Local Recurrence and Disease-Free Survival After Transanal Total Mesorectal Excision: Results From the International TaTME Registry

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ABSTRACT

Background: The oncologic safety of transanal total mesorectal excision (TaTME) for rectal cancer has recently been questioned, with high local recurrence (LR) rates reported in Dutch and Norwegian experiences. The objective of this study was to evaluate the oncologic safety of TaTME in a large cohort of patients with primary rectal cancer, primarily in terms of LR, disease-free survival (DFS), and overall survival (OS).

Patients and Methods: This was a prospective international registry cohort study, including all patients who underwent TaTME for primary rectal adenocarcinoma from February 2010 through December 2018. The main endpoints were 2-year LR rate, pattern of LR, and independent risk factors for LR. Secondary endpoints included 2-year DFS and OS rates. Kaplan-Meier survival analysis was used to calculate actuarial LR, DFS, and OS rates. **Results:** A total of 2,803 patients receiving primary TaTME were included, predominantly men (71%) with a median age of 65 years (interquartile ratio, 57–73 years). After a median follow-up of 24 months (interquartile ratio, 12–38 months), the 2-year LR rate was 4.8% (95% CI, 3.8%–5.8%) with a unifocal LR pattern in 99 of 103 patients (96%). Independent risk factors for LR were male sex, threatened resection margin on baseline MRI, pathologic stage III cancer, and a positive circumferential resection margin on final histopathology. The 2-year DFS and OS rates were 77% (95% CI, 75%–79%) and 92% (95% CI, 91%–93%), respectively. **Conclusions:** This largest TaTME cohort to date supports the oncologic safety of the TaTME technique for rectal cancer in patients treated in units that contributed to an international registry, with an acceptable 2-year LR rate and a predominantly unifocal LR pattern.

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Background

Surgery for rectal cancer, based on total mesorectal excision (TME) principles,¹ remains a challenging procedure, irrespective of the surgical approach. The difficulties of anatomic access to the depths of the pelvis affect the surgeon's ability to achieve a meticulous cancer dissection. This may impair oncologic outcomes, particularly for locally advanced lower rectal cancer in male patients.^{2–4} A laparoscopic rectal cancer operation results in short-term patient benefits, although widespread adoption of laparoscopic rectal excision remains low and oncologic benefit compared with open surgery was not proven in 2 recent randomized controlled trials.^{5,6} The clinical need to mitigate and overcome challenges in rectal cancer surgery, together with surgical innovation, have led to the development of transanal total mesorectal excision (TaTME). This technique was first performed in a live patient in 2009 and has been adopted in numerous centers globally.⁷

The addition of a transanal phase to a purely abdominal TME approach was hypothesized to improve visualization and optimize dissection, particularly in low rectal cancer, improving the quality of the TME specimen. It

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was thought to optimize oncologic outcomes and in particular lead to a reduction in local recurrence (LR) rates.⁸ Histopathologic results for TaTME have been favorable in many reported studies,^{9–11} but the exact role and benefits of TaTME in rectal cancer have recently been challenged.^{12,13} Contemporary publications on the learning curve data from Dutch and Norwegian multicenter datasets have reported high LR rates (up to 12%) with a predominantly multifocal LR pattern, which has heightened the controversy.^{14,15} These outcomes are at variance with reports from cohort series by early adopters of the technique and publications from expert centers.^{16–19} From an oncologic perspective, overall survival (OS) and disease-free survival (DFS) are the key outcomes of TaTME, but LR remains a very important outcome after rectal cancer surgery, which can result in major morbidity and poor outcomes.

Careful assessment of the site, rate, and pattern of LR in large datasets provides necessary oncologic quality control of novel operative techniques. For these reasons, the international TaTME registry was initiated to provide data on procedural safety, efficacy,^{10,20} and long-term oncologic safety. The evaluation of disease recurrence rates after TaTME from a large dataset of patients treated for rectal cancer can contribute to the paucity of information currently available and may help address some of the recent controversy in the published literature on oncologic outcomes after TaTME.

The purpose of this prospective report from the international TaTME registry was to evaluate the oncologic outcomes in patients who underwent TaTME for primary rectal cancer, focusing primarily on the rate and pattern of LR in addition to OS and DFS.

Methods

Patient Selection and Study Design

Prospective registry-based data were analyzed. The international TaTME registry²¹ is a secure online voluntary database where surgeons from 203 centers worldwide provide data on their patients who undergo TaTME. Ethical approval for the registry was granted by the UK Health Research Authority and Research Ethics Committee (REC reference 15/LO/0499, IRAS project identification 156930).

The registry is designed to prospectively collect data on patient demographics, tumor staging and neoadjuvant therapy (NAT), operative details, postoperative clinical and histologic outcomes, readmission details, late morbidity, and long-term oncologic follow-up.²² Before data extraction and analysis, collaborating centers were contacted individually to update oncologic surveillance, with subsequent reminders throughout 2019, to optimize data completeness. Data analysis and extraction were performed in February 2020. The dataset was updated, and surgeons were contacted individually to clarify results.

All records with an operation date before January 1, 2019, were reviewed to allow for a minimum follow-up period of 1 year. Centers were excluded if >10% of their patient records had ≥ 1 missing values for the main outcome parameters; we considered these centers as not having their data accurately reported. Other exclusion criteria were benign disease, previous completion TaTME (ie, previous local excision of a malignant polyp or early rectal cancer), rectal cancer >10 cm from the anorectal junction (ARJ), locally recurrent rectal cancer, palliative procedures, and any pathologic diagnosis other than adenocarcinoma on final histopathology.

Outcome Parameters

The primary outcome of this study was the 2-year LR rate. Secondary endpoints were the pattern of LR (whether unifocal or multicentric), independent risk factors for LR, and 2-year DFS and OS rates.

DFS was defined as patients who were alive without evidence of local or distant recurrence. OS was defined as those who were alive with or without cancer at the end of follow-up. With regard to histopathologic details, nonradical resection margin status was defined as the presence of a tumor or malignant lymph nodes at or within 1 mm of the circumferential resection margin (CRM) and/or distal resection margin (DRM) of the specimen. The optimal pathologic outcome was defined as a composite of clear resection margin status, complete or nearly complete TME specimen, and no rectal perforation. The TME specimen quality was categorized as outlined by Nagtegaal et al.⁸ TNM stages I–IV were defined as follows: stage I: pT0–2pN0M0; stage II: pT3–4pN0M0; stage 3: pT0–4pN1–2cM0; and stage IV: pT0–4pN0–2cM1.

Statistical Analysis

All categorical data are presented as the number of patients and percentages, and continuous data are shown as median and interquartile range (IQR). Missing data did not exceed 15% for each variable, and percentages shown represent the data available, excluding missing values. Independent risk factors were identified by univariable and multivariable Cox regression analysis. Factors with a *P* value <.10 in univariable analysis were entered into multivariable Cox regression analysis. Factors showing a *P* value <.05 were considered significant and therefore predisposed for LR, presented as odds ratios (ORs) and 95% confidence intervals. Kaplan-Meier analysis was used to determine the actuarial cumulative proportion of LR, DFS, and OS rates at 2 years from the date of surgery, censored for the patients not reaching the follow-up timepoint. Regarding DFS, patients with LR or distant metastasis or death at 2 years were included as an event. TNM stages I–IV of disease, based on the 8th

Table 1. Patient and Tumor Characteristics

Characteristic	n (%)
Male sex	1,991/2,803 (71.0)
Age, median (IQR), y	65 (57–73)
ASA ≥ 3	640/2,760 (23.2)
BMI, median (IQR), kg/m ²	25.8 (23.3–28.9)
≥ 30	504/2,708 (18.6)
Tumor height from ARJ, median (IQR), cm	4 (2–6)
≤ 1 cm	583/2,778 (21.0)
Anterior and/or circumferential tumor	1,211/2,431 (49.8)
MRI performed	2,614/2,803 (93.3)
cT stage on baseline MRI	
T1	75/2,442 (3.1)
T2	620/2,442 (25.4)
T3	1,544/2,442 (63.2)
T4	176/2,442 (7.2)
Tx	27/2,442 (1.1)
cN stage on baseline MRI	
N0	1,043/2,570 (40.6)
N1	1,047/2,570 (40.7)
N2	446/2,570 (17.4)
Nx	34/2,570 (1.3)
cM1 stage	231/2,750 (8.4)
Threatened MRF on baseline MRI	654/2,377 (27.5)
EMVI on baseline MRI	
Positive	304/1,126 (26.9)
Not reported/missing	1,677/2,803 (56.9)
Received NAT	1,746/2,803 (62.3)
SC-RT—immediate surgery	151/2,803 (5.4)
SC-RT—delayed surgery	71/2,803 (2.5)
LC-RT	116/2,803 (4.1)
CRT	1,313/2,803 (46.8)
Chemotherapy only	56/2,803 (2.0)
Contact RT	3/2,803 (0.1)

(continued)

Table 1. Patient and Tumor Characteristics (cont.)

Characteristic	n (%)
mTRG response on restaging after downsizing NAT ^a	
mTRG 1/2 (good response)	493/1,082 (45.6)
mTRG 3 (intermediate response)	359/1,082 (33.2)
mTRG 4/5 (poor response)	230/1,082 (21.2)
Not reported/missing	510/1,592 (32.0)
Anastomotic technique	
Stapled	1,763/2,470 (71.4)
Manual	707/2,470 (28.6)
If stapled	
E-E	994/1,763 (56.4)
S-E	761/1,763 (43.2)
IPAA	8/1,763 (0.5)
If manual	
E-E	461/707 (65.2)
S-E	217/707 (30.7)
IPAA	9/707 (1.3)
Colonic J-pouch	20/707 (2.8)

Abbreviations: ASA, American Society of Anesthesiologists classification; ARJ, anorectal junction; BMI, body mass index; cM1 stage, clinical metastatic stage; cN stage, clinical nodal stage; CRT, chemoradiotherapy; cT stage, clinical tumor stage; EMVI, extramural vascular invasion; IQR, interquartile range; LC-RT, long-course radiotherapy; MRF, mesorectal fascia (defined as threatened if the distance of tumor or malignant lymph node to the mesorectal fascia was ≤ 1 mm); mTRG, tumor regression grade on restaging MRI; NAT, neoadjuvant therapy; RT, radiotherapy; SC-RT, short-course radiotherapy. ^amTRG was only given for patients who received downsizing NAT. Downsizing NAT was considered because all types of NAT exclude SC-RT, immediate surgery, and contact RT (N=1,592 [1,746 – 154]).

edition of the Union for International Cancer Control TNM classification,²³ were compared using Kaplan-Meier analysis. Data were analyzed using SPSS Statistics, version 25.0 (IBM Corp).

Results

A total of 4,108 patients registered in the database underwent a TaTME for a malignant indication between February 2010 and December 2018. Of these patients, 2,803 were included as presented in supplemental eFigure 1 (available with this article at JNCCN.org). The remainder were excluded because 227 had completion TaTMEs; 66

had tumors >10 cm from the ARJ; 51 had local recurrence, palliative procedures, or diagnosis other than adenocarcinoma on final histopathology; and 1,001 were treated in centers where $>10\%$ of their cases had ≥ 1 missing values for the main outcome parameters. Patient and tumor characteristics are outlined in Table 1. Overall, 71% of the 2,803 patients were male, and the mean age of the cohort was 65 years (IQR, 57–73 years). Median tumor height from the ARJ was 4 cm (IQR, 2–6 cm). Half of the patients had anterior tumors, and the mesorectal fascia was threatened in 28% of patients on the staging MRI scan. Approximately two-thirds of patients received some form of NAT. After NAT, good tumor regression grade was reported in 46% of patients. A low anterior resection was performed in most patients (91%). Complete details on intraoperative and postoperative characteristics are provided in supplemental eTable 1.

Histopathologic Outcomes

Histopathologic outcomes are shown in Table 2. A complete TME was achieved in 86% of patients, whereas

major defects of the mesorectum were found in 3%. An incomplete resection (nonradical resection margin) was reported in 7% of patients, after excluding the patients with a complete pathologic response (ypT0N0). The CRM was positive (CRM+) in 5.1% of patients, the DRM was involved (DRM+) in 1.0% of patients, and a combination of both CRM+/DRM+ was found in 0.7%. A higher rate of DRM+ (5% vs 0.9%; $P<.001$) and CRM+ (3.7% vs 1.9%; $P<.001$) was observed in patients with low tumors (<1 cm from the ARJ). In 1.6% of patients, a rectal perforation at the time of surgery occurred. An optimal pathologic outcome was achieved in 90% of patients.

Local Recurrence

After a median follow-up of 24 months (IQR, 12–38 months), the actuarial 2-year LR rate was 4.8% (95% CI, 3.8%–5.8%) (Table 3, Figure 1A). This rate varied from 1.9% (95% CI, 0.9%–3.0%) for patients with TNM stage I disease up to 11.1% (95% CI, 6.1%–16.0%) for patients with TNM stage IV disease (Figure 1B). Median time to detection of LR was 14 months (IQR, 9–24 months). LR was mostly located in the presacral space (30%), at the anastomotic site (25%), or in the lateral pelvic side wall (23%). A multifocal pattern was reported in 4% of patients. LR was diagnosed in 73 of 122 (60%) of patients without any metastatic disease, 48 of whom (66%) had salvage surgery.

Independent risk factors for LR in multivariate Cox regression analysis were male sex (OR, 1.6; 95% CI, 1.1–2.5; $P=.029$), a threatened mesorectal fascia on baseline MRI (OR, 1.5; 95% CI, 1.1–2.3; $P=.024$), (y)pN1–2 stage disease (OR, 2.1; 95% CI, 1.5–3.0; $P<.001$), and CRM+ on final histopathology (pCRM+; OR, 2.3; 95% CI, 1.3–3.9; $P=.004$) (Table 4). Other pathologic outcomes, such as TME quality, rectal perforation, and DRM+, were significantly associated with LR on univariate analysis but not on multivariate analysis.

Survival

The 2-year actuarial DFS was 76.6% (95% CI, 74.7%–78.5%). This rate varied from 89.2% (95% CI, 86.8%–91.6%) for patients with TNM stage I disease to 33.6% (95% CI, 26.2%–41.1%) for those with TNM stage IV disease (Figure 1C, D). The 2-year actuarial OS was 91.9% (95% CI, 90.7%–93.2%). This rate ranged from 96.1% (95% CI, 94.7%–97.5%) for patients with TNM stage I disease to 72.3% (95% CI, 65.1%–79.5%) for those with TNM stage IV disease (Figure 1E, F).

Discussion

In this largest cohort to date of patients who had a TaTME for rectal cancer who were registered in a prospective international registry, the 2-year LR rate was 5%. LRs were generally unifocal, with few multifocal LR

Table 2. Histopathologic Outcomes

Outcome	n (%)
(y)pT stage	
T0	304/2,767 (11.0)
T1	293/2,767 (10.6)
T2	872/2,767 (31.5)
T3	1,213/2,767 (43.8)
T4	77/2,767 (2.8)
Tx	8/2,767 (0.3)
(y)pN stage	
N0	1,886/2,764 (68.2)
N1	586/2,764 (21.2)
N2	281/2,764 (10.2)
Nx	11/2,764 (0.4)
No residual tumor and nodes	279/2,767 (10.1)
pEMVI	
Positive	254/1,293 (19.6)
Not reported/missing	1,510/2,803 (53.9)
TME specimen	
Complete	2,280/2,644 (86.2)
Nearly complete	285/2,644 (10.8)
Incomplete	79/2,644 (3.0)
R1 (excluding no residual tumor and nodes)	170/2,469 (6.9)
Only DRM+	25/2,469 (1.0)
Only CRM+	125/2,469 (5.1)
DRM+ and CRM+	17/2,469 (0.7)
Unknown	3/2,469 (0.1)
Rectal perforations	41/2,624 (1.6)
Composite optimal pathology ^a	2,303/2,568 (89.7)

Percentages for the variables were calculated from the total number of actual results available, excluding missing values.

Abbreviations: CRM+, positive circumferential resection margin; CRM–, negative circumferential resection margin; DRM+, positive distal resection margin; DRM–, negative distal resection margin; pEMVI, pathologic extramural vascular invasion; R1, nonradical resection margin (defined as tumor or malignant lymph nodes at or within 1 mm from the resection plane); TME specimen, total mesorectal excision specimen; (y)pN stage, pathologic nodal stage; (y)pT stage, pathologic tumor stage.

^aComposite optimal pathology: CRM– and DRM– and complete or nearly complete TME specimen and no perforations.

presentations at a median follow-up period of 2 years. These findings are in contrast to data from a Norwegian national audit, with an estimated LR rate at 2.4 years of 11.6% and a multifocal or extensive pattern of LR in two-thirds of the patients.¹⁵ Similarly, poor results were reported in a Dutch study that looked at the implementation of TaTME in a national training program.¹⁴ In the first 10 patients reviewed from 12 centers, a crude LR rate of 10% was reported with a similar pattern of multifocal recurrence in 8 of 12 patients with LR.

Table 3. Oncologic Outcomes

Outcome	n (%)
Follow-up, median (IQR), mo	24 (12–38)
Adjuvant treatment	1,146/2,564 (44.7)
2-year LR (95% CI) ^a	4.8 (3.8–5.8)
TNM stage I	1.9 (0.9–3.0)
TNM stage II	3.9 (2.1–5.8)
TNM stage III	8.2 (5.5–10.9)
TNM stage IV	11.1 (6.1–16.0)
Time to LR, median (IQR), mo	14 (9–24)
Location of LR	101/122
Anterior	11/103 (10.7)
Presacral	31/103 (30.1)
Inferior	4/103 (3.9)
Lateral (pelvic sidewall)	24/103 (23.3)
Central	3/103 (2.9)
Anastomotic	26/103 (25.2)
Multifocal	4/103 (3.9)
Missing	18/121 (14.9)
2-year DFS (95% CI) ^a	76.6 (74.7–78.5)
TNM stage I	89.2 (86.8–91.6)
TNM stage II	79.9 (76.0–83.8)
TNM stage III	66.1 (62.1–70.2)
TNM stage IV	33.6 (26.2–41.1)
2-year OS (95% CI) ^a	91.9 (90.7–93.2)
TNM stage I	96.1 (94.7–97.5)
TNM stage II	93.2 (90.9–95.4)
TNM stage III	89.8 (87.0–92.6)
TNM stage IV	72.3 (65.1–79.5)

Percentages for the variables were calculated from the total number of actual results available, excluding missing values.

TNM staging is based on the 8th edition of the Union for International Cancer Control TNM classification.

Abbreviations: DFS, disease-free survival; IQR, interquartile range; LR, local recurrence; OS, overall survival.

^aLR, DFS, and OS rates represent the actuarial rate and were calculated by Kaplan-Meier survival analysis, accounting for patients who did not reach the 2-year follow-up timepoint.

A number of other studies from early adopters of TaTME reported good oncologic outcomes with regard to pelvic recurrence, similar to the findings in this study. Hol et al¹⁶ published a 2% 3-year LR rate in 159 patients who received TaTME, with no multifocal pattern of LR, and Kang et al²⁴ reported a 6.2% LR rate after a median follow-up of 35 months in 211 patients who received TaTME. Outcomes on 767 patients from 6 tertiary referral centers were reported by Roodbeen et al,¹⁸ with a 2-year LR rate of 3.3% and no multifocal pattern of LR reported. Similarly, Perdawood et al¹⁷ reported a 4.7% LR rate after 120 TaTME procedures with a multifocal LR pattern in 1.5%. More recently, Simo et al¹⁹ published outcomes

after 173 TaTME procedures in 10 Chinese centers with an LR rate of 3% after a median follow-up of 23 months.

Our findings compare favorably with published 2-year LR rates after laparoscopic and open TME. Respectively, the ACOSOG Z6051 and ALaCaRT randomized trials reported LR rates of 4.6% and 5.4% for laparoscopic TME and 4.5% and 3.1% for open TME.^{5,6} Both trials also used a composite endpoint of pathologic factors indicating adequate surgical resection. In the patients treated using laparoscopic TME in the ACOSOG and ALaCaRT trials, respectively, this was achieved in 81.7% and 82%, compared with 86.9% and 89% of patients after open TME.^{25,26} In our study, this composite endpoint was achieved in 90% of patients, suggesting more precise surgery compared with the laparoscopic groups in both of the randomized trials and similar results to those for patients treated using open surgery. However, caution is warranted when comparing registry data with randomized controlled trial data given the known limitations of registry-based data collection and analysis.²⁷ However, in contrast, the strict inclusion and exclusion criteria in randomized controlled trials may result in difficulties extrapolating data from a selected group to population-based treatments.²⁸

Population-based studies reflecting routine rectal cancer surgical practice may be a better benchmark, although long-term outcomes from national audits are limited in detail and somewhat outdated. A Dutch snapshot study included all TME procedures (n=2,095) performed in 2011 and reported a 3-year LR rate of 6% and a DFS rate of 67%.²⁹ A Norwegian national colorectal audit reported a 5-year LR rate ranging from 4% to 5% for the period 2010 to 2018 in patients with stages I–III rectal cancer.³⁰ A Swedish population-based study including 2,318 patients undergoing TME between 1995 and 2003 reported an LR rate of 6%.³¹ A Korean study by Yun et al³² reported a 6% LR rate in 2,485 patients after rectal cancer surgery between 1994 and 2008. The LR rate in the present study is in line with the results reported in these large registry-based datasets, suggesting that TaTME results in equivalent or superior local disease control.

The strongest independent risk factor for the development of LR was pCRM+, with an OR of 2.27 (95% CI, 1.31–3.94). The other individual components of the composite endpoint of optimal pathology, DRM+ or a perforated specimen, were significant on univariate analysis but were not independent predictors for LR on multivariate analysis. It has previously been reported that pCRM+ after TME is one of the most important predictors for the development of LR.⁸ It is therefore unsurprising that the Norwegian TaTME national cohort study had a high LR rate given that the CRM+ rate was 13%.³³ This high pCRM+ rate for TaTME and a specimen

Figure 1. Kaplan-Meier analysis of 2-year (A) LR; (B) LR, TNM stage^a-specific; (C) DFS; (D) DFS, TNM stage^a-specific; (E) OS; and (F) OS, TNM stage^a-specific.

Abbreviations: DFS, disease-free survival; LR, local recurrence; OS, overall survival; TaTME, transanal total mesorectal excision.

^aBased on the 8th edition of the *UICC TNM Classification of Malignant Tumours*.

Table 4. Univariate and Multivariate Cox Regression Analysis Risk Factors for Local Recurrence

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Sex (Ref: female)				
Male	1.527 (0.996–2.341)	.052	1.615 (1.051–2.484)	.029
BMI, kg/m ² (Ref: <30 kg/m ²)				
≥30	1.223 (0.787–1.898)	.371		
MRF threatened (Ref: no)				
Yes	1.918 (1.338–2.749)	<.001	1.544 (1.060–2.249)	.024
Distance from ARJ (Ref: >1 cm)				
≤1 cm	1.434 (0.904–2.276)	.126		
Anterior tumor (Ref: no)				
Yes	1.060 (0.743–1.512)	.747		
NAT (Ref: none)				
Yes	1.027 (0.711–1.484)	.887		
APE (Ref: no)				
Yes	1.137 (0.596–2.172)	.696		
Abdominal approach (Ref: MIS)				
Open	2.792 (1.030–7.570)	.044	2.397 (0.872–6.587)	.090
Adverse event (intraoperative) (Ref: no)				
Yes	1.093 (0.637–1.877)	.746		
Tumor stage (Ref: (y)pT0–3)				
(y)pT4	2.762 (1.348–5.660)	.005	1.442 (0.667–3.116)	.352
Nodal stage (Ref: (y)pN0)				
(y)pN1–2	2.311 (1.619–3.297)	<.001	2.118 (1.475–3.040)	<.001
Rectal perforation (Ref: no)				
Yes	2.383 (0.879–6.457)	.088	0.962 (0.289–3.203)	.949
TME quality (Ref: intact/minor defects)				
Major defects	2.226 (1.037–4.779)	.040	1.767 (0.722–4.326)	.213
CRM status (Ref: CRM–)				
CRM+	3.831 (2.370–6.194)	<.001	2.268 (1.306–3.937)	.004
DRM status (Ref: DRM–)				
DRM+	3.290 (1.447–7.480)	.004	1.985 (0.835–4.720)	.121

Bold indicates statistically significant P values.

After single imputation of BMI, MRF threatened, tumor height from ARJ, anterior tumor, NAT, APE, abdominal approach, (y)pT–4 stage, (y)pN1–2 stage, rectal perforation, TME quality, and CRM and DRM status.

Abbreviations: APE, abdominoperineal excision; ARJ, anorectal junction; BMI, body mass index; CRM, circumferential resection margin; CRM+, positive circumferential resection margin; CRM–, negative circumferential resection margin; DRM, distal resection margin; DRM+, positive distal resection margin; DRM–, negative distal resection margin; MIS, minimally invasive surgery; MRF, mesorectal fascia; NAT, neoadjuvant therapy; TME, total mesorectal excision; (y)pN stage, pathologic nodal stage; (y)pT stage, pathologic tumor stage.

perforation rate of 4.4% suggest suboptimal surgery in that national cohort.

However, the high LR rate of 10% in the Dutch TaTME cohort¹⁴ is difficult to explain given the low pCRM+ rate of 5%. Moreover, pathologic CRM positivity does not provide an explanation for the multifocal pattern of LR in either recent report.^{14,33} There are features of the TaTME technique that may account for the noted multifocal pelvic recurrence, such as tumor spillage

when the transanal purse string fails, or omitting rectal washout together with high insufflation pressures, which could enhance multifocal implantation of viable malignant cells. Detailed analysis of TaTME operations, perhaps through systematic video analysis, could help evaluate this hypothesis. Furthermore, data from the Dutch cohort suggest that multifocal LR may be a consequence of technical problems early in the learning curve of surgeons. In the expanded Dutch cohort of 266

patients, the overall LR rate was 5.6% and dropped to 4% if the first 10 procedures at each center were excluded.¹⁴ Surprisingly, Dutch surgeons selected patients with a threatened resection margin early on in their experience, suggesting that careful patient selection is a key aspect of the learning curve. This notion is particularly important, given that the current data confirm that these patients have an increased risk of LR.

This prompts the question of whether the widespread and rapid adoption of TaTME was in the best interests of patients. Centralization and high-volume experience may result in more optimal outcomes. A structured TaTME training program incorporating a sufficient caseload under the supervision of an experienced proctor, before independent practice of TaTME, may also address some of the pitfalls.²⁹ In addition to strict adherence to oncologic principles, more rigid and structured implementation of TaTME may also reduce perioperative morbidity, and particularly procedure-specific complications, such as urethral injuries.

The current data reveal the low penetrance of the robotic approach to the abdominal phase of TaTME. The transanal phase of a TaTME procedure provides a clear view of the dissection plane low down in the pelvis, thereby limiting the benefit of a robotic approach from above. Omission of the robot to obtain an optimal oncologic TME dissection potentially renders TaTME more cost-effective.

There are limitations in the current study, mainly that the data reported are from a voluntary registry. This source introduces the potential for selection and reporting bias because not all surgeons performing TaTME contributed to the registry, and centers that contributed may not have recorded all patients. In addition, there is currently no formal external validation process for the registry and the accuracy relies on collaborators' probity. We attempted to increase data accuracy by requesting that surgeons update their data on the registry before data extraction, by contacting surgeons individually in situations of unexpected or incongruous data, and by excluding centers with >10% of patients with missing outcome variables. In addition, local hospital protocols, including surgical resection details, histopathologic assessment, and oncologic follow-up protocols, may vary between the collaborating centers, thereby reducing quality assurance. Finally, not all relevant factors were accurately reported, such as extramural vascular invasion status, which did not allow

extramural vascular invasion to be analyzed in the multivariate model. However, despite these limitations, this registry study provides the largest international TaTME cohort reporting on oncologic outcomes, and includes surgeons and centers at all stages of their learning curve experience.

Conclusions

Findings from this prospective registry study support the oncologic safety of TaTME in patients undergoing surgery by surgeons participating in the TaTME registry. Our results expand on the paucity of data on oncologic outcomes and address some of the controversies in the published literature on pelvic recurrence rates and patterns of recurrence after TaTME. Future studies should focus on understanding the patterns and mechanisms contributing to development of LR after TaTME.²⁹ Definitive answers on the oncologic safety of TaTME compared with laparoscopic TME will be shown in outcomes of the ongoing COLOR III and ETAP-GRECCAR 11 trials.^{31,34} As in all operative procedures for rectal cancer, patient selection, technique, training, and experience are pivotal in optimizing the outcomes of TaTME.

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Supplemental online content for:

Local Recurrence and Disease-Free Survival After Transanal Total Mesorectal Excision: Results From the International TaTME Registry

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eFigure 1: Flow Diagram of Patient Inclusion

eTable 1: Perioperative Details

eAppendix 1: International TaTME Registry Collaborative

eFigure 1. Flow diagram of patient inclusion.

Abbreviations: ARJ, anorectal junction; TaTME, transanal total mesorectal excision.

eTable 1. Perioperative Details (N=2,803)

Perioperative Details	n (%)
Procedure	
LAR	2,555/2,795 (91.4)
APE	76/2,795 (2.7)
isAPE	131/2,795 (4.7)
Proctocolectomy	26/2,795 (0.9)
Other	7/2,795 (0.3)
Anastomosis created	2,560/2,776 (92.2)
Defunctioning stoma (if anastomosis)	2,188/2,497 (87.6)
Two-team procedure	1,498/2,797 (53.6)
Operative time, median (IQR), min	260 (190–326)
Abdominal approach	
Open	42/2,752 (1.5)
Conventional laparoscopy	2,451/2,752 (89.1)
SILS	243/2,752 (8.8)
Robotic	16/2,752 (0.6)
Conversion	
Abdominal ^a	124/2,584 (4.8)
Perineal ^b	58/2,575 (2.3)
Adverse events (intraoperative)	330/2,797 (11.8)
Purse string failure	70/2,797 (2.5)
Bleeding	135/2,797 (4.8)
Incorrect plane	131/2,797 (4.7)
Urethral injury	20/2,797 (0.7)
Other visceral injury	19/2,797 (0.7)
Hospital stay, median (IQR), d	8 (5–13)
Morbidity <30 d	1,124/2,604 (43.2)
Clavien-Dindo <30 d	
1	264/2,604 (10.1)
2	445/2,604 (17.1)
3	354/2,604 (13.6)
4	33/2,604 (1.3)
5	28/2,604 (1.1)

Percentages for the variables are calculated from the total number of actual results available, excluding missing values.

Abbreviations: APE, abdominoperineal excision; isAPE, intersphincteric abdominoperineal excision; LAR, anterior resection; SILS, single-incision laparoscopic surgery.

^aAbdominal conversion was defined as a procedure that was started with the intention to perform a minimally invasive abdominal dissection but required a midline laparotomy.

^bPerineal conversion was defined as a change in operative approach from transanal to a more extensive abdominal approach than initially planned.

eAppendix 1. International TaTME Registry Collaborative (alphabetized by surname)

Adamina, Michel; Aignerm Felix; Al Furajii, Hazar; Arezzom Alberto; Arnold, Steven J.; Aryal, Kamal; Austin, Ralph; Baekkelund, Oliver; Baloyiannis, Ioannis; Bandyopadhyay, Dibyendu; Banky, Balazs; Barugola, Giuliano; Basany, Eloy Espin; Belgers, Eric H.J.; Bell, Stephen; Bemelman, Willem; Berti, Stefano; Biebl, Matthias; Bloemendaal, Bobby; Boni, Luigi; Bosker, Robbert J.I.; Box, Benjamin; Brown, Carl; Bruegger, Lukas; Brunner, Walter; Buchli, Christian; Cahill, Ronan; Campana, Juan Pablo; Candido, Francesca di; Capolupo, Gabriella T.; Caricato, Marco; Caro-Tarragó, Aleidis; Casati, Massimiliano; Cassinotti, Elisa; Chadwick, Michael; Chitsabesan, Pramithra; Christoforidis, Dimitri; Coetzee, Emile; Coget, Julien; Collera, Pablo; Courtney, Edward; Cunningham, Chris; Dagbert, Francois; Dalton, Stephen J.; Damietta, Marta Pascual; Dapri, Giovanni; Dayal, Sanjeev; de Manzini Nicolo; de Pooter, Karl; DeLacy, Borja; Delgado, Salvadora; Dimitrov, Dobromir; Duff, Sarah; Dzhumabaev, Khasan Erkinovich; Edwards, Tom; Egenvall, Monika; Estevez-Schwarz, Lope; Færden, Arne E.; Faes, Seraina; Feleppa, Cosimo; Ferrero, Alessandro; Forsmo, Havard; Freitas, Christiano Denoni; Frontali, Alice; Gamage, Bawantha; García-Florez, Luis J.; Geissmann, Daniel; Glöckler, Markus; Gloor, Severin; Grolich, Tomas; Hahnloser, Dieter; Harikrishnan, Athur; Hasegawa, Hiro; Haunold, Ingrid; Hevia, Maria Fernandez; Hol, Jeroen; Horwood, James; Ial, Roshan; Ito, Masaaki; Julião, Guilherme Pagin São; Karamanliev, Martin; Killeen, Shane; Kneist, Werner; Kok, Siu Yan; Korsgen, Stephan; Kusters, Miranda; la Terra, Antonio; Lacy, Antonio; Lakatos, Lorand; Lambrecht, Jan R.; Lavik, Sigmund; Lee, Larence; Liberman, Sender A.; Lorenzon, Laura; Mackey, Paul; Mamedli, Zaman Zaur; Marcy, Tobias; Maroon, Tohmeh; Marti, Lukas; Massucco, Paolo; Mattacheo, Adrián Ezequiel; McCallum, Iain; Meyer, Jeremy; Michalopoulos, Antonios; Mikalauskas, Saulius; Miroshnychenko, Yevgen; Mitermair, Christof; Moore, Tim; Mooslechner, Barbara; Morino, Mario; Muñoz C., Muratore, Andrea; Mutaftchyski, Ventsislav Metodiev; Myers, Alistair; Navarro, Joaquim; Nicol, Deborah; Nishizaki, Daisuke; Nolan, Gregory John; Ochsner, Alex; Oh, Jae Hwan; Osenda, Edoardo; Ourô, Susana; Panis, Yves; Papavramidis, Theodosios; Paraoan, Marius; Pastor, Carlos; Pei, Cherylin Fu Wan; Penchev, Dimitar; Pera, Miguel; Perdawood, Sharaf; Perez, Rodrigo Oliva; Persiani, Roberto; Pfeffer, Frank; Phang, P. Terry; Poskus, Eligijus; Ris, Frederic; Rockall, Timothy Alexander; Romero-Marcos, Juan Manuel; Roquete, Paulo; Rossi, Gustavo; Ruffo, Giacomo; Ruiz, Marcos Gomez; Sagar, Jayesh; Sakai, Yoshiharu; Sanchon, Lorena; Scala, Andrea; Schaap, Dennis; Scheiding, Monica Millan; Schiavo, Marcello; Schmidt, Eduardo Miguel; Sevá-Pereira, Gustavo; Sguinzi, Raffaella; Shalaby, Mostafa; Sharma, Abhiram; Shashank, Gurjar; Sietses, Colin; Sileri, Pierpaolo; Slesser, Alistair; Sohn, Dae Kyung; Solis-Peña, Alejandro; Soravia, Claudio; Sosef, Meindert M.N.; Spinelli, Antonino; Storms P.; Studer, Peter; Syk, Erik; Talsma, Aaldert Konraad; Tejedor, Patricia; Temple, Sara; Tognelli, Joaquín; Tong, Weihua; Torkington, Jared; Tuech, Jean-Jacques; Tzovaras, George; Van de Putte, Dirk; van Nieuwenhove, Yves; von Papen, Michael; Vorburger, Stephan; Wang, Quan; Warrior, Satish; Weiss, Helmut; Witzig, Jacques-Alain; Wolff, Torsten; Wynn, Greg; Zingg, Urs.