**95% CI Upper**	**P-value**	**RR**	**95%CI Lower**	**95% CI Upper**	**P-value**
Ileostomy	2.120	1.517	2.961	<0.001	2.037	1.434	2.892	<0.001
Sex	0.375	0.265	0.531	<0.001	0.398	0.278	0.569	<0.001
Age	1.006	0.989	1.023	0.491				
BMI	1.013	0.973	1.055	0.527				
ASA	1.516	1.167	1.968	0.002	1.550	1.175	2.045	0.002
Distance ARJ on MRI	0.966	0.913	1.023	0.238				
Neoadjuvant	1.492	1.071	2.078	0.018				
Conversion	1.364	0.709	2.622	0.353				
Intra-operative complication	0.767	0.371	1.586	0.474				
Anastomotic failure grade C								
Univariate analysis					**Multivariate analysis PSA****			
	RR	**95%CI Lower**	**95% CI Upper**	**P-value**	**RR**	**95%CI Lower**	**95% CI Upper**	**P-value**
Ileostomy	0.340	0.187	0.620	<0.001	0.263	0.138	0.505	<0.001

CHAPTER 12

GENERAL SUMMARY

The aim of this thesis was to explore the current three minimally invasive techniques for total mesorectal excision (TME). TME was implemented in the 1980s and there has been a shift from open towards laparoscopic TME. Recent developments in the field of minimally invasive techniques have led to the question in which way robot-assisted TME and transanal TME (TaTME) could be beneficial to patients. The profit could be substantial, as colorectal cancer is the third most common malignancy worldwide and TME is still the golden standard for curative treatment of rectal cancer (1). The first step in exploring robot-assisted and TaTME is exploring their implementation.

PART ONE: IMPLEMENTATION

In **chapter 2** the feasibility and long-term oncological safety of TaTME was investigated in two high volume referral centres that started the technique in the Netherlands. In 159 procedures, the local recurrence rates were 2.0% at three year 2.0% and 4.0% at five year follow-up. High tumour stage, severe postoperative complications and presence of a presacral abscess were risk factors for local recurrence. A 97.5% rate of good quality specimen was seen, comparable to earlier reports (2). This study demonstrated good oncological outcomes after TaTME in experienced hands.

However, data from an external audit in 120 patients, comprising the first 10 patients in each 12 centres from the structured training pathway in the Netherlands showed different results in **chapter 3**. The local recurrence rate during the learning curve was 10% with a median follow-up of 21.9 months, despite low circumferential resection margin (CRM) involvement rates. Most of the recurrences were multifocal. This confirmed the local recurrence rates and multifocality encountered during implementation of TaTME in Norway, which were published in 2019 (3). We performed a second analysis in centres that continued the technique and performed at least 45 cases. Local recurrence rate was 15% in the first 10 patients in each centre, which dropped to an overall 5.6% over time in a total of 266 patients.

Comparable results were seen in **chapter 4** in a cohort from the centres that continued the technique. In 624 cases a local recurrence rate of 12.5% was seen during implementation of TaTME in the first 10 cases from each centre, which lowered to an acceptable rate of 3.4% when experience increased. Thus the learning curve appeared to be associated with high local recurrence rate, which diminished as experience increased. These findings may be explained by suboptimal execution during the learning curve rather than the technique itself.

To assess morbidity, oncological and functional outcome during implementation of robot-assisted TME, a study was conducted in a large teaching hospital with extensive previous laparoscopic experience. A total of 105 operations were performed by a total of five different surgeons. As the learning curve is assumed to be around 20 cases per surgeon, it was assumed all surgeons were in their learning curve (4, 5). In **chapter 5**, the local recurrence rate after robot-assisted TME was 7.4% at 3 years. Acceptable rates of morbidity and other short-term outcomes were seen. Despite the learning curve, the incidence of functional complaints was comparable to that in literature (6). The incidence of major low anterior resection syndrome (LARS) was 55.3%.

PART TWO: COMPARISON

Because comparative data between laparoscopic, robot-assisted and TaTME is lacking, a study was conducted comparing the three techniques. Because most studies often do not take into account the learning curve of new techniques, data was compared from eleven Dutch hospitals with profound experience with one of the three techniques. A total of 1078 patients were included in the study.

In **chapter 6** short-term outcomes were compared. Short-term outcomes were comparable in experienced centres. The primary anastomosis rate was higher in robot (61.9%) and TaTME (61.9%) centres, compared to laparoscopy (39.4%). After propensity score matching of specialized techniques in expert centres excluding APR: the rate of primary anastomosis was again higher in robot (89.8%) and TaTME (84.3%), compared to laparoscopy (66.7%). Conversion rates did not differ. Quality of the specimen, rate of CRM involvement and morbidity did not differ between the techniques. The rates of anastomotic leakage were 23.6% in laparoscopic, 21.6% in robot-assisted and 17.6% in TaTME. Although the rate of primary anastomosis was higher in robot-assisted and TaTME centres, this did not lead to a higher rate of anastomotic leakage. Dutch national audits reported similar anastomotic leakage rates (7, 8). This confirms safe execution of robot-assisted TME and TaTME in experienced hands.

When looking at the three-year oncological results in **chapter 7**, equal oncological outcomes were seen for all three techniques. Three-year overall survival was 90.0% after laparoscopic, 90.4% after robot-assisted and 87.6% after transanal low anterior resection (LAR). Three-year disease-free survival was 77.8% after laparoscopic, 75.8% after robot-assisted and 78.8% for transanal LAR. Three year local recurrence rate was 6.1% in laparoscopic, 6.4% in robot-assisted and 5.7% in transanal LAR. These numbers are comparable with large trials comparing laparoscopic and open TME (9-11). Cox-re-

gression did not show a significant difference between the techniques while taking confounders into account. Again, this confirmed safe execution of robot-assisted TME and TaTME in experienced hands.

In **chapter 8**, three-year oncological results did not differ between laparoscopic, robot-assisted or TaTME when looking at MRI-defined low-rectal cancers. Nor was there any difference in three year oncological results between MRI-defined low rectal cancers and proximal rectal cancers. However a non-restorative LAR technique was associated with worse overall survival, worse disease free survival and higher local recurrence rates.

To see what proportion of patients would meet the criteria of the sigmoid-take off definition of the rectum, pre-treatment MRI imaging was re-assessed for all patients in **chapter 9**. 13.6% of the rectal cancers would have been diagnosed with sigmoid cancer according to the sigmoid take-off. This has implications for their treatment, as 56.4% of these patients would have received other (neo) adjuvant treatment. Sigmoid cancers seemed to benefit from adjuvant chemotherapy, whereas chemotherapy is hardly administered in rectal cancer patients.

PART THREE: STOMA RELATED MORBIDITY

Regardless of the approach used, the role of diverting ileostomy is debated in TME with primary anastomosis. In **chapter 10** 101 patients with ileostomy were compared to 46 without ileostomy after TaTME. Anastomotic leakage did not significantly differ; the anastomotic leakage rate was 21.7% in patients without ileostomy and 15.8% in patients with ileostomy. The grade of leakage and number of anastomotic takedowns did not differ. However, the ileostomy related morbidity resulted in median increased hospital costs of € 9,647.52 within one year after primary surgery. The main cost driver was longer total length of hospital stay in patients with an ileostomy.

To evaluate the risk of permanent stoma after ileostomy construction, the same comparison was made in a larger cohort of 595 patients undergoing laparoscopic, robot-assisted or TaTME, of which 353 had ileostomy construction. In **chapter 11** the permanent stoma rate at one year was lower (9.9%) in patients without ileostomy and higher (18.7%) in patients with ileostomy. Again, anastomotic leakage rates were comparable. Overall 30-day complication rate was higher in patients with ileostomy, indicating ileostomy related morbidity.

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CHAPTER 13

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

During the last decades, efforts have been made in decreasing morbidity and improving outcomes of total mesorectal excision (TME) for patients with rectal cancer by implementation of novel techniques. More restorative procedures are performed, efforts have been made to reduce anastomotic leakage rates and neoadjuvant therapy was introduced to gain local control in advanced tumours (1-3). Local recurrence rates dropped to 5% at three years and disease free survival and overall survival improved gradually as well. Neoadjuvant chemo- and or radiation therapy serve as adjuvants to improve outcomes after surgery (4). However, these adjuvants are not a substitute for TME. Despite the efforts in the past decades; open TME, laparoscopic TME, robot-assisted TME and transanal TME (TaTME) are still associated with severe morbidity and a significant risk of anastomotic leakage. Moreover, long-term functional outcome after TME remains poor, and over half of the patients develop urogenital complaints, gastrointestinal complaints, sexual dysfunction or stoma-related problems (5). The morbidity, oncological outcomes and poor functional outcomes associated with TME are important issues for future research.

PART ONE: IMPLEMENTATION

TaTME is a promising but complex technique, associated with a considerable learning curve. Concerning reports have been published, detailing specific morbidity: CO2 embolus, ureteral injury and contamination due to purse string failure (6, 7). The most concerning report is a moratorium on TaTME from Norway. This moratorium published in 2019 reported a 9.5% local recurrence rate after median 11 months of follow-up in 110 patients operated within a 3-year period (8). National audit data revealed an estimated early local recurrence rate of 11.6% in all 157 cases of TaTME in Norway (9). This is in contrast with the 3.4% local recurrence rate from the Norwegian Colorectal Cancer Registry and double the rate in the COLOR II trial (1). Moreover, most local recurrences were multifocal or extensive. If the cases were evenly distributed among the four participating centres, this would result in an average of 9 cases of TaTME per year. This is a relatively low volume and suggests the surgeons were in the beginning of their learning curve. It is known that higher volumes are associated with better outcomes in terms of less conversion, decreased rate of severe complications and higher rates of good quality specimen (10). The learning curve for TaTME for surgeons with single port experience is at least 40 cases to reach sufficiency in terms of conversion rate and rate of major complications (11, 12). Because TaTME is such a complex procedure (13), several countries started a structured training program (14, 15). Even when proficiency is reached, caution is needed. In laparoscopic TME significantly higher rates of recurrences were seen among the first 100 cases, compared to the following 200 (16).

In experienced hands, TaTME can be an attractive alternative for the resection of challenging mid- and low rectal cancers. Promising initial results led to rapid globalization of the technique. An estimated number of 300 centres worldwide have implemented the technique (17). There are a growing number of cohort studies from all over the world, showing excellent long-term oncological results after TaTME (18-20). In the Australasian structured training pathway, the observed local recurrence rate was 1.9% (21). However, the multifocal pattern seen in the Norwegian cohort and the Netherlands external audit of structured training pathway cohort appears to be new. It is not reported in open, laparoscopic or robot-assisted TME and the multifocal pattern was not seen in the Dutch TME trial (3). This raises the question if the multifocal local recurrence pattern might be related to TaTME. The endoluminal approach used in TATME is different and might lead to bacterial contamination from the rectum (22). A study examining intra-abdominal cultures during TaTME showed contamination in one third of the patients, but this did not lead to a higher rate of postoperative infectious complications (23). Contamination with tumour cells is a controversial explanation. In a recent study examining tumour spill during TaTME, no signs of intraluminal or presacral tumour spill were seen (24). The mechanism could be the same mechanism responsible for the port-site metastases that were seen during the implementation of laparoscopic TME (25). Careful evaluation of a technique is the only way to identify such risk factors. Even though the risk of local recurrence is multifactorial, it appears to be associated with the learning curve. The risk for local recurrence seems to diminish with gained experience. Suboptimal execution of the technique during the learning curve might be an explanation for this, rather than TaTME itself.

The learning curve of TaTME and the associated risk for local recurrence have important consequences. In the Netherlands, enrolment of new centres in the structured training program was postponed, to allow for further evaluation of oncological safety. The Idea, Development, Exploration, Assessment and Long-term follow-up (IDEAL) framework aims to prevent new surgical techniques from being implemented to early (26). Many reports focussed on the implementation of TaTME in a fraction of the centres that use the technique, and only few focussed on long-term outcome. Even though the international TaTME registry is useful in capturing morbidity, this registry is not obligatory and highly depends on completeness of the data, which is a potential source of bias (27). Eventually, oncological safety after TaTME should be demonstrated in a multicentre international setting. Long-term data from the COLOR III trial are awaited. This non-inferiority trial comparing laparoscopic and TaTME is currently enrolling, ensuring quality assessment using central MRI review, intra-operative video assessment and central specimen evaluation (28).

Robot-assisted TME is associated with a learning curve as well. The use of robot-assisted TME has expanded rapidly during the past decade. Many surgeons were convinced by the 3D depth of field, stable camera platform and articulating instruments. Also, superior ergonomics made it an attractive alternative for conventional laparoscopy (29). Superiority over laparoscopic TME has not been proven in terms of short-term and pathological outcomes (2, 30). The learning curve of the technique is believed to be relatively short: around 20 cases for surgeons with previous laparoscopic experience curve (31, 32). These learning curves assessments are however based on short-term surrogate outcomes such as duration of the operation, CRM involvement rates and short-term morbidity instead of long-term outcome (33, 34). Safety of the learning curve should ideally be confirmed by long-term oncological outcomes. Although the technique is widely implemented; reports on long-term outcomes after robot-assisted TME are scarce (35). Earlier small retrospective cohorts showed low local recurrence rates, but had shorter follow-up times, younger patients and lower rates of neoadjuvant treatment, suggesting selection bias in these studies (36-41). A high recurrence rate has been reported in a comparative study: the learning curve was associated with a local recurrence rate of 9.5% (42).

PART TWO: COMPARISON

Choices for a specific technique depend on surgeon's preference and experience, together with patient characteristics and patient's preferences. Studies directly comparing TaTME and robot-assisted TME are scarce (43). Some comparing studies contain only small series of patients (44-47). Others lack important outcome measures such as conversion rates (45, 48). The differences between the techniques complicate such comparisons. Both techniques are used for different indications. Robot-assisted TME seems to be feasible for the multivisceral resection of clinical T4 tumours (49), whereas TaTME is hardly used for this indication (50). Robot-assisted TME can be used for APR, whereas TaTME is not used for APR (51). An argument in favour of robot-assisted TME is that it has the potential to be more nerve sparing, leading to less functional complaints (31). In theory, the good quality vision and superior instrument handling should allow for meticulous dissection, preserving the autonomic nerve plexus. This could reduce postoperative urinary and sexual dysfunction (52). However, this potential benefit of robot-assisted TME has not been confirmed by the largest randomized trial (2). If a good and meticulous TME dissection can be performed, good oncological and functional outcomes can be achieved. The same thing applies for TaTME. Meticulous dissection and improved visualisation of the neurovascular bundles by using TaTME might protect sexual function. Similar functional outcomes and quality of life were seen after laparo-

scopic TME and TaTME (53). As seen in part two of this thesis, good quality surgery can be achieved by robot-assisted TME and TaTME in experienced hands.

A major drawback of robotic surgery is that it seems to be more time consuming, because draping and docking of the surgical robot takes additional operating time (54). The biggest criticism of robotic surgery is that it comes at higher financial costs (55, 56). The biggest expenses are the high fixed costs of the robotic surgical systems. Robot surgical systems also require maintenance and the use of disposable instruments. Currently, there seems to be one sole producer of robotic surgical systems. Prices might decline if there would be more competition in the market for robotic surgical systems and related consumables. Details on specific price agreements are often not released, which hampers cost-effectiveness analyses. Suppliers offer disposables used in robotic surgery at lower prices if the number of purchased disposables increases. This motivates centers to use the robotic platform for other indications as well, in order to increase volume and be more price competing. Because of the decentralized system, hospitals are in a hard negotiating position when willing to buy a robotic system. Transparency of the market and centralization of robotic surgery might lead to a better negotiating position and could decrease prices further. The decision to purchase a robotic surgical system is made by individual hospitals. Hospitals want to keep up with the market to attract patients and hospitals are seeking for volume and want to compete with another. This led to the purchase of an expensive surgical robotic system in numerous hospitals. Patient preference can play a role in this decision as well. In robot assisted prostatectomy, although not proven to be superior, patient preference led to a rapid expense of robot surgery (57). On the other hand, expansion of the use of robot surgery is likely to make robot surgery more price competing. The question is whether the proposed benefits of robot-assisted TME justify the high costs of robotic surgery (55, 58, 59). In the past, laparoscopy used to be more expensive than open surgery, due to the use of more disposable products. But laparoscopy was clearly associated with shorter hospital stay and less postoperative morbidity (60). In the future, robot-assisted surgery might be further improved with innovations in computer guided surgery. Examples include the combination of robot-assisted surgery and enhanced reality or image guided surgery. Ultimately, the introduction of new robotic systems into the market may alter the cost-effectiveness.

TaTME might be a valuable option in hospitals in pursuit of a low-priced alternative, where previous experience with single port laparoscopic platforms can be used. The problem with distal cross stapling is not solved in robot-assisted surgery, whereas TaTME does not use cross stapling, enabling the creation of a very low anastomosis. This makes TaTME a favorable technique in patients in pursuit of a very low anastomosis,

who would otherwise undergo APR. These are patients in which the creation of a very low anastomosis is the only option to regain continuity. However, such patients need to be carefully selected, as anorectal function is not necessarily better in patients with a very low anastomosis. TaTME might also be in favor in patients where a solely abdominal approach is hampered due to adhesions, fibrosis or radiation effects. Furthermore, using a rectotomy without the need for distal cross stapling makes TaTME a more favorable technique in obese patients with a narrow pelvis. In theory, this should lead to a reduced number of conversion and anastomotic leakages after TaTME, but this is not confirmed (27, 61).

One of the main focus points in research on TME is the creation of an anastomosis. In contrast to daily practice, the proportion of non-restorative procedures in randomized trials is relatively small (60). Although there is a trend toward more sphincter preserving LAR, rates of non-restorative LAR and APR are still high (62, 63). The use of non-restorative LAR is currently debated, as oncological outcome might be comprised after non-restorative LAR (64, 65). This relationship remains unclear, but might be due to technical difficulty during the procedure (66). Furthermore, perforation of the rectum stump could lead to pelvic sepsis, and pelvic sepsis can increase the risk for recurrence (67-69). In case of a non-restorative procedure, an intersphincteric APR might be considered. APR has equal risk of abscess formation (69). The results from an ongoing trial comparing APR with non-restorative LAR are currently awaited (70).

With the expansion of robot-assisted and TaTME the number of restorative procedures seems to increase. An explanation for this is that the new techniques enable the safe creation of a low anastomosis. Restorative procedures are being performed in patients who would otherwise undergo APR. However, this raises the question whether a patient might actually benefit from this. There is no doubt that the anorectal function of patients with a proximal is superior to that in patients with a distal or true colo-anal anastomosis (71). Patients with a low anastomosis are at high risk of developing low anterior resection syndrome (LARS), which has a significant impact on quality of life (5, 72). LARS is still a major problem and occurs in more than half of all patients (72). The construction of an anastomosis in patients who would otherwise undergo APR does not necessarily contribute to better functional outcome or quality of life. Despite promising oncological outcomes, functional outcome after TME remains poor. Over half of the patients develop urogenital complaints, anorectal complaints or sexual dysfunction (5). Functional outcome after laparoscopy, robot-assisted and TaTME is still to be determined, preferably in a prospective setting, such as the RESET trial (73). In the Netherlands, the VANTAGE trial is expected to start enrolling shortly.

One could ask itself; why not combine the advantages of robot-assisted and TaTME? In hybrid robotic TaTME a robotic platform is used for the abdominal approach, simultaneously with conventional TaTME. Small series showed this approach was feasible, safe and quick in case of a two-team approach but the indications were unclear (74-77). In robotic TaTME a robotic platform is used to perform TaTME. Improved visibility and superior instrument handling of the robot are combined with the concept of TaTME. In theory, the steep learning curve of TaTME would be favoured with the aid of robotic technology. However, most series showed that although it was feasible, the technique was unquestionably complex to perform (78-83). The development of next-generation single-port robotic-platforms might reduce the complexity and allow complete omission of the abdominal approach, performing scar-less, true NOTES surgery. In 2017 Marks et al published a cadaveric feasibility study (84). Several cases on human patients have been published since (85, 86).

PART THREE: STOMA RELATED MORBIDITY

Anastomotic leakage is a severe but common complication (87). It can result in severe morbidity and takedown of the anastomosis (88). It even predisposes patients to an increased risk of local recurrence (89). Routine diversion after LAR with anastomosis has become standard practice worldwide, but results in significant disadvantages (90, 91). Over half of the patients with an ileostomy get ileostomy related complications (92). The reduction of leakage rates and reoperation rates is often not accomplished by use of an ileostomy. The number of anastomotic takedown was expected to be higher in patients without ileostomy, but an ileostomy actually resulted in more permanent stoma (93). Therefore routine diversion is increasingly debated.

Omission of an ileostomy could lead a reduction of stoma-related morbidity and costs (94). Several studies showed high selective diversion appears to be safe (64, 95). However, widespread omission of stoma construction seems to be hampered. There are several explanations for this. Firstly, an often used quality parameter is the rate of short-term reinterventions after surgery. Most surgeons do expect that an ileostomy reduces the need for reoperation in case of anastomotic leakages. Reducing the reintervention rates might encourage surgeons to perform routine diversion. Secondly, there appears to be a large practice variation in diversion (96). The current selection criteria for diversion remain arbitrary. Patient factors and even surgeon personality seems to play a role in the decision to create an ileostomy (97). This now seems to result in a large overtreatment. Ideally, we want to be able to identify the patients at the highest risk of an anastomotic leakage, so a defunctioning ileostomy can be used in a specific patient group only.

FUTURE PERSPECTIVES

If the debate is to be moved forward, a better understanding of anastomotic leakage needs to be developed. Research on several modifiable aspects of perioperative care showed promising outcomes. This includes research on faecal biome and selective decontamination (98). Other modifiable factors include nutrition and prehabilitation, which might reduce postoperative morbidity in colorectal cancer in general (99). There is a growing body of literature that recognises the usefulness of intra-operative bowel perfusion assessment using indocyanine green (ICG) and fluorescence angiography. ICG is a safe and easy to use technique to assess perfusion at the anastomotic site; possibly reducing AL rates by reducing ischemia in case of poor bowel perfusion (100). Further effort should be put in the implementation and development of ICG to reduce the incidence of anastomotic leakage. The use of ICG combined with future developments in augmented reality and artificial intelligence might contribute to the understanding and reduction of anastomotic leakage. Another promising combination might be computer guided surgery and robot-assisted surgery. Such combination might lead to new opportunities in the field of image guided surgery and artificial intelligence.

Because anastomotic leakage is a severe complication, the necessity of a standardized protocol for early detection and treatment of anastomotic leakage should be emphasized. Patients with a clinically manifest leakage should be considered for early relaparoscopy to ensure optimal control of pelvic sepsis and anastomotic healing (101). Another valuable alternative treatment option is vacuum-assisted drainage (EVAC) of the abscess cavity in combination with early transanal closure of the anastomotic defect (102). This technique has shown to result in an earlier and more successful closure of the anastomotic defect (103). Close attention should be paid to signals of anastomotic leakage to allow for urgent re-intervention in all patients to assure early treatment of the leakage in a comparable matter.

Organ preserving therapy is becoming increasingly popular, and is likely going to reduce the number of TME performed in the future. The morbidity associated with TME have led to the pursuit of organ preserving therapies for rectal cancer (104). Especially in early stage rectal cancer, without lymph node spread, TME might be omitted by the use of other treatment strategies. The use of screening programmes led to a shift towards more early stage colorectal cancers (105, 106). Low risk T1 tumours can be hard to distinguish from high risk T1 or T2 by current imaging techniques (107, 108). Local excision can be diagnostic in such cases or therapeutic in case of low-risk T1. Local excision is associated with low morbidity and good functional outcomes (109). Local excision alone it is not oncological safe in high risk T1 tumours because of a high recurrence risk, and in case

of local excision such tumours should be treated with completion TME (110). Another potential treatment option for such tumours is adjuvant chemo radiation, which is currently being evaluated in the TESAR trial (111). With the shift towards more early stage cancers and thus more local excision, completion TME has gained more interest. Initial series after TaTME looked promising but these should be interpreted with caution, as they contain small numbers of patients (112). Considerably more work will need to be done to determine the outcome after completion TME and what approach is most suitable for completion TME.

Centralization might be the key to improve outcome and to reduce costs in rectal cancer surgery. TME remains complex and learning curves for TME are steep. Therefore, procedures should be restricted to expert centres with high volume, and well trained surgeons. Less individual learning curves would expose fewer patients to the learning curve. Centralization could helpful in exposing fewer patients to the risk associated with the learning curves of TME. Furthermore, high volume surgeons in high-volume centres perform better (113). Surgeons and staff in high volume centres tend to have more experience. Especially patients with advanced rectal cancer have better outcome in high volume centres (62). More experience might lead to more adequate treatment of anastomotic leakage and improved outcome after anastomotic leakage. In the future, the rate of TME surgery is likely to decline because of an increase in local treatment options and wait-and-see protocols and a decrease of the incidence of rectal cancer itself. The introduction of the sigmoid take-off definition will cause a part of the former proximal rectal cancers will be classified as sigmoid cancers and thus treated differently. Subsequently, the number of rectal cancer patients might drop below a certain caseload cut-off threshold for rectal cancer treatment in some centres. Certainly, there is a link between case volume and outcome and therefore surgeon's workload is often used as a marker for proficiency. However, surgeon's competencies cannot be evaluated by volume alone. Technical competency in colorectal surgery is shown to be related to the supervised training volume, and not the overall case volume (114). Surgical quality assurance has shown to influence important outcomes after surgical oncology (115). Competency assessment tools can be used to assess the competency levels of surgeons. Competency assessment tools were shown to be useful in the national training programme in laparoscopic colorectal surgery in England to determine whether a participant was qualified for independent practice (114, 116). Such assessment tools might be used in training programmes for robot-assisted TME and TaTME as well. The pass of fail benchmark has shown to be clinically relevant in laparoscopy (117). Therefore, skills assessment can be implemented for the evaluation of performance and should become a part of training programmes. In the future, the value of such tools needs to be investigated for accrediting surgeons.

Healthcare professionals and hospitals do have the responsibility to share data on the effectivity and safety before large scale introduction of a new technique takes place. The order in which a clinical issue needs a technical solution seems to be applied in reverse in robot-assisted TME and TaTME.

At first, the technology was there and then surgeons looked for a medical indication. This could result in suboptimal use globally of technology that might be promising. For TaTME efforts have been made to collect and publish data from centres that started the technique. TaTME is a complex, but promising technique and upcoming randomized controlled trials will have to confirm oncological safety (28, 118). Even though the implementation of TaTME seemed to be associated with increased local recurrence rates, the risk for local recurrence is multifactorial and careful evaluation of new techniques is essential to acknowledge risk factors for recurrence. Most hospitals that introduced robot-assisted TME had no contribution to evaluation of the effectivity of robot-assisted TME. Meanwhile, large randomized trials failed to show any benefits of robot-assisted TME (2, 30). Hospitals do have the opportunity to perform systemic evaluation of their techniques, presumably in multicentre settings.

The treatment of rectal cancer is becoming increasingly tailored. Centralization and quality control might play an essential role in further improving outcome in the future. Because rectal cancer treatment is associated with relatively favourable oncological outcome and survival, functional outcomes and quality of life are becoming increasingly important outcome measures for patients these days. However, over half of the patients develop urogenital complaints, anorectal complaints or sexual dysfunction. Future efforts should be made to decrease these rates of functional complaints. Patients should be informed about the risks, morbidity and functional outcomes of TME and diversion. Such information should be used in shared decision making because in the end, it is the patient that matters most.

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APPENDICES

DUTCH SUMMARY / NEDERLANDSTALIGE SAMENVATTING

Het doel van dit proefschrift was om verschillende minimaal invasieve technieken voor de totale mesorectale excisie (TME) te analyseren. Bij de TME wordt het aangedane deel van het rectum en het mesorectum (welke onder andere lymfeklieren bevat) verwijderd. Colorectaal carcinoom is een van de meest voorkomende vormen van kanker en TME is de gouden standaard voor de curatieve behandeling van rectumcarcinoom (1). De ontwikkeling van TME begon in de jaren 1980. Later is men overgestapt van open naar een laparoscopische benadering. Van daaruit zijn robot-geassisteerde TME en trans-anale TME (TaTME) ontwikkeld. De centrale vraag is hoe deze technieken bij kunnen dragen aan het verbeteren van de zorg voor patiënten met een rectumcarcinoom. In dit proefschrift worden de klinische uitkomsten van de implementatie van robot-geassisteerde TME en TaTME in Nederland onderzocht.

Deel één: de implementatie van robot-geassisteerde en transanale totale mesorectal excisie

In **hoofdstuk 2** worden de haalbaarheid en lange-termijn oncologische veiligheid van TaTME in twee grote centra onderzocht, welke als eerste gestart zijn met TaTME in Nederland. In 159 procedures was het percentage lokaal recidief na 3 jaar 2.0% en na 5 jaar 4.0%. Een hoger tumor stadium, ernstige postoperatieve complicaties en presacraal abces waren risicofactoren voor een lokaal recidief. In 97.5% van de gevallen werd een intact preparaat gezien, wat eveneens is vastgesteld in eerdere studies (2). Deze studie liet goede oncologische uitkomsten zien na TaTME uitgevoerd door ervaren chirurgen.

In **hoofdstuk 3** worden echter andere uitkomsten gezien na TaTME. Hierin wordt de data van een externe audit met 120 patiënten geanalyseerd. Dit betrof de eerste 10 patiënten uit 12 centra die deelnamen aan het gestructureerde implementatieprogramma van TaTME in Nederland. Het percentage lokaal recidief tijdens de leercurve betrof 10% tijdens een mediane follow-up van 21.9 maanden. Dit was ondanks een laag percentage positieve circumferentiële snijvlakken. De meeste recidieven waren multifocaal. Deze bevindingen kwamen overeen met de alarmerende bevindingen tijdens de implementatie van TaTME in Noorwegen (3). Een tweede analyse werd gedaan in de centra die na deelname aan het Nederlandse implementatieprogramma gebruik bleven maken van de techniek en tenminste 45 operaties door middel van TaTME hadden uitgevoerd. Het percentage lokaal recidieven was 15% in de eerste 10 patiënten in deze centra, en daalde naar 5.6% in totaal 266 patiënten. Deze studie toont aan dat er mogelijk een leercurve effect verantwoordelijk is voor de hoge percentages lokaal recidieven na TaTME.

Vergelijkbare resultaten werden gezien in **hoofdstuk 4** in een groter cohort van 624 patiënten in centra die gebruik bleven maken van de techniek. Het percentage lokaal recidieven na TaTME was 12.5% in de eerste 10 operaties en een acceptabele 3.4% nadien. De leercurve lijkt dus inderdaad geassocieerd met een hoog percentage lokaal recidieven, wat aanzienlijk afneemt als de ervaring toeneemt. Een minder goede uitvoering van de techniek lijkt een voor de hand liggende verklaring voor het hoge percentage lokaal recidieven tijdens de implementatie. Hoewel het risico op lokaal recidief multifactorieel bepaald is, lijkt de techniek zelf niet verantwoordelijk, mits goed uitgevoerd.

In **hoofdstuk 5** werd de implementatie van robot-geassisteerde TME onderzocht in een groot opleidingsziekenhuis met veel ervaring met laparoscopie. De eerste 105 robot-geassisteerde TME uitgevoerd door vijf chirurgen werden onderzocht. Als aangenomen wordt dat de leercurve tenminste 20 operaties betreft, dan kan worden aangenomen dat de chirurgen zich allemaal in de leercurve bevonden (4, 5). Het percentage lokaal recidieven na 3 jaar was 7.4%. Morbiditeit en andere korte-termijn uitkomsten waren acceptabel. Ondanks de leercurve was de incidentie van functionele klachten vergelijkbaar met de literatuur (6). De incidentie van darmklachten, geduid als ernstig "Low Anterior Resection Syndrome" (LARS) was 55.3%.

Deel twee: een vergelijking van robot-geassisteerde en transanale totale mesorectal excisie

Een vergelijking tussen de drie technieken voor TME; laparoscopische TME, robot-geassisteerde TME en TaTME ontbrak tot op heden. Ook wordt in de meeste vergelijkende studies geen rekening gehouden met de leercurve van robot-geassisteerde TME en TaTME. Deze technieken zijn relatief nieuw, waardoor chirurgen zich vaker in de leercurve bevinden. Daarom werd een studie uitgevoerd waarin data werd verzameld van 1078 patiënten geopereerd in elf Nederlandse ziekenhuizen met veel ervaring met een van de technieken: laparoscopische TME, robot-geassisteerde TME of TaTME.

In **hoofdstuk 6** worden de korte termijn uitkomsten vergeleken. De incidentie van primaire anastomosen was hoger in de robot-geassisteerde (61.9%) en TaTME (61.9%) centra, vergeleken met laparoscopische centra (39.4%). Na propensity score matching en exclusie van abdomino perineale rectumextripaties (APR) werd een analyse gedaan van TME waarbij de voorkeurstechniek in het desbetreffende centrum werd gebruikt. In deze analyse was de incidentie van primaire anastomosen nog steeds hoger voor robot-geassisteerde TME (61.9%) en TaTME (84.3%), vergeleken met laparoscopische TME (66.7%). Het aantal conversies naar open chirurgie verschilde niet. Ook was er geen verschil in kwaliteit van het preparaat, het aantal positieve circumferentiële snijvlakken en de morbiditeit. Het percentage naadlekkages was 23.6% na laparoscopische

TME, 21.6% na robot-geassisteerde TME en 17.6% na TaTME. Hoewel de incidentie van primaire anastomosen hoger is in robot-geassisteerde en TaTME centra, leidde dit dus niet tot meer naadlekkages. In Nederlandse audits werden vergelijkbare percentages naadlekkages gezien (7, 8). Dit bevestigt dat robot-geassisteerde TME en TaTME veilig uitgevoerd kunnen worden in centra met ervaring.

In **hoofdstuk 7** worden van dezelfde patiënten de oncologische uitkomsten na 3 jaar vergeleken. Deze waren vergelijkbaar voor de drie technieken. De 3-jaar overleving was 90.0% na laparoscopie, 90.4% na robot-geassisteerde TME en 87.6% na TaTME. De 3-jaar ziektevrije overleving was 77.8% na laparoscopie, 75.8% na robot-geassisteerde TME en 78.8% na TaTME. Het percentage lokaal recidieven na 3 jaar was 6.1% na laparoscopische TME, 6.4% na robot-geassisteerde TME en 5.7% na TaTME. Deze percentages zijn vergelijkbaar met de percentages die gezien worden in grote studies waarin laparoscopische TME en open TME worden vergeleken (9-11). Een cox-regressie analyse waarin gecorrigeerd werd voor beïnvloedende factoren liet eveneens geen significant verschil zien tussen de technieken. Ook dit bevestigt dat robot-geassisteerde en TaTME veilig uitgevoerd kunnen worden in centra met ervaring.

In **hoofdstuk 8** wordt specifiek gekeken naar lage rectum tumoren. Deze werden op basis van anatomisch vlak, zichtbaar op MRI gedefinieerd. Er was er geen verschil in oncologische uitkomsten na 3 jaar tussen laparoscopische TME, robot-geassisteerde TME of TaTME. Ook was er geen verschil tussen MRI gedefinieerde lage rectum tumoren en hogere rectum tumoren. Wel werd gezien dat een niet-restoratieve low anterior resectie (LAR) geassocieerd werd met slechtere overleving, slechtere ziektevrije overleving en een hoger percentage lokaal recidieven.

In de studie in **hoofdstuk 9** werden alle MRI beelden die voorafgaand aan de behandeling gemaakt waren opnieuw beoordeeld om te zien hoeveel patiënten voldoen aan de sigmoid take-off definitie van het rectum. Gebruikmakende van de sigmoid take-off definitie zou 13.6% van de voorheen als rectumcarcinoom geclassificeerde rectumtumoren, nu gediagnosticeerd zijn met een sigmoidcarcinoom. De implementatie van deze nieuwe definitie heeft gevolgen voor toekomstige behandelingen, omdat 54.6% van deze patiënten een andere vorm van (neo)adjuvante behandeling zouden hebben ondergaan. Sigmoïd tumoren lijken meer baat te hebben bij adjuvante chemotherapie, terwijl chemotherapie nauwelijks wordt toegediend bij patiënten die gediagnosticeerd zijn met rectumcarcinoom.

Deel drie: stoma gerelateerde morbiditeit bij totale mesorectale excisie

De rol van een deviërend ileostoma staat ter discussie bij TME waarbij een anastomose wordt aangelegd. Het doel van het aanleggen van een deviërend ileostoma is dat dit in opzet tijdelijke stoma het risico en de ernst van naadlekkage zou verminderen. In **hoofdstuk 10** werden 101 patiënten, waarbij een ileostoma werd aangelegd tijdens een TaTME ingreep, vergeleken met 46 patiënten zonder ileostoma. Het aantal naadlekkages was vergelijkbaar: 15.8% in patiënten met ileostoma en 21.7% in patiënten zonder ileostoma. De ernst van de lekkage en het aantal patiënten waarin de anastomose moest worden opgeheven in verband met lekkage was eveneens vergelijkbaar. De ileostoma gerelateerde morbiditeit leidde tot een mediane toename van € 9,647.52 van de gemaakte ziekenhuiskosten in het eerste jaar. De grootste kostenpost was de langere totale ziekenhuisopnameduur in patiënten met ileostoma, dat voortvloeit uit de stoma-gerelateerde morbiditeit. Het niet aanleggen van een ileostoma zou dus kunnen lijden tot minder morbiditeit en minder kosten.

Eenzelfde vergelijking werd gemaakt in **hoofdstuk 11** in een groter cohort met 595 patiënten die laparoscopische TME, robot-geassisteerde TME of TaTME ondergingen. Hier lag de focus op het risico op een permanent stoma. Het aantal permanente stoma na 1 jaar was lager (9.9%) in patiënten zonder ileostoma en hoger (18.7%) in patiënten met ileostoma. Het risico op een permanent stoma is dus hoger in de groep met ileostoma. Ook hier was het aantal naadlekkages vergelijkbaar. De incidentie van complicaties binnen 30 dagen na ingreep was hoger in patiënten met ileostoma. Dit duidt wederom op de omvang van de stoma-gerelateerde morbiditeit.

Conclusie

Zorgverleners hebben de verantwoordelijkheid om nieuwe technieken zorgvuldig te evalueren voordat de introductie daarvan op grote schaal plaatsvindt. Tijdens de introductie van TaTME in Nederland werd een verhoogd aantal lokaal recidieven geobserveerd. Het risico vermindert sterk naarmate centra meer ervaring opdoen. Patiëntselectie, volume en goede technische uitvoering lijken dus een rol te spelen. TaTME lijkt een complexe maar veelbelovende techniek te zijn omdat de klinische uitkomsten van de centra met ervaring bovengemiddeld goed blijken. Prospectieve data, waaronder de gerandomiseerde COLOR III trial zullen in de toekomst de veiligheid van de techniek vast moeten stellen (12). Grote gerandomiseerde trials waarin robot-geassisteerde TME werd onderzocht lieten geen verschil in uitkomsten zien vergeleken met laparoscopische TME (13, 14). De hoge kosten die gepaard gaan met de aanschaf en het gebruik van operatierobots dienen echter verantwoord te worden (15-17). Ook hier is dus zorgvuldige monitoring van de techniek noodzakelijk.

In ervaren handen lijken robot-geassisteerde TME en TaTME betere uitkomsten te hebben dan laparoscopische TME. Een mogelijk voordeel van robot-geassisteerde TME en TaTME is dat er meer restoratieve ingrepen worden uitgevoerd. Maar ook in ervaren handen blijven laparoscopische TME, robot-geassisteerde TME en TaTME geassocieerd met ernstige complicaties, waaronder een hoog risico op naadlekkage. Ook blijft de incidentie en ernst van functionele klachten aanzienlijk. De helft van de patiënten ontwikkelt urogenitale klachten, gastro-intestinale klachten, seksuele dysfunctie of stoma-gerelateerde problematiek (18). Een belangrijke vraag voor de toekomst is of het aanleggen van meer anastomosen daadwerkelijk een voordeel voor de patiënt biedt. Het aanleggen van een anastomose hoeft niet noodzakelijkerwijs te leiden tot betere kwaliteit van leven. Na aanleg van een anastomose ontwikkelt ruim de helft van de patiënten ernstig LARS (19).

Bezorgdheid over de mogelijk ernstige gevolgen van naadlekkage motiveert chirurgen in veel gevallen om een deviërend ileostoma aan te leggen. Echter leidt dit vaak tot veel stoma-gerelateerde morbiditeit en een verhoogd risico op een permanent stoma. Patiënten dienen geïnformeerd te worden met betrekking tot de risico's, complicaties en functionele uitkomsten na TME. Dit geldt ook voor de aanleg van een deviërend stoma. Deze informatie dient gebruikt te worden bij de gezamenlijke besluitvorming door dokter en patiënt.

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PHD PORTFOLIO

Name PhD student:	Jeroen Clemens Hol
PhD period:	July 2019 - October 2022
Names of PhD supervisors:	Prof. dr. H.J. Bonjer, Dr. C. Sietses, Dr. J.B. Tuynman

1. PhD training

	Year	ECTS
General courses		
CCA oncology course	2020	3.0
Scientific integrity course	2020	2.0
OOA introduction in R	2021	1.3
OOA medical statistics in R	2021	1.5
Specific courses		
Writing a scientific article	2020	3.0
OOA course Indesign	2020	0.1
Writing a data management plan	2021	1.0
Introductory Clinical Research Organization (BROK) course	2021	1.5
Seminars, workshops and master classes		
Wetenschapsdag chirurgie 2019	2019	1.0
Wetenschapsdag chirurgie 2021	2021	1.0
AMS PhD day 2020	2020	0.2
WCP meeting	2021	0.2
WCP meeting	2022	0.2
Presentations		
ESCP fourteenth meeting, poster presentation	2019	0.5
ESCP sixteenth meeting, poster presentation	2021	1.0
SEOHS 2022, oral presentation	2022	0.2
(Inter)national conferences		
TaTME congress 2019, Switzerland	2019	0.9
Chirurgendagen 2022	2022	0.4
Other		
Invited peer review for various international journals	2019-2022	3.0

2. Teaching

	Year	ECTS
Lecturing		
Invited guest lecture at Ziekenhuis Gelderse Vallei	2021	0.2
Educating medical doctors	2021	0.2
Tutoring, Mentoring		
Writing scientific articles under supervision	2019	2.0
Supervising		
Student thesis supervisor	2020	6.0
Other		
Attending multidisciplinary meetings at Ziekenhuis Gelderse Vallei	2020-2021	3.0
Attending multidisciplinary meetings at Rijnstate ziekenhuis	2019-2020	2.3

3. Publications

Peer reviewed	
Publications in thesis	2019-2022
Other peer reviewed publications	2013-2022
Other	
Guest blog BJS	2021

LIST OF PUBLICATIONS

Chrispijn M, Gevers TJ, **Hol JC**, Monshouwer R, Dekker HM, Drenth JP. *J Hepatol*. 2013; 59(1):153-159. Everolimus does not further reduce polycystic liver volume when added to long acting octreotide: Results from a randomized controlled trial.

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CURRICULUM VITAE

Jeroen Clemens Hol was born on July 6th 1989 in Nijmegen, where he grew up with his parents and his younger sister. He attended HAVO at the Notre Dame des Anges (Ubbergen) and subsequently VWO at the Montessori College (Nijmegen). In 2009 he started studying biology at the Radboud University in Nijmegen and switched to medicine in 2010. He completed his research internship and final medical internships at the department of surgery at Radboudumc in Nijmegen. After graduation in 2017 Jeroen started working as surgical resident not in training at Elisabeth Tweesteden Ziekenhuis in Tilburg. In 2018 he switched to Ziekenhuis Gelderse Vallei in Ede, where he met surgeon Colin Sietses. Together they established a scientific research project on rectal cancer surgery in association with the VU (Amsterdam), which resulted in this PhD thesis. Meanwhile Jeroen worked as surgical resident not in training at Rijnstate Ziekenhuis in Arnhem, to return to the department of surgery at Ziekenhuis Gelderse Vallei in Ede in October 2020.

Jeroen currently lives together with Kirsten Daniels in Nijmegen. In his spare time he enjoys fitness, judo and spending time with his family and close friends.

In dit proefschrift worden drie minimaal invasieve technieken voor totale mesorectale excisie (TME) vergeleken: laparoscopische TME, robot-geassisteerde TME en transanale TME. Ook wordt de implementatie van robot-geassisteerde TME en transanale TME onderzocht. Daarnaast komt stoma gerelateerde morbiditeit aan bod.

Omslagfoto: “sleutelgatchirurgie”.

In this PhD thesis three minimally invasive approaches for total mesorectal excision (TME) are compared: laparoscopic TME, robot-assisted TME and transanal TME (TaTME). Another focus is the implementation of robot-assisted TME and transanal TME (TaTME). The morbidity related to diverting ileostomy creation in TME is addressed as well.

Cover photo: “keyhole surgery”.

Vrije Universiteit Amsterdam