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A prospective European trial comparing laparotomy, laparoscopy, robotic-assisted, and transanal total mesorectal excision procedures in high-risk patients with rectal cancer: the RESET trial

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ABSTRACT

Objective: To compare total mesorectal excision (TME) techniques combined with sphincter-sparing procedure in high-risk patients (HRPs).

Background: TME is the standard treatment for rectal cancer, but can be challenging in HRPs. The available surgical approaches must be compared, especially in HRPs.

Methods: Prospective, observational, multicenter trial to compare laparotomy (OTME), laparoscopy (LTME), robotic-assisted surgery (RTME), and transanal surgery (TaTME) in HRPs. The composite primary outcome included circumferential radial margin (CRM) ≥1mm, TME grade II-III, and absence of Clavien-Dindo grade III-IV complications. Three propensity score analyses were performed (LTME *vs.* RTME, RTME *vs.* TaTME, LTME *vs.* TaTME).

Results: 1078 HRPs (75% of men, median body mass index of 27 kg/m^2, 50% of tumors in the lower third of the rectum) underwent surgery. The RTME and TaTME groups included patients with more advanced and lower tumors and coloanal anastomosis (P<0.001). Operative time was longer for RTME surgery (P<0.001). Conversion rate was similar for minimally invasive procedures (4.5%). The global R0 resection rate was 96% without difference among techniques. The primary outcome rates were 82.4%, 64.3%, 74.7%, and 80.3% for LTME, OTME, RTME, and TaTME, respectively. None achieved the expected

success rate (85%), and propensity score analyses found no differences. Operative results were similar between high- and low-volume inclusion centers only for RTME.

Conclusions: The RESET trial yielded high-quality results despite focusing on HRPs. Minimally invasive procedures showed similar sphincter-sparing procedure outcomes, but LTME included patients with more favorable tumors. Oncologic and functional outcomes will be evaluated at 2 years (ClinicalTrials.gov, ID: NCT03574493).

INTRODUCTION

The standard treatment for rectal cancer is total mesorectal excision (TME) that may be combined with a sphincter-sparing procedure (SSP) in patients with mid-to-low rectal cancer. Currently, four surgical techniques are used: laparotomy (OTME), laparoscopy (LTME), robotic-assisted surgery (RTME), and transanal surgery (TaTME). RTME offers many advantages, including articulating wrists and a stable, surgeon-driven camera with 3D vision that helps to overcome challenging situations.[1–4] TaTME was promoted to reduce the conversion rate in high-risk patients (HRPs).[5] These procedures can be technically challenging, especially in HRPs with unfavorable factors, such as narrow pelvis (mainly men), high body mass index (BMI), large tumors (i.e., circumferential radial margin (CRM) <1mm), fatty mesorectum, or when a coloanal anastomosis is required.[6–9] These factors can be determined objectively using preoperative magnetic resonance imaging (MRI).[10–12] Several meta-analyses and, retrospective and prospective studies have been carried out to compare the efficacy of these different procedures, but none demonstrated the superiority of one technique.[13–15] The ROLARR trial emphasized the significant impact of the surgeon's learning curve on the results.[16] However, it is challenging to carry out a randomized controlled trial (RCT) that takes into account the surgeon's preferences and experience with a specific surgical technique.[17,18] Nonetheless, the ROLARR trial showed that RTME provided a significant advantage in HRPs (men, obesity, tumors in the lower third of the rectum). Only the REAL trial showed a significant advantage of RTME over LTME.[19]

The Rectal Surgery Evaluation Trial (RESET) is the first prospective European trial that compared the four TME techniques, combined with a SSP, in HRPs. Its aim was to provide conclusive insights into the optimal approach for this challenging population.

METHODS

Study design and setting

The RESET study was a prospective, observational, case-matched, four-cohort, multicenter trial designed to evaluate the oncological, morbidity, and functional outcomes of LTME, OTME, RTME, and TaTME in HRPs with mid-to-low rectal cancer. The full study protocol has been previously published.[20] The efficacy of each surgical procedure was assessed using a composite primary outcome (CPO) that included three equally weighted success measures to evaluate the surgery quality and safety: CRM ≥ 1 mm, TME grade II-III, and absence of Clavien-Dindo (CD) grade III–IV complications within 30 days after surgery. These measures were binary variables, whether they were met or not. Surgery was considered successful if it met all three conditions. Early secondary outcomes included unplanned conversion rate, operative time, distal resection margin rate, length of hospital stay (LOS), and effect of the centers' inclusion volume on surgery type, operative time, and anastomotic leakage, infection, and ileus rates.

This trial (NCT03574493) was approved by the French Ethics Committee (CPP Ouest II, Angers, France – ID RCB number: 2018-A01293-52) before study initiation and by all European participating centers' ethics committees. A site initiation visit was performed in all participating centers before the enrollment of the first patient. This trial was carried out in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

For each arm, surgeons were selected based on their experience (i.e. ≥30 surgical procedures).

Participants

The main inclusion criteria were ≥ 18 years of age, adenocarcinoma of the middle and lower third of the rectum (<12 cm from the anal verge) with a SSP, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and being a HRP. HRPs were defined as patients with

at least two of the following factors: obesity (BMI > 30), narrow pelvis (i.e., inter-tuberous distance <10 cm on MRI), large tumor volume (i.e., CRM ≤1 mm), expected coloanal or ultra-low colorectal anastomosis.

Exclusion criteria included metastatic disease, T4b tumors requiring pelvectomy, need of abdominoperineal resection (APR), concurrent or previous invasive pelvic malignant tumor within 5 years before enrollment, patient undergoing emergency surgery, and rectal surgery planned with major concomitant procedures.

All patients signed an informed consent form before inclusion in the study.

Interventions

Patients were assigned to one surgical procedure based on the surgeons' experience and standard practice. The original chosen procedure could be changed to another if deemed necessary.

Data collection and statistical analysis

Data were prospectively collected using the secure Ennov Clinical® software. Data management included a validation plan and remote monitoring to ensure data integrity and quality. The sample size was determined based on the incidence of CRM ≥1 mm and CD grade ≥III reported in the literature to achieve a 85% success rate for the CPO, with a lower 95% confidence interval limit within 4% of the estimated success rate. To account for 10% of patients lost to follow-up, 1300 patients were required. Both cohort analyses and final analyses were planned and, the database was locked on May 2, 2023.

Two-tailed tests with a significance threshold of 5% (P<0.05) were used. Continuous variables are presented as median and interquartile ranges. Categorical variables are reported as number of observations (n) and frequencies (%). Missing values also are reported. Group

differences were tested globally using the Kruskal-Wallis and Chi-squared tests for continuous and categorical variables, respectively. Surgical outcomes and the associated *P*-values were compared for exploratory purposes only and do not confirm efficacy differences due to the lack of randomization.

Three Propensity Score (PS) analyses were carried out to compare LTME *vs.* RTME, RTME *vs.* TaTME, and LTME *vs.* TaTME. Centers with at least five patients per technique and participants with evaluable CPO were selected. To estimate the PS, a logistic model was used that included sex, BMI, topography, initial CRM, anastomosis type, ECOG performance status (<2 *vs.* ≥ 2), and neoadjuvant treatment (NAT) as covariates. Parameters were selected when they showed significant baseline differences between groups and based on clinical knowledge. Missing data for these parameters were imputed using the k-nearest neighbor's algorithm. Success rates were estimated using PS-based matching (1:1 ratio) without replacement, using the greedy nearest neighbor algorithm and a caliper distance of 0.15. Balance was assessed graphically and by ensuring that the standardized mean difference between groups was <0.1 for each covariate. Inverse probability of treatment weighting was used as supportive analysis. To assess the influence of the centers' inclusion volume, high-volume inclusion centers (HVIC) and low-volume inclusion centers (LVIC) (i.e., ≥ 15 and <15 patients included, respectively) were compared, independently of the number of surgeons involved at each center.

Statistical analyses were performed with SAS®, version 9.4 (SAS Institute, Cary, NC, USA) and PS analyses with R®, version 4.3.1 (R Development Core Team, 2023) and the VIM, MatchIt, and cobalt packages.

RESULTS

Between November 2018 and December 2022, 1115 patients were enrolled across 64 centers by 82 surgeons, and 1078 patients eventually underwent surgery: 404 LTME, 58 OTME, 458 RTME, and 158 TaTME. The reasons for exclusion are listed in Figure 1.

Study population

The median age was 65 (56-73) years and the percentage of men was higher in the RTME and TaTME groups than LTME and OTME groups (79 *vs.* 70%, *P*=0.002). The median BMI was 27 kg/m^2; 31.7% of patients were overweight (BMI 25-30) and 32.4% obese (BMI ≥ 30). The highest median BMI and poorer ECOG performance status (*P*=0.001) were observed in the OTME group (Table 1).

Patients in the RTME and TaTME groups had the lowest tumors (i.e., lowest median distance between the inferior pole of the lesion and the upper part of the levator ani muscle: 30 *vs.* 40 mm (*P*=0.006), and 59% of patients in the TaTME group had tumors in the lower third of the rectum (*P*=0.010). Patients in the RTME and TaTME groups also had more aggressive lesions with shorter CRM (1 *vs.* 3 mm for the LTME and OTME groups, *P*=0.001). The percentage of patients with N1-2 lesions was higher in the OTME group (*P*=0.008). More patients received NAT in the RTME and TaTME groups (82.5 and 84.8%, respectively, *P*<0.001). NAT led to a tumor volume decrease in 70% of patients. In the whole cohort, 10% of patients had a complete clinical response.

Assessment of HRPs' risk factors for each procedure confirmed that obesity (BMI ≥ 30) was equally represented in all groups. The TaTME group included fewer patients with narrow pelvis (56.3 *vs.* 68.9%, *P*<0.001). CRM was larger in the LTME and OTME groups

(P=0.001). Ultra-low or coloanal anastomosis was more frequent in the RTME and TaTME groups (P<0.001).

Surgical results

Intraoperative characteristics

Operative time was longest in the RTME group and shortest in the OTME group (285 *vs.* 180 min, P<0.001) (Table 2). Conversely, the estimated blood loss was lowest in the RTME group and highest in the OTME group (50 *vs.* 125 ml, P=0.015). Splenic flexure mobilization was higher in the LTME and RTME groups (87.4 and 92.3%, respectively, P<0.001). A single team performed all procedures except in the TaTME group where two teams operated in 69% of patients. The rates of coloanal anastomosis were significantly higher in the RTME (32.4%) and TaTME (37.3%) groups (P<0.001). The LTME group had the lowest rate of temporary diverting ileostomy (P<0.001). Conversion rates were similar in the LTME, RTME, and TaTME groups (6.2%, 4.2%, and 2.5%; P=0.37).

Postoperative characteristics

The 30-day postoperative period confirmed that LOS was longer after OTME compared with minimally invasive procedures (MIP) (9 *vs.* 7 days, P<0.001). Reoperation (P=0.352), bleeding (P=0.106), anastomotic leakage (P=0.082), postoperative ileus (P=0.574) and other morbidity rates were not different among groups (Table 2). The highest surgical site infection rate was observed after OTME (25.5%, P<0.001). Postoperative morbidity was lower in the MIP groups than in the OTME group (38%, P=0.038), and the CD III-IV rate was higher after OTME than MIP (28%, P=0.009).

Pathological outcomes

The percentage of patient with TME grade III was higher in the LTME (89.8%) and RTME (89.7%) groups than OTME and TaTME groups (*P*=0.001) (Table 3). The number of harvested lymph nodes was higher in the LTME (*n*=17) and RTME (*n*=16) groups (*P*<0.001). The rate of positive CRM was higher in the OTME group (3.8%) than in the MIP groups (1.8%, *P*=0.013). The median distal margin, pT and pN staging, and R0 status were not different among groups. The median curative resection rate (CRM ≥1mm) was 98% (*P*=0.777). Moreover, in the whole cohort, 15% of patients achieved a pathological complete response.

Comparison of high- and low-volume inclusion centers

There were 20 HVIC (772 patients) and 62 LVIC (306 patients) (Table 4). The most frequently used procedures was RTME in HVIC (49%, 379 patients) and LTME in LVIC (50%, 153 patients) (*P*<0.001). Twelve centers used only one technique (6 RTME, 4 LTME, 2 TaTME), ten centers used two techniques (5 LTME and RTME, 3 LTME and TaTME, 2 LTME and OTME) and one center used all three MIP.

At LVIC, operative time for LTME (210 *vs.* 240 min; *P*<0001) and OTME (168 *vs.* 208, *P*=0.010) was longer, infection rate after LTME was higher (17% *vs.* 8.9%, *P*=0.015), and postoperative ileus rate after TaTME was higher (10.2% *vs.* 2%, *P*=0.021) compared with HVIC. RTME results were similar at LVIC and HVIC.

Composite primary outcome and propensity scores

CPO was defined as a CRM ≥ 1 mm, TME grade II-III, and absence of CD grade III-IV complications within 30 days after surgery. The success rates [95% confidence interval] were 82.4% [78.2-86.2] for LTME, 64.3% [48.0-78.4] for OTME, 74.7% [70.4-78.7] for RTME, and 80.3% [73.0-86.3] for TaTME. No group achieved the expected success rate (85%).

Table 5 summarizes the results of the PS analyses. CPO rates were significantly different between LTME and RTME (80.3 *vs.* 72.8%, P=0.03) when considering the whole cohort. No other significant difference was observed when considering the whole cohort or only centers with more than five patients per procedure.

DISCUSSION

Sometimes, evidence-based medicine does not agree with the surgeons' subjective feelings. Recent RCT and a meta-analysis failed to demonstrate the superiority of a specific TME technique [13,15–17,21–25]. However, the results of the REAL [19] and ROLARR trials [16] in HRPs (men, with obesity, small tumors) suggested a potential trend towards better outcomes with RTME (OR=0.50). In the RESET trial, we compared different TME methods (combined with SSP) in HRPs. The early outcomes showed similar results for the three MIP, but patients in the LTME group had tumors with more favorable features.

TME outcomes in HRPs

Clinical trials usually include a limited number of HRPs. Today, morphological parameters and anatomic pelvic risk assessment allow the preoperative identification of HRPs. Using an MRI-based predictive score, we previously found that BMI >30 kg/m^2 (P=0.021), coloanal anastomosis (P=0.034), small intertuberous distance (P=0.041), and high mesorectal fat area (P=0.051) were associated with higher surgical complexity. [11] Yamamoto et al.[10] confirmed these results and added large tumors, short pelvic outlets, and high anastomotic leakage rate (53 *vs.* 9.6%, P<0.001). Hong et al.[26] also confirmed the association between bone pelvic measurements and surgical complexity. Albayati et al.[6] retrospectively compared LTME and RTME in obese patients and found that conversion rate was higher in the LTME group (P<0.0001), and operative time was longer in the RTME group (P<0.0001). Peacock et al.[1]

compared RTME outcomes in obese (30.2%) and non-obese patients and did not find any association between obesity and adverse short-term clinical outcomes. Ahmed et al.[7] prospectively compared LTME and RTME in HRPs. They reported that the conversion rate was lower (0 *vs.* 5%, *P*=0.043), LOS (7 *vs.* 9 days, *P*=0.001) and operative time (240 *vs.* 270 min, *P*=0.013) were shorter, and sphincter preservation rate was higher in the RTME than LTME group (86 *vs.* 74%, *P*=0.045).

The RESET patient population

In this study, we encountered two challenges: the heterogeneity of European administrative procedures for reporting RCT to local ethics committees, and the COVID-19 pandemic (March 2020 - March 2021), which disrupted clinical research, sometimes permanently. The most used techniques were LTME and RTME, followed by TaTME that was the preferred technique at the centers where it was used. Very few centers used OTME. We found significant differences in the four groups. In the LTME group, there were more women, fewer patients with tumors in the lower third of the rectum, and fewer patients who received NAT. Patients in the OTME group had more N1-2 lesions. In the RTME and TaTME groups, there were more men, more patients with tumors in the lower third of the rectum or with larger tumors, more tumors with predicted CRM < 1 mm by MRI, and more patients who underwent NAT. The rate of TME grade I was lower in the LTME group than in the RTME and TaTME groups, and the number of harvested lymph nodes was higher in the LTME than TaTME group. Conversely, resection quality and postoperative morbidity were similar. Morbidity was significantly higher in the OTME group, without differences in the resection quality, and operating time was much shorter with OTME than the other procedures. No technique reached the expected 85% success rate, and no difference was observed among the three MIP. The PS analysis only found a significant CPO difference between LTME and RTME in the

whole population, but this difference disappeared after excluding centers that included less than five patients.

The inclusion volume and used procedure were heterogeneous across centers. At HVIC (85% of patients, n=951), one (52%) or two (43%) TME techniques were used. Previous studies showed that surgeons at HVIC mainly perform one procedure, especially in HRPs[18]. The rates of anastomotic leakage, pelvic infection, and ileus obstruction were not different between HVIC and LVIC (but for infection that was higher after LTME). Operative times for LTME and OTME were longer in the LVIC group.

Recent large phase III trials

The most recent meta-analysis that compared OTME and MIP included data from 32 RCTs (6151 patients) and found that only the distal resection margin distance and LOS were improved after RTME. The authors concluded that the overall quality of evidence was low. [3] Recently, the ROLARR[16], REAL[19], COLRAR[17] RCTs compared LTME and RTME and the TALAR[21] RCT compared LTME and TaTME. Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F303 summarizes the main outcomes of these trials and the RESET results.

The ROLARR trial[16] was the only RCT to include more than 200 patients per arm before 2020. The authors concluded that RTME did not provide any advantage over LTME for surgeons with varying levels of experience.

Since 2022, the REAL[19], COLRAR[17], and TALAR[21] trials included, in total, 1274 patients who underwent LTME, 737 patients who underwent RTME, and 544 patients who underwent TaTME. The REAL trial[19] included 1240 patients in eleven Chinese hospitals where TME was performed by highly experienced surgeons (at least 50 RTME and 50 LTME before the trial). The early outcomes seem to favor RTME based on the comparison of positive CRM

(*P*=0.023), R0 resection (*P*=0.042), APR rate (*P*=0.021), conversion rate (*P*=0.021), CD grade > II (*P*=0.003), bleeding (*P*<0.001), perioperative morbidity (*P*=0.030), and LOS (*P*=0.0001) (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/SLA/F303). The COLRAR trial[17] enrolled 295 patients at three Korean hospitals, but was prematurely closed due to poor data accrual, mainly because of the cost discrepancy between LTME and RTME. They found no difference in complete TME rate (*P*=0.567) and positive CRM (*P*=0.777) between techniques. However, in the LTME group, operative time was shorter (*P*=0.003) and stoma creation rate was shorter (*P*=0.027). The TALAR trial[22] included 1115 patients at sixteen Chinese hospitals. The early results showed no difference in intraoperative complications (*P*=0.42), postoperative morbidity (*P*=0.53), mortality (*P*=1), and R0 resection (*P*<0.99) between LTME and TaTME.

Overall, the main objective was not reached in three of these five trials (ROLARR, COLRAR, and RESET), and is not available yet for the REAL and TALAR trials[16,17,19,21]. The clinical characteristics of patients in the RESET trial were worse than in the REAL, COLRAR, and TALAR trials: more men, higher BMI, more low tumors, and higher percentage of patients receiving NAT, particularly in the RTME and TaTME groups. Yet, surgical curability, positive CRM, and R0 were better in the RESET than REAL trial. Conversely, postoperative surgical criteria (conversion, anastomotic leakage, CD grade >III for RTME) were better in the REAL than RESET trials. However, the results of Chinese and Korean RCTs may not be generalizable to the Western populations due to the lower mean BMI (<24 kg/m^2) of their patients. These elements strengthen the RESET trial results.

PS are often used in non-RCT to reduce the selection bias. Panteleimonitis et al.[2] compared LTME and RTME in 222 obese patients. Patients were matched based on the American Society of Anesthesiology (ASA) score, NAT, and T stage. The operative time was longer

(260 *vs.* 215 min, *P*=0.000), whereas LOS (6 *vs.* 8 days; *P*=0.014) and 30-day readmission rate were lower (6.3 vs. 19.7%; *P*=0.033) in the RTME group. Hol et al.[27] compared MIP in 1078 patients after PS-based matching. The overall rates of primary anastomosis were 39.4, 61.9, and 61.9% for LTME, RTME and TaTME, respectively (*P*<0.001). For specialized techniques in expert centers excluding APR, the rates of primary anastomosis were 66.7, 89.8, and 84.3, respectively (*P*<0.001). Conversion rates were 3.7, 4.6, and 1.9 %, respectively (*P*=0.134). The number of incomplete specimens, CRM involvement rate, and morbidity rates were comparable.

In the RESET study, we did not find any difference between MIP using the PS analysis, despite considering all possible patients and tumor baseline parameters. Therefore, we confirmed that the surgeon's experience and expertise can overcome any operating differences, as previously shown[3,6], even in HRPs. RTME was the only technique with similar outcomes at both HVIC and LVIC and may increase the average dexterity of surgeons.

Limitations

We included patients who underwent TME with SSP, and we excluded those who underwent APR because this indication varies greatly across surgeons and countries. In the REAL trial[19], APR rates were 16.9 and 22.7%, for RTME and LTME, respectively. In the RESET trial, it is possible that patients with low tumors in LTME group underwent APR, while patients with low tumors in the RTME and TaTME groups had more frequently SSP and thus more complicated postoperative outcomes. We also used TME grading in our CPO. However, a phase II trial reported a major discordance rate of 14% among pathologists regarding this criterion.[28] The recruitment rate in the OTME arm was lower than anticipated. However, some centers that primarily use this technique declined to participate. To account for the observed differences among groups and to reduce bias in the estimation of surgical efficacy,

we performed a PS analysis. However, we might not have taken into account some confounding parameters. The comparison of HVIC *vs.* LVIC also may have introduced a bias in the results. In addition, the terms LVIC and HVIC did not necessarily reflect centers with low volume and high volume of surgical procedures. Finally, some centers did not include all consecutive patients.

CONCLUSION

The RESET trial included only HRPs, yet the early surgical outcomes were comparable to those of the recent RCTs that enrolled more favorable patients. We found that the early surgical outcomes were similar after RTME, TaTME and LTME, but patients undergoing LTME had more favorable tumor characteristics. Long-term results on oncological, functional, and sexual outcomes are expected at the 2-year follow-up.

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Authors' contributions

P.R.: conceptualization, methodology, investigation, writing— original draft, and writing—review & editing, funding acquisition and project administration. P.L.: methodology, statistical analysis, original draft, and writing—review. M.G: investigation, writing—review. E.Ö: investigation, writing—review. E.C: investigation, writing—review. A.S investigation, writing—review.

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Figure 1: Study flowchart

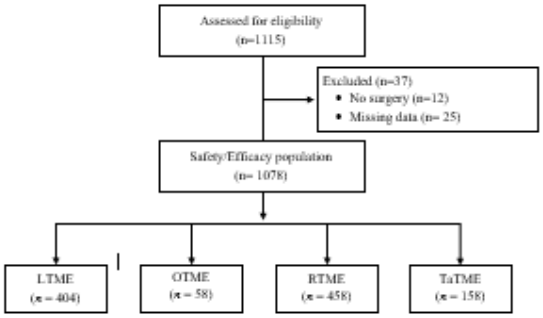

Table 1: Baseline characteristics of patients with rectal cancer according to the surgical procedure

	Surgical procedure					
	LTME *n* = 404	**OTME** *n* = 58	**RTME** *n* = 458	**TaTME** *n* = 158	**All** *n* = 1078	***P***
Patients characteristics						
Age (years)*	66 (56-73)	66 (57-76)	66 (57-73)	63 (56-71)	65 (56-73)	*0.435*
Sex ratio (M:F)	278/126	41/17	363/95	126/32	808/270	*0.002*
% Men	68.8	70.7	79.3	79.7	75.0	
Weight (kg)*	78 (67-89)	84 (70-95)	79 (69-89)	78 (68-88)	78 (68-89)	*0.226*
BMI (kg/m^2)*	27 (24-31)	29 (24-32)	27 (24-31)	26 (24-31)	27 (24-31)	*0.122*
25-29.9	136 (34.0)	19 (32.8)	140 (30.6)	45 (28.5)	340 (31.7)	
≥30	132 (33.0)	24 (41.4)	143 (31.2)	49 (31.0)	348 (32.4)	
ECOG-PS						*<0.001*
0-1	352 (87.1)	44 (75.9)	436 (95.2)	151 (95.6)	983 (91.2)	
Tumor characteristics						
T stage						*0.784*
T1	6 (1.8)	0 (0.0)	7 (1.6)	2 (1.3)	15 (1.6)	
T2	60 (17.6)	8 (20.0)	78 (18.2)	19 (12.5)	165 (17.2)	
T3	237 (69.5)	28 (70.0)	278 (65.0)	106 (69.7)	649 (67.5)	
T4	34 (10.0)	4 (10.0)	55 (12.9)	23 (15.1)	116 (12.1)	
N stage						*0.008*

N0	85 (24.9)	4 (10.0)	132 (30.8)	34 (22.4)	255 (26.5)	
N1	144 (42.2)	15 (37.5)	166 (38.8)	55 (36.2)	380 (39.5)	
N2	92 (27.0)	17 (42.5)	91 (21.3)	52 (34.2)	252 (26.2)	
Predictive CRM (mm)*	3 (1-8)	3 (0-10)	1 (0-5)	1 (0-4)	1 (0-5)	*<0.001*
Tumor size (cm)*	5 (4-6)	5 (4-6)	5 (4-6)	5 (4-6)	5 (4-6)	*0.954*
Distance IP-LA (mm)*	40 (10-60)	40 (9-70)	30 (10-53)	30 (9-50)	35 (10-60)	*0.006*
Rectal tumor location (cm)*						*0.010*
≥11 (high)	12 (3.1)	2 (3.4)	11 (2.4)	0 (0.0)	25 (2.4)	
6-10 (middle)	217 (55.2)	29 (50.0)	219 (48.7)	64 (41.0)	529 (50.0)	
≤5 (low)	164 (41.7)	27 (46.6)	220 (48.9)	92 (59.0)	503 (47.6)	
Neoadjuvant treatment	249 (61.8)	41 (70.7)	378 (82.5)	134 (84.8)	802 (74.5)	*<0.001*

Values are n (%) unless otherwise indicated; *values are median (IQR). LTME, Laparoscopy Total Mesorectal Excision; OTME, Open Total Mesorectal Excision; RTME, Robotic Total Mesorectal Excision; TaTME, Transanal Total Mesorectal Excision; BMI, Body Mass Index, ECOG-PS, Eastern Cooperative Oncology Group – Performance Status; CRM, Circumferential Resection Margin, distance IP-LA: distance between the tumor inferior pole and the upper part of the levator ani muscle evaluated by rectal examination.

Table 2: Intraoperative and postoperative characteristics

	Surgical procedure					
	LTME	**OTME**	**RTME**	**TaTME**	**All**	***P***
	n = 404	*n* = 58	*n* = 458	*n* = 158	*n* = 1078	
Intraoperative characteristics						
Operative time (min)*	220 (163-283)	180 (135-223)	285 (240-347)	256 (210-300)	255 (200-310)	*<0.001*
EBL (mL)*	70 (10-100)	125 (20-250)	50 (30-150)	85 (30-150)	60 (20-150)	*0.015*
SFM	362 (92.3)	37 (68.5)	389 (87.4)	116 (74.4)	904 (86.3)	*<0.001*
Anastomosis type						*<0.001*
Coloanal	63 (15.9)	6 (11.5)	145 (32.4)	57 (37.3)	271 (25.8)	
Colorectal	328 (82.6)	44 (84.6)	292 (65.3)	91 (59.5)	755 (72.0)	
Other	6 (1.5)	2 (3.8)	10 (2.2)	5 (3.3)	23 (2.2)	
Stoma type						*<0.001*
Colostomy	16 (4.0)	16 (27.6)	15 (3.3)	11 (7.0)	58 (5.4)	
Ileostomy	286 (71.3)	33 (56.9)	378 (82.7)	129 (81.6)	826 (76.9)	
None	99 (24.7)	9 (15.5)	64 (14.0)	18 (11.4)	190 (17.7)	
Conversion	25 (6.2)	0	19 (4.2)	4 (2.5)	48 (4.5%)	*0.137*
Postoperative characteristics						
LOS (days)*	7 (5-10)	9 (7-12)	7 (5-11)	6 (5-8)	7 (5-10)	*<0.001*
Readmission	40 (10)	5 (8.9)	63 (14)	18 (11.6)	126 (11.9)	*0.279*
Re-operation#	20 (5.0)	3 (5.5)	35 (7.7)	8 (5.1)	66 (6.2)	*0.352*
Bleeding	19 (4.7)	5 (9.3)	13 (2.9)	5 (3.3)	42 (4.0)	*0.106*
AL	34 (8.4)	9 (16.4)	60 (13.3)	16 (10.3)	119 (11.2)	*0.082*
Infection	48 (12.0)	14 (25.5)	82 (18.3)	12 (7.8)	156 (14.7)	*<0.001*
Ileus	23 (5.7)	4 (7.4)	33 (7.4)	7 (4.5)	67 (6.3)	*0.574*

Other¤	86 (21.5)	11 (20.4)	102 (22.7)	35 (22.7)	234 (22.1)	*0.961*
CD						*0.038*
0	235 (60)	19 (38)	238 (54)	95 (62)	587 (57)	
I-II	103 (27)	17 (34)	121 (27)	36 (23.7)	277 (27)	
III	47 (12)	11 (22)	74 (17)	20 (13.2)	152 (15)	
IV	6 (1.5)	2 (4)	7 (1.6)	1 (0.7)	16 (1.5)	
V	-	1 (2)	2 (0.5)	-	3 (0.3)	
III+IV	53 (13.6)	14 (28)	83 (19)	21 (14)	171 (16. 5)	*0.009*

Values are n (%) unless otherwise indicated; *values are medians (IQR). LTME, Laparoscopy Total Mesorectal Excision; OTME, Open Total Mesorectal Excision; RTME, Robotic Total Mesorectal Excision; TaTME, Transanal Total Mesorectal Excision; EBL, Estimated Blood Loss; SFM: Splenic Flexure Mobilization. #Except patients with stoma problems. ¤Urinary infection, phlebitis, pneumonia, dysuria, urinary retention and prolonged ileus. LOS, Length Of hospital Stay; AL, Anastomotic Leakage; CD, Clavien-Dindo grade.

Table 3: Pathology

	Surgical procedure					
	LTME *n* = 404	**OTME** *n* = 58	**RTME** *n* = 458	**TaTME** *n* = 158	**All** *n* = 1078	***P***
TME grade						*0.001*
1	13 (3.4)	1 (2.0)	26 (5.8)	9 (5.8)	49 (4.7)	
2	26 (6.8)	8 (16.0)	20 (4.5)	21 (13.5)	75 (7.3)	
3	344 (89.8)	41 (82.0)	400 (89.7)	125 (80.6)	910 (88.0)	
HLN*	17 (13-24)	15 (12-23)	16 (11-23)	13 (10-21)	16 (12-23)	*0.001*
pT						*0.043***
TX	2 (0.5)	0 (0.0)	2 (0.5)	0 (0.0)	4 (0.4)	
T0	62 (15.7)	2 (3.7)	68 (15.4)	24 (16.0)	156 (15.0)	
T1	47 (11.9)	5 (9.3)	31 (7.0)	19 (12.7)	102 (9.8)	
T2	109 (27.5)	16 (29.6)	139 (31.5)	53 (35.3)	317 (30.5)	
T3	170 (42.9)	29 (53.7)	195 (44.2)	54 (36.0)	448 (43.0)	
T4	6 (1.5)	2 (3.7)	6 (1.4)	0 (0.0)	14 (1.3)	
pN						*0.065***
N0	296 (73.4)	32 (58.2)	303 (67.3)	108 (69.2)	739 (69.5)	
N1	79 (19.6)	14 (25.5)	104 (23.1)	35 (22.4)	232 (21.8)	
N2	26 (6.5)	9 (16.4)	38 (8.4)	12 (7.7)	85 (8.0)	
R0	386 (97.5)	50 (96.2)	430 (95.8)	146 (94.2)	1012 (96.2)	*0.357*
Distal margin (mm)*	20 (10-30)	20 (11-30)	17 (8-30)	15 (10-30)	20 (10-30)	*0.242*
CRM (mm)*	7 (3; 15)	7 (4; 13)	7 (2; 13)	6 (3; 12)	7 (3; 14)	*0.690*
CRM ≥ 1 mm	394 (98.3)	51 (96.2)	445 (98.2)	153 (98.1)	1043 (98)	*0.777*

Values are *N* (%) unless otherwise indicated; *values are medians (IQR); **Comparison T0-T1 vs T2-T3-T4; ***Comparison N0 vs N1-N2. LTME, Laparoscopy Total Mesorectal Excision; OTME, Open Total Mesorectal Excision; RTME, Robotic Total Mesorectal

Excision; TaTME, Transanal Total Mesorectal Excision; TME, Total Mesorectal Excision; CRM, Circumferential Resection Margin; HLN, Harvested Lymph Nodes.

Table 4: Surgical results according to the number of inclusions

	HVIC[1]	LVIC[2]	*P*
Participating centers, *n*	20	62	*<0.001*
Number of surgeries*	28 (25-49)	3 (1-7)	
Surgery type			*<0.001*
LTME	32	50	
OTME	5	7	
RTME	49	26	
TaTME	14	17	
LTME			
Operative time (min)*	210 (155-269)	240 (180-300)	*<0.001*
AL	6.4	11.8	*0.058*
Infection	8.9	17	*0.015*
Ileus	4	8.5	*0.060*
OTME			
Operative time (min)*	168 (128-205)	208 (183-242)	*0.010*
AL	17	15	*0.836*
Infection	25.7	25	*0.953*
Ileus	3	16	*0.083*
RTME			
Operative time (min)*	280 (240-347)	290 (260-335)	*0.340*
AL	12.7	16.2	*0.415*
Infection	19.1	13.9	*0.294*
Ileus	7.7	5.6	*0.542*
TaTME			
Operative time (min)*	260 (211-300)	240 (210-300)	*0.815*
AL	7.6	16	*0.109*

Infection	5.7	12.2	*0.159*
Ileus	2	10	*0.021*

Values are shown as percentages unless otherwise indicated; *values are medians (IQR). HVIC, High-Volume Inclusion Centers; LVIC, Low-Volume Inclusion Centers; LTME, Laparoscopy Total Mesorectal Excision OTME, Open Total Mesorectal Excision; RTME, Robotic Total Mesorectal Excision; TaTME, Transanal Total Mesorectal Excision; AL, Anastomotic Leakage.

[1] Centers that included ≥15 patients.

[2] Centers that included <15 patients.

Table 5: Propensity scores

	LTME vs RTME		*P*	**RTME vs TaTME**		*P*	**LTME vs TaTME**		*P*
Propensity scores: whole cohort									
n	302	302		152	152		148	148	
CPO success rate	80.3	72.8	*0.03*	80.9	80.3	*0.88*	77.9	80.4	*0.60*
CRM≥1 + absence CD≥3	82.3	77.2	*0.12*	86.8	84.2	*0.51*	79.3	84.5	*0.25*
CRM≥1 +absence AL	88.7	85.1	*0.26*	87.5	88.2	*0.86*	87.8	89.2	*0.56*
CRM≥1	98.3	99	*0.47*	98.7	98	*0.65*	98	98	*0.61*
Absence CD ≥3	83.3	78.1	*0.17*	88.2	86.2	*0.61*	80.8	86.5	*0.44*
TME group II-III	96	94.3	*0.33*	93.4	94	*0.80*	95.9	93.9	*0.42*
Propensity scores: centers with at least 5 patients/procedure									
n	285	285		126	126		125	125	
CPO success rate	82.6	78.6	*0.23*	74.6	81.0	*0.23*	79.5	80.8	*0.80*
CRM≥1 + absence CD≥3	83.7	81.8	*0.54*	79.4	84.9	*0.25*	82	84.8	*0.55*
CRM≥1	98.9	98.6	*0.56*	98.4	97.6	*0.65*	99.2	97.6	*0.37*
Absence CD ≥3	84.1	82.8	*0.68*	81.0	87.3	*0.17*	82.1	87.2	*0.27*
TME group II-III	97.1	95.8	*0.36*	92.9	93.7	*0.80*	96.8	93.6	*0.24*

Values are shown as percentages. LTME, Laparoscopy Total Mesorectal Excision; RTME, Robotic Total Mesorectal Excision; TaTME, Transanal Total Mesorectal Excision; CRM, Circumferential Resection Margin; CD, Clavien-Dindo grade; AL, Anastomotic Leakage; TME, Total Mesorectal Excision, CPO: Composite Primary Outcome.