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Oncological safety of transanal total mesorectal excision (TaTME) for rectal cancer: mid-term results of a prospective multicentre study

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Abstract

Background There is no consensus regarding the gold standard technique for rectal cancer as Total Mesorectal Excision (TME) may be safely performed either by open or minimally invasive surgery. The laparoscopic approach, however, may carry technical difficulties. For this reason, a novel technique has emerged in the last decade combining a dual laparoscopic dissection (abdominal and transanal) to perform the TME technique (TaTME). When focusing on oncological outcomes, there is a lack of literature regarding mid-long term results.

The aim of this study is to evaluate the mid-term oncological impact of TaTME for treating rectal cancer.

Methods A prospective multicentre study was performed in four tertiary centres including consecutive patients who underwent TaTME for mid-low rectal cancer by the same group of experienced surgeons. The analysed data included pathological results on the quality of TME and mid-term oncological outcomes.

Results In total, 173 patients were included throughout a study period of 6 years. Our series included 70% males and 68% of patients with neoadjuvant treatments. The median follow-up was 23 [15–37.5] months. Regarding pathological results, a complete TME was achieved in 72.8%, while circumferential and distal margins were affected in 1.4 and 1.1%, respectively. Five patients developed local recurrences (3%) and 8.1% presented distant disease during the follow-up. The 2-year disease-free survival and the overall survival rates were 88% and 95%, respectively.

Conclusions There is currently a lack of evidence in the literature regarding TaTME and oncological outcomes with no data available from randomized clinical trials. In the meantime, the reported results from different multicentre series are controversial. This study showed positive mid-term outcomes at 2 years of follow-up and supported notable oncological outcomes with TaTME. However, it must be emphasized that previous experience in minimally invasive and transanal surgeries is essential for surgeons before intending to perform TaTME.

Keywords Laparoscopic surgery · Rectal cancer · Transanal total mesorectal excision · TaTME · Total mesorectal excision

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The rectum is anatomically enfolded in a fatty tissue coverage known as the mesorectum and it lies in the pelvis following the sacrum shape to the anal canal. When treating a rectal cancer, it is crucial to perform surgery through the anatomical and embryological planes, as Professor Bill Heald postulated years ago [1]. This technique called Total Mesorectal Excision (TME) has demonstrated improvement in the outcomes for rectal cancer patients, especially in terms of reducing the possibilities of developing local recurrence.

Currently, there is no consensus regarding the gold standard technique for rectal cancer as TME may be safely performed either by open or minimally invasive surgery (MIS) including robotic and laparoscopic techniques. Laparoscopic TME has demonstrated several advantages compared to

open surgery such as reduced postoperative pain, shorter hospital stay and a faster return to normal activities [2]. This approach, however, may carry technical difficulties especially when facing bulky rectal cancers in male, obese patients leading to more complications and conversion rates in this group of patients [3]. Therefore, to date, the majority of surgeons consider MIS for TME a highly demanding procedure. For instance, in the European Society of Coloproctology (ESCP) snapshot published in 2017, only about 20% of TME is performed by MIS compared to an open approach [4]. The use of robotic surgery may overcome some of the adversities related to the laparoscopic approach in low rectal cancer cases. It has demonstrated better outcomes in terms of reducing conversion rates, however, it increases operative times and costs. Moreover, the adoption of robotic TME worldwide remains low likely due to a lack of availability in many centres [5]. In addition to these procedures, a novel technique has emerged in the last decade combining a dual laparoscopic dissection (abdominal and transanal) to perform the TME technique (TaTME). The TaTME promises were (1) to achieve a better visualization of the mesorectal plane, (2) obtain higher rates of free circumferential and distal margins and (3) reduce the percentage of anastomotic leakages due to the avoidance of staple firings during the division of the rectum. On the other hand, there exists some drawbacks related to TaTME, such as the need of two laparoscopic sets, the need for more personnel involved in the operation and a complex learning curve for non-experienced surgeons in minimally invasive rectal cancer techniques.

P. Sylla and A. Lacy et al. [6] performed the first clinical case of TaTME in 2009, since then the adoption of TaTME has increased globally. Several retrospective and prospective studies have been published and analysed in a recent meta-analysis [7]. The International TaTME registry collaborative has reported the largest prospective series to date showing the feasibility of this novel operation with satisfactory perioperative and pathologic results. Despite the practicality of this technique, some concerns exist regarding intraoperative complications and technical problems during the transanal phase [8, 9].

When focusing on oncological outcomes, there is a lack of literature concerning mid-long term results. There are only preliminary results published from retrospective or uncontrolled prospective studies; moreover, the first known national results from Norway [10] and Netherlands [11] are opposite, leading to a global debate on survival after TaTME [12]. In the meantime, two multicentre European clinical trials (COLOR III and GRECCAR 11) [13, 14] will provide new data on local recurrence rates and survival after TaTME, but both are currently in the recruitment process.

Our group designed the present study aiming to support with additional data the TaTME oncological safety and pathological results. This prospective trial evaluates the combined mid-term oncological results from a multicentre experience with the TaTME technique for rectal cancer.

Methods

The primary outcome was to assess the TaTME results on quality of the surgical specimen and the percentage of success in achieving negative distal and circumferential margins. The secondary point was to evaluate the postoperative evolution, the local and distant recurrence rates and the 2-year disease-free survival (DFS) and overall survival (OS).

To obtain the study objectives, retrospective analysis was performed based on a prospectively maintained database over a 6-year period from four tertiary centres in Spain: (1) The University Hospital of Leon (Leon); (2) The University Hospital Fundacion Jimenez-Diaz (Madrid); (3) The University Hospital Gregorio Marañon (Madrid) and (4) The University Clinic of Navarre (Madrid). The local Ethics Committees of the participating Centres approved the study.

We included consecutive uncontrolled patients with histologically proven rectal tumour (disease stages I-IV), expecting to require a complete TME with or without neoadjuvant chemoradiation therapy (CRT); in whom we performed a sphincter-sparing low-anterior resection by TaTME. Exclusion criteria included patients with recurrent tumours, palliative or urgent resections and those patients in which we performed an abdominoperineal, Hartmann's resection or pelvic exenteration.

Per protocol, a complete physical examination, a total colonoscopy, and abdominopelvic CT scan and pelvic MRI were performed in all patients preoperatively. Those tumours showing a $\geq$ cT3 and/or N + on MRI or tumours with preoperative threatened circumferential margins ($\leq$ 1 mm) were discussed at the Multi-Disciplinary sessions in each centre to proceed with CRT. The protocol for all centres included a long-term course of radiation therapy (50.4 Gy, 28 days) with concurrent oral Capecitabine. Surgery was completed at 8–10 weeks after finishing CRT.

The extracted data to further analyse included patient's and tumour's baseline characteristics; sex, BMI, ASA score, preoperative distance to anal verge-DRM (by rigid rectoscopy), preoperative clinical TN staging based on suspected lymph nodes and circumferential margin status-CRM (by MRI), and distant staging (by chest–abdomen–pelvis CT scan). We also recorded the operative time, estimated blood loss, surgical morbidity (Dindo–Clavien classification) and the length of hospital stay (LOS).

Surgical procedure

The same group of colorectal surgeons with previously proven expertise in MIS and transanal surgeries conducted

the TaTME procedures at the participating centres. Each centre has two surgeons TaTME trained, although the majority of the procedures were performed by three main surgeons (VS, LMJ, CP) who completed the Structured TaTME Training Curriculum defined by Francis et al. [15].

Per protocol, either one or two-teams of surgeons performed the TaTME procedure in two consecutive phases:

- Abdominal laparoscopic approach: High ligation of the inferior mesenteric artery and vein, and complete splenic flexure mobilization. Pelvic dissection was continued in the TME plane to the level of the puborectal sling posteriorly and of the seminal vesicles anteriorly in men and to the rectovaginal septum level in women.
- Transanal laparoscopic approach: A LoneStar® retractor was placed previous to platform's insertion (Gelpoint Path®). Under tumour visualization, a purse string suture was done to obtain a secure distal margin and a completed closure of the lumen. Afterwards, a complete circumferential full-thickness rectotomy was performed before facing the dissection cranially via the TME plane. Both planes, transanal and abdominal, were connected by the two surgical teams.

The next step was specimen extraction through a suprapubic incision or transanally. The anastomosis was performed either by a circular end-to-end stapler or a hand-sewn anastomosis, depending on the length of the rectal stump. Finally, a loop ileostomy was performed if considered necessary by the surgical team.

Pathological reports

The pathologist from each centre evaluated the surgical specimens following the protocols of TME evaluation described by Nagtegaal et al. [16]. A complete TME specimen is defined by a mesorectum that is intact with a smooth surface or with only minor defects (less than 5 mm) in the mesorectal fascia. A nearly complete TME is considered when the mesorectum shows deeper defects (> 5 mm), but not affecting the muscularis propria and incomplete when the muscularis propria is visible in the deeper part of the mesorectal tear. Other pathological results included TNM classification (7th edition) [17], the presence/absence of a perforated tumour, the number and presence/absence of affected lymph nodes, a positive/negative DRM (≤ 1 mm.) or CRM (≤ 1 mm.) and the presence/absence of lymphovascular and perineural invasion. The tumour regression grade (TRG) was reported according to the Ryan tumour regression grade in three of the study centres, based on the volume of persistent tumour cells after CRT [18]. Grade 0, complete response without viable cancer cells; Grade 1, moderate response showing a small volume of cancer cells; Grade 2, minimal response showing residual visible cancer mixed with fibrosis, and Grade 3, poor response showing extensive visible cancer without signs of tumour response. In one of the study centres, the UHGM, the TRG was reported by the pathologist following the Rödel tumour regression grade (Grade 0, no regression; Grade 1, fibrosis $< 25\%$ of tumour mass; grade 2, fibrosis 25–50% of tumour mass; grade 3, fibrosis over 50% of tumour mass; grade 4, complete regression).

Patient follow-up

We standardized the follow-up protocol of 5 years for every participating centre. Medical oncologists at each site evaluated patients after a postoperative recovery period of one month. Adjuvant chemotherapy was indicated based on the patient's status and the histopathology report. Molecular tumour markers (including CEA) and a whole-body CT scan were performed every 6 months during chemotherapy or at one year after surgery for patients without further treatments. A complete colonoscopy was required at one year after surgery and repeated based on findings every 1 or 2 years.

Local recurrence (LR) was described as any clinical/radiological-detected evidence of tumour relapse in the anastomosis or in the primary site; all suspected LR would require a complete colonoscopy or a guided biopsy to establish the diagnosis of recurrence. Distant recurrence (DR) was described as any clinical/radiological-detected evidence of tumour relapse at any organ outside the primary site of the tumour. All suspected DR would require a PET-CT scan and a guided biopsy to establish the diagnosis of recurrence. DFS was defined as the length of time after treatment during which no evidence of disease was found. OS was defined as the percentage of patients diagnosed with rectal cancer at the start of the study that were alive at the time of evaluation. Survival was calculated according to disease stages reported by the pathologist. Patients with stage IV disease at the time of diagnosis were excluded for the survival analysis.

Statistical analysis

Descriptive statistics are presented with mean and standard deviation (SD) or median and lower quartile range–upper quartile range (LQ–UQ) for quantitative variables. The comparison of the differences between groups was carried out using Chi-Squared analysis with Fisher's exact test when any value observed in the contingency table was less than 5. Differences between median values of the groups were assessed

using Mann–Whitney U test. A time-to-event analysis was performed using the Kaplan–Meier method.

All statistical analyses were conducted using SPSS® version 22 software (SPSS, Inc., Chicago, IL) and p values of < 0.05 were considered statistically significant.

Results

Between May 2013 and February 2019, 173 patients who underwent TaTME were included in the study, with a minimum follow-up of 1 year. The technique was gradually adopted at each centre since 2013 until the end of the study in 2019 as presented in Fig. 1. By centres, one of them (UHL) entered 110 cases until February 2019, two hospitals (UHFJD and UHGM) included 35–40 cases and the fourth centre (UCN) added 6 patients. Patients and tumour characteristics are shown in Table 1; of note, the majority of patients were men (70%), with a median age of 69 [56–77] years and BMI of 27 [24–29] Kg/m^2. Median distance of the tumour to the anal verge was 5 [4–7] cm. The clinical TNM grading showed that 60.7% of cases were classified as stage III disease and 12/60 (20%) had threatened circumferential margins on the preoperative MRI. The TaTME procedure was performed at 6.8 [8–10.5] weeks after CRT. Mean operative time was 240 ± 42 min with an estimated mean blood loss of 500 ± 600 ml. Major complications (Dindo–Clavien ≥ III) were observed in 10% of patients. The median length of hospital stay was 6 [5–10] days.

The Pathological results are shown in Table 2. A stage III disease was reported in 29% of cases. The median number of lymph nodes harvested was 13 [9–17]. DRM was found affected in two cases (1.1%) while the percentage of cases with CRM involvement was 1.4% ($n = 2$). Macroscopic grading of the mesorectum was complete or nearly complete in 87% of the patients. TRG grades are shown in Table 2. A complete pathological response was observed in 17% of cases. The combination of complete mesorectal excision, negative CRM and negative DRM was achieved in 97.6% of the evaluated cases ($n = 124/127$).

The median follow-up for the entire population was 23 [15–37.5] months, with at least 50% of patients having more than 2 years of follow-up. In Table 3, we present the oncological outcomes during the follow-up. Five patients developed LR (3%) at the site of the anastomosis and required salvage surgery (abdominoperineal resection); one of them also had synchronic distant metastasis. Median time to the LR was 15 [11–35] months. One of these patients was operated in 2014, 3 patients had surgery in 2017 and another one in 2018. Regarding poor pathological outcomes for developing LR, 4 patients had ypT3 staging and 2 patients had yN-positive disease after CRT. Lymphovascular invasion was found in one case and only one specimen had a nearly complete mesorectum. All LR cases had negative distal and circumferential margins. In the latest follow-up, 3 patients remained alive after salvage treatment, whereas the other 2 died during the follow-up.

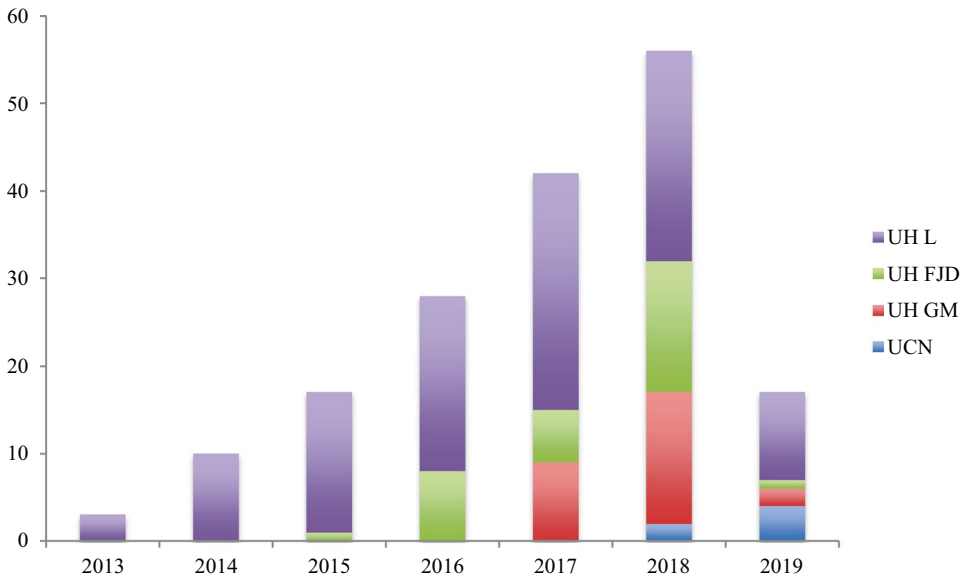

Fig. 1 Distribution of cases in each centre over the years

UH L = University Hospital of Leon
UH FJD = University Hospital Fundacion Jimenez-Diaz
UH GM = University Hospital Gregorio Marañon
UCN = University Clinic of Navarre

Table 1 Patients and tumour characteristics

	Global data ($n=173$)
Age (median, LQ-UQ) (year)	69 [56–77]
Sex (Male:Female) (%)	70:30
BMI	27 [24–29]
ASA	
I-II	66%
III	34%
Preoperative TNM staging	
Tx[a]	7 (4%)
T1[a]	14 (8.2%)
T2	44 (25.4%)
T3	94 (54.3%)
T4	11 (6.4%)
Missing	2 (1.2%)
N0	66 (38.2%)
N1	73 (42.2%)
N2	32 (18.5%)
Missing	3 (1.7%)
M1	14 (8.2%)
Tumour distance from AV (on MRI) (cm); (median, LQ-UQ)	5 [4–7]
Neoadjuvant chemoradiotherapy	118 (68.2%)
LOS (days); (median, LQ-UQ)	6 [5–10]
Adjuvant chemotherapy	65%
Follow-up (months); (median, LQ-UQ)	23 [15–37.5]

ASA American Society of anesthesiologists; *BMI* body mass index; *LOS* length hospital stay

[a]Tx, previous endoscopic/local resections with affected margins or poor oncological outcomes reported in the specimen

A total of 14 (8.1%) patients developed distant metastasis (9 liver deposits, 4 pulmonary and 1 retroperitoneal). The 2-year DFS rate and the OS rate for all stages were 88% and 95%, respectively. A total of 13 patients died of disease during the follow-up period. In Figs. 2 and 3, we represent the OS and DFS for all the disease stages.

The grades in quality of TME are reported in Fig. 4a showing how the percentage of complete TME was maintained around 80% throughout the years. In Fig. 4b, we presented the increasing percentage of irradiated tumours during the study period, from 60% of irradiated tumours in the beginning to over 70% by the end of the study.

Discussion

The present multicentre study shows a positive mid-term impact of the TaTME technique for rectal cancer surgery in oncological results at a 2-year period. This study demonstrates the oncological safety of the procedure when expert surgeons with previous experience in minimally invasive and transanal surgical procedures perform TaTME. Based on our data, we obtained a high percentage of OS (95%) and DFS

Table 2 Postoperative pathological outcomes

	Global data ($n=173$) (%)
Pathological TNM staging	
T0	38 (22)
ypT0[a]	20 (17)
pT0[b]	18 (5)
T1	18 (10.4)
T2	61 (35.3)
T3	51 (29.5)
T4	2 (1.2)
N0	120 (69.4)
N1	43 (24.9)
N2	7 (4)
Missing	3 (1.7)
TME	
Complete	126 (72.8)
Nearly complete	24 (13.9)
Incomplete	6 (3.5)
Missing	17 (9.8)
Lymphatic invasion	25 (14.5)
Missing	22 (12.7)
Venous invasion	44 (25.4)
Missing	4 (2.3)
TRG (Ryan)	
0	4 (4.1)
1	18 (18.4)
2	41 (41.8)
3	19 (19.4)
4	3 (3.1)
Missing	13 (13.3)
TRG (Rödel)	
0	–
1	4 (20)
2	8 (40)
3	5 (25)
4	1 (5)
Missing	2 (10)
Lymph nodes harvested (median, LQ-UQ)	13 [9–17]
DRM ≤ 1 mm (n, %)	2 (1.1)
CRM ≤ 1 mm (n, %)	2 (1.4)
Missing	32 (18,5)

CRM circumferential rectal margin; *DRM* distal resection margin; *TRG* tumour regression grade; *TME* total mesorectal excision

[a]Pathological complete response

[b]Previous endoscopic/local resections with affected margins or poor oncological outcomes reported in the specimen

Table 3 2-year overall survival (OS) and disease-free survival (DFS) by disease stages

	Global data $n = 173$ (%)
Local recurrence (n,%)	5 (3)
Distant metastasis (n, %)	14 (8.1)
2-y OS	
Stage 0	94
Stage I	96
Stage II	100
Stage III	92
2-y DFS	
Stage 0	93
Stage I	98
Stage II	77
Stage III	76

(88%), while LR rate remained low (3%) during the 2-year follow-up.

Although TaTME was originally described 10 years ago, the adoption of the procedure has been mainly developed in the last 5 years because of its challenging technique and the gradual learning curve required. Nowadays, there is a need for growing evidence on two major points regarding TaTME; the safety of the procedure in terms of postoperative complications and the mid-long term oncological outcomes.

Initial concerns regarding intraoperative complications were reported in the first TaTME series [8]; the registry reported the presence of urethral lesions in 0.8%, abdominal conversion rate of 6.3% and errors in the dissection planes during the transanal phase in 8% with a transanal conversion needed in 2.3%. Both problems were observed in the earliest studies due to lack of the surgeon's experience and the learning curve in the surgical technique. Our group has recently published a prospective cohort study on the outcomes of our first 100 TaTME cases [19]. In this study we reported safe postoperative outcomes, comparable to other TaTME published series; 36% of patients had morbidities, 8% of patients with major Dindo–Clavien complications (anastomotic leakage, pelvic abscess) and one case of postoperative mortality. The length of hospital stay was 5.5 days. Conversion to open surgery due to difficulties during the perineal approach occurred in 4 patients in the first 20 cases mainly due to the surgeon's learning curve.

To date, in the absence of clinical trials, there exists increasing evidence based on the results of meta-analysis comparing TaTME vs. LapTME [7, 20]. A recently published meta-analysis included 14 studies (10 of them prospective series) comparing 495 patients in the TaTME group vs. 547 in the LapTME group. The pooled data showed significant differences in terms of less major comorbidities, less percentage of anastomotic leakage, and less length of hospital stay and readmission rates in the TaTME group [7].

Despite the initial reports on good oncological outcomes with TaTME [8], much debate is ongoing particularly due to a recently launched national moratorium on TaTME in Norway [12]. The Norwegian decision to ban TaTME was made based on the reports published by Larsen and Wasmuth et al. on behalf of the Norwegian Colorectal Cancer Group [10, 21]. They analysed 157 patients who underwent TaTME in four reference hospitals in the country. The updated report showed a LR rate of 7.6% at a median follow-up of 20 months, and an estimated LR rate at 2.4 years of 11.6%, which doubled the expected '< 5% rule' from the literature. Moreover, these cases of LR occurred early in the follow-up and with an unexpected pattern of multifocal pelvic involvement compared to traditionally known single-site recurrence in the pelvis or at the level of the anastomosis. The author's insight was that these abnormal LR patterns might be caused by technical failures in performing the transanal purse string. These data from Norway were conflicting with previous TaTME results including the TaTME International Registry [8, 22] and other prospective multicentre series including ours, and recent meta-analysis [7, 22]. Alternatively, Hol JC et al. recently published a multicentre study from two centres in Netherlands showing good oncological results with TaTME; a recurrence rate below the benchmark of 5%, and equivalent to our data on DFS (81%) and OS (77.3%) with an extended 5-year period of follow-up [11]. Our results are in line with the Netherland's report in terms of LR rates and survival data and to our knowledge, our study is the second multicentre study publishing data on mid-term results in terms of survival and recurrences. Moreover, the pretreatment clinical staging including about 50% of cT3N + tumours and the rates of patients who underwent neoadjuvant chemoradiation (60–70%) are comparable between this report and our study.

The quality of the TME specimen remains a concern in LapTME. Access to bulky low tumours with a lack of space to work properly within a narrow pelvis, plus the need for using cross stapling for rectal division, are major problems faced by surgeons when performing LapTME. Based on the data from the CLASSIC trial, patients who underwent LapTME were found to have higher rates of affected CRM compared to openTME [3]. More recently, two non-inferiority designed clinical trials, the ACOSOG Z6051 [23] and the ALaCarT [24] also reported lower percentages of patients with negative CRM when comparing LapTME vs. openTME. The use of TaTME may overcome some of these LapTME drawbacks. It gives surgeons the possibility of achieving higher rates of negative distal margins by choosing an adequate distance to the tumour under vision. It may also help to obtain a better quality of TME specimens due to the avoidance of linear stapling during rectal division.

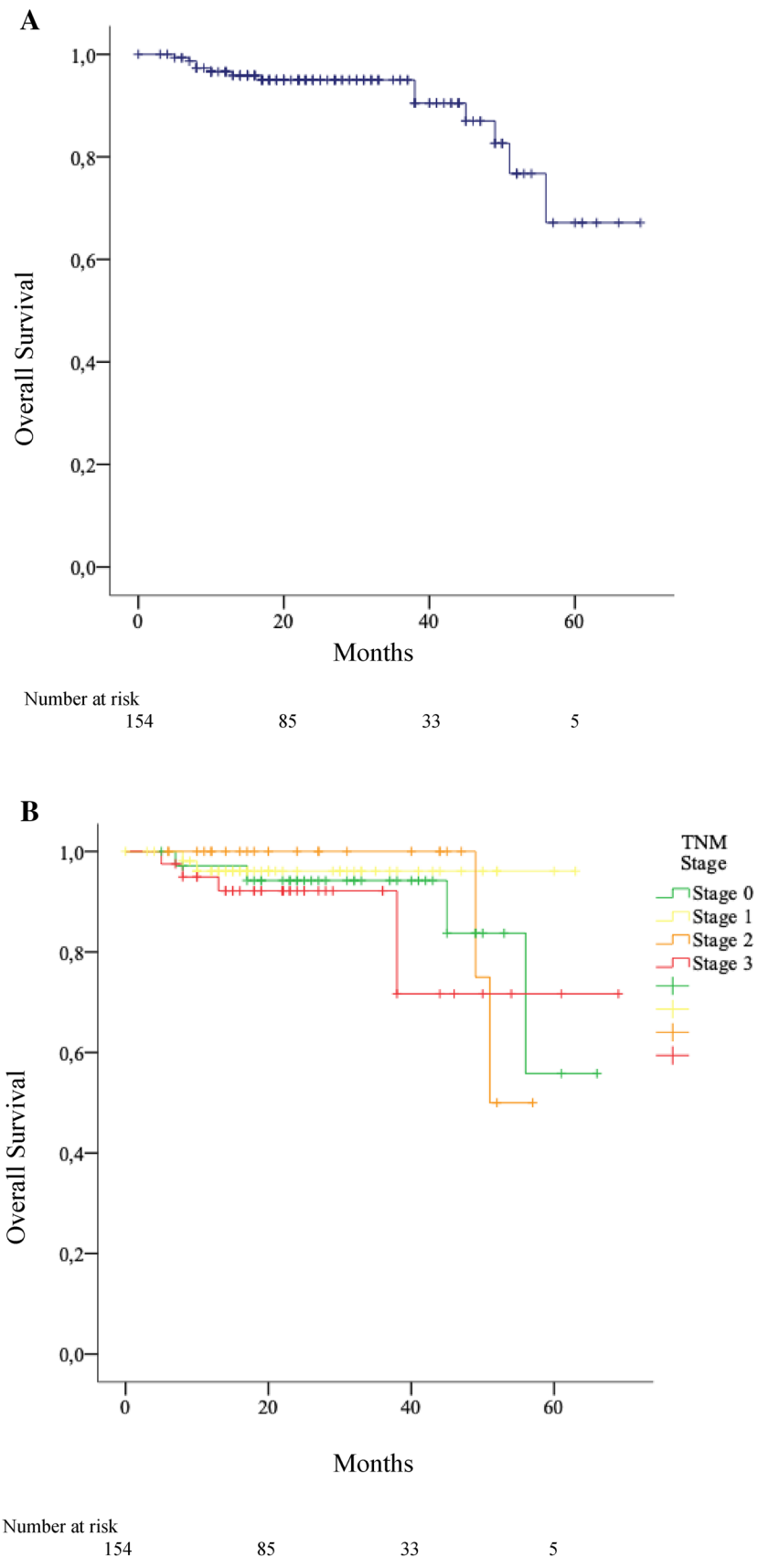

Fig. 2 OS. **A** All stages (excluding M1 disease) **B** By disease stages

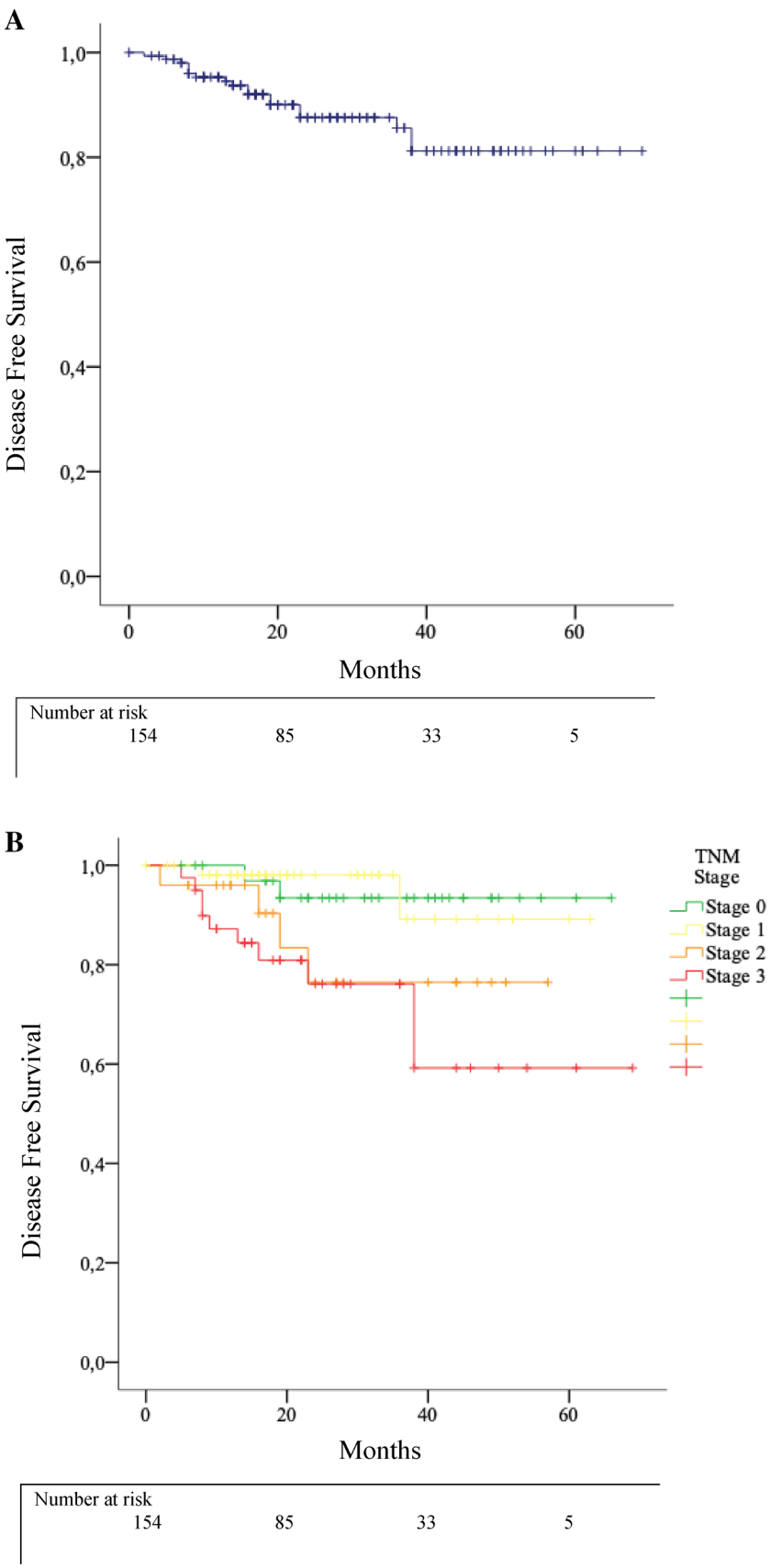

Fig. 3 DFS. **A** All stages (excluding M1 disease). **B** By disease stages

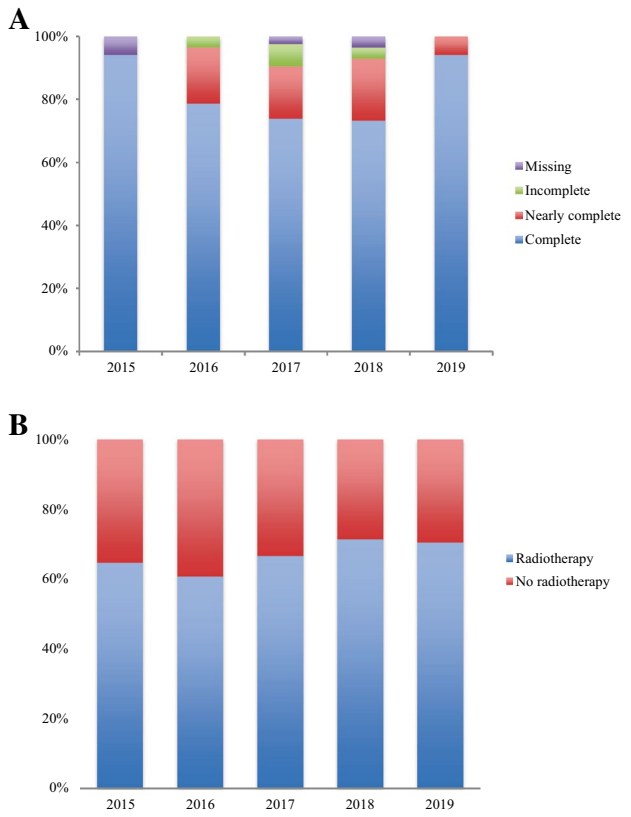

Fig. 4 **A** Distribution of mesorectal grade over the years. **B** Percentage of patients with preoperative radiotherapy over the years

Based on the resumed data presented in Table 4, the completeness of TaTME specimens varied in the literature, from 73% in our study to 80% in the TaTME Registry reports to around 95% in Barcelona´s experience [11, 20, 22, 25]. As shown in Fig. 4A, our percentage of complete TME remained stable and close to 80% over the years in the study. However, the percentage of irradiated tumours increased to 70% in the last period of the study (Fig. 4B). These data reflect some selection bias in the initial period of our study, but highlight the importance of the learning curve in TaTME as we were capable of stabilizing rates of complete TaTME specimens with high percentage of irradiated tumours. On the contrary, other studies reported higher rates of complete TaTME specimens, but included less preoperative radiation. In terms of other important TME measures, the majority of studies on TaTME reported close to zero rates of positive DRM and variable, but low CRM rates from 0.6% to 8%. LR rates were only reported in the Netherlands study (3.8%) and in our study with expected comparable data with longer follow-up in our series. In our experience, LR cases were at the level of the anastomosis; all these patients underwent salvage surgery (abdominoperineal resections). Regarding poor pathological outcomes for developing LR, four patients had ypT3 staging and two patients had yN-positive disease after CRT. Lymphovascular invasion was found in one case and only one specimen had a nearly complete mesorectum. All LR cases had negative distal and circumferential margins.

Our study has some limitations and biases that deserve to be mentioned. The data were analysed in a retrospective manner, but over a prospective well-maintained database from four tertiary referral centres in our country. We believe that our outcomes are in accordance with the average TaTME results published in the literature, however, as mentioned before, the learning curve on performing a TaTME is crucial and these data may be difficult to be reproduced by non-experienced groups. The sample size may be considered small, but this is the largest series published regarding mid-term oncological outcomes after TaTME for rectal cancer.

Conclusions

With two ongoing randomized clinical trials about oncological safety on performing TaTME for rectal cancer, there is a current lack of evidence in the literature and some results are controversial. To the best of our knowledge, this is the second multicentre study showing mid-term oncological safety and positive outcomes with two-year follow-up. Our reported pathological and survival outcomes are comparable to the previously published Open and LapTME series. However, we believe that TaTME is a challenging procedure, highlighting that previous experience in minimally invasive and transanal surgery must be a prerequisite for surgeons aspiring to perform TaTME for rectal cancer.

Table 4 TaTME series (> 120 cases) with mid-long term oncological outcomes

TaTME series (n = years of recruitment)	De Lacy B. et al., 2017 n = 186 (2011–2016)	Zeng. Z et al., 2019 n = 128 (2016–2018)	Hol JC. et al., 2019 n = 159 (2012–2016)	Roodbeen et al., 2019 (International TaTME Registry) n = 2653 (2014–2018)	Wasmuth HH et al., 2020 n = 157 (2014–2018)	Present study, 2020 n = 173 (2013–2019)
Study design	One Centre Prospective cohort	Multicentre RCT TaTME vs. LapTME	Multicentre Prospective cohort	Multicentre Prospective cohort	Multicentre Prospective cohort	Multicentre Prospective cohort
Patients baseline characteristics	Age (yrs)* 65 M/F (%) 63/36 BMI (kg/m^2)** 25.1 ± 3.9	Age (yrs)* 56 M/F (%) 64/35 BMI (kg/m^2)** 22.5 ± 3.1	Age (yrs)* 66.9 M/F (%) 66/34 BMI (kg/m^2)** 26.4 ± 4.3	Age (yrs)* 64.4 M/F (%) 69/31 BMI (kg/m^2)** 26.3 ± 4.5	Age (yrs)* 65 M/F (%) 70/30 BMI (kg/m^2)* -	Age (yrs)* 69 M/F (%) 70/30 BMI (kg/m^2)* 27
Tumour height (cm. to anal verge)	Mid rectum** 7.9 ± 1.5 Low rectum** 3.5 ± 1.3	5.0 ± 1.7**	5.7 ± 3.5**	3.8 ± 2.6**	8 [2–13]*	5 [4–7]*
cTNM staging by MRI (%)	T1 3.2 N0 54.8 T2 20.4 N + 44.1 T3 67.7 M0 89.8 T4 7.5 M + 10.2	T1 2.3 N0 59.4 T2 14.8 N + 38.3 T3 78.1 M0 n/d T4 0.8 M + n/d Tx 3.9	T1 1.3 N0 51.6 T2 24.5 N + 46 T3 64.8 M0 95.6 T4 6.9 M + 4.4 Tx 2.5	T1 3.3 N0 44.7 T2 25.6 N + 55.3 T3 63.9 T4 6.5	n/d	T1 8.2 N0 38.3 T2 25.4 N + 60.7 T3 54.3 T4 6.4 Tx 4
Neoadjuvant CRT (%)	Yes 62.4 No 37.6	Yes 46.1 No 53.9	Yes CRT 27, RT:70 No 30	Yes 59.1 No 40.9	Yes 21 No 79	Yes 68 No 32
pTNM staging (%)	pT0 16.1 pN0 65 pT1 6.5 pN + 29.6 pT2 29.6 pNx 5.4 pT3 41.9 pT4 1.6	pT0 6.3 pN0 63 pT1 8.6 pN + 36.6 pT2 28.1 pT3 54.7 pT4 2.3	pT0 8.2 pN0 74.2 pT1 9.4 pN + 25.8 pT2 46.5 pT3 34.6 pT4 1.3	pT0 11 pN0 70.3 pT1 11.2 pN + 29.7 pT2 31.4 pT3 42.4 pT4 2.5	pT0 5.1 pN0 68.8 pT1 17.2 pN + 31.2 pT2 36.3 pT3 36.3 pT4 5.1	pT0 22 pN0 69.4 pT1 10.4 pN + 28.9 pT2 34.3 pT3 29.5 pT4 1.2
Quality of TME (%)	Complete 95.7 Nearly Complete 1.6 Incomplete 1.1 Unknown 1.6	Complete 94.5 Nearly Complete 5.5 Incomplete 0 Unknown n/d	Complete 87.4 Nearly Complete 10.1 Incomplete 2.5 Unknown n/d	Complete 80.9 Nearly Complete 10.3 Incomplete 3.4 Unknown n/d	n/d	Complete 72.8 Nearly Complete 13.9 Incomplete 3.5 Unknown 9.8
Affected Margins ≤ 1 mm n (%)	Distal margin 6 (3.2) Radial margin 15 (8.1)	Distal margin 0 Radial margin 2 (1.6)	Distal margin[a)] 0 Radial margin 1 (0.6)	Distal margin[a)] 26 (1) Radial margin 107 (4)	Distal margin - Radial margin (5.1)	Distal margin 2 (1.1) Radial margin 2/141 (1.4)
Lymph nodes harvested	14 (11–18)*	15 (2–35)*	n/d	17.7 ± 10.3**	n/d	13 [9–17]

Table 4 (continued)

TaTME series (n = years of recruitment)	De Lacy B. et al., 2017 n = 186 (2011–2016)	Zeng. Z et al., 2019 n = 128 (2016–2018)	Hol JC. et al., 2019 n = 159 (2012–2016)	Roodbeen et al., 2019 (International TaTME Registry) n = 2653 (2014–2018)	Wasmuth HH et al., 2020 n = 157 (2014–2018)	Present study, 2020 n = 173 (2013–2019)	
Tumour regression grade n (%)	Grade 0 24 (12.9) Grades 1–2 64 (34.4) Grade 3 12 (6.5) Unknown 33 (28.5)	Grade 0 24 (12.9) Grades 1–2 64 (34.4) Grade 3 12 (6.5) Unknown n/d	Grade 0 n/d Grades 1–2 n/d Grade 3 n/d Unknown n/d	Grade 0 293 (11) Grade ≤ 0–2 612 (43) Grade 3 810 (57)	Grade 0 8 (24.2) Grade 1–2 - Grade 3 -	RYAN Grade 0 4 (4.1) Grades1-2 59 (60.2) Grade 3 19 (19.4) Grade 4 3 (3.1) Unknown 13 (13.3)	RÖDEL Grade 0 - Grades 1–2 12(60) Grade 3 5 (25) Grade 4 1 (5) Unknown 2 (10)
Perineural/ vascular invasion (%)	Perineural 15 (8.1) Vascular 31 (16.7)	n/d	n/d	n/d	n/d	Lymphatic 25 (14.5) Vascular 44 (25.4)	
Follow-up period (months)	n/d	n/d	54.8 [36–88]	n/d	19.5 [0–51]	23 [15–37.5]	
Adjuvant chemotherapy n (%)	n/d	n/d	n/d	n/d	n/d	Yes 65 No 35	
Local recurrence n (%)	n/d	n/d	6 (3.8)	n/d	12/152 (7.6)	5 (3)	
Distant recurrence n (%)	n/d	n/d	22 (13.8)	n/d	n/d	14 (8.1)	
DFS (%)	n/d	n/d	92 at 3 yrs, 81 at 5 years	n/d	n/d	88 at 2 yrs	
OS(%)	n/d	n/d	83.6 at 3 yrs, 77.3 at 5 years	n/d	n/d	95 at 2 yrs	

*Median

**Mean

[a]DRM < 5 mm

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Compliance with ethical standards

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Research involving human and animal participants All procedures performed in studies involving humans were in accordance with ethical standards of the institutional research committee and the 1964 Helsinki declaration and its later amendments.

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