

Outcomes of completion total mesorectal excision are not compromised by prior transanal minimally invasive surgery

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Abstract

Aim Transanal minimally invasive surgery (TAMIS) is used increasingly often as an organ-preserving treatment for early rectal cancer. If final pathology reveals unfavourable histological prognostic features, completion total mesorectal excision (cTME) is recommended. This study is the first to investigate the results of cTME after TAMIS.

Method Data were retrieved from the prospective database of the Elisabeth-TweeSteden Hospital. Completion TME patients were case matched with a control group of patients undergoing primary TME (pTME). Primary and secondary outcomes were surgical outcomes and oncological outcomes, respectively.

Results From 2011 to 2017, 20 patients underwent cTME and were compared with 40 patients undergoing pTME. There were no significant differences in operating time (238 min *vs* 226 min, $P = 0.53$), blood loss (137 ml *vs* 158 ml, $P = 0.88$) or complications (45% *vs* 55%, $P = 0.07$) between both groups. There was no 90-day mortality in the cTME group. The mesorectal fascia was incomplete in three patients (15%) in the cTME group compared with no breaches in the pTME group ($P = 0.083$). There were no local recurrences in

either group. In three patients (15%), distant metastases were detected after cTME compared with one patient (2.5%) in the pTME group ($P = 0.069$). After cTME patients had a 1- and 5-year disease-free survival of 85% compared with 97.5% for the pTME group ($P = 0.062$).

Conclusion Completion TME surgery after TAMIS is not associated with increased peri- or postoperative morbidity or mortality compared with pTME surgery. After cTME surgery patients have a similar disease-free and overall survival when compared with patients undergoing pTME.

Keywords Transanal minimally invasive surgery, completion, TEMS, organ preservation

What does this paper add to the literature?

The literature reporting the oncological results of completion total mesorectal excision (TME) surgery after local excision of early rectal cancer is scarce and contradictory. This is the first study on completion TME after transanal minimally invasive surgery. The present study shows that overall and disease-specific survival of patients after complete TME surgery is not compromised.

Introduction

Rectal resection according to the principles of total mesorectal excision (TME) is still considered to be the gold standard for the treatment of rectal cancer [1]. Since its introduction in 2010 by Atallah and co-workers, transanal minimally invasive surgery (TAMIS) has been used often as an alternative to TME for local

excision of early rectal cancer [2]. Local excision is associated with good quality of life and functional outcomes, as well as a decreased morbidity, short hospital stay and cost [3–6]. Furthermore, local excision can be considered in the treatment of elderly patients with rectal cancer who are unfit (or unwilling) to undergo conventional TME surgery [7].

Unfortunately, histopathological examination after TAMIS can reveal unfavourable histological prognostic features, including tumour invasion beyond the muscularis propria (>T1), poorly differentiated tumour grading, lymphovascular invasion or incomplete resection

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[8]. Several studies have shown that this occurs in up to 24% of patients treated by local excision [3,9–11]. In these cases, completion total mesorectal excision (cTME) is recommended.

This treatment strategy can only be considered when cTME yields similar outcomes to primary TME (pTME) [8,10,12–14]. However, contradictory results in terms of perioperative complications [15] as well as high colostomy rates and high abdominoperineal excision (APR) rates are reported when completion surgery is performed after TEMS [16,17].

To the best of our knowledge, no literature exists on the outcomes of cTME surgery following previous TAMIS compared with primary TME (pTME) surgery for rectal cancer. The aim of the present study was therefore to evaluate the effects and consequences of previous TAMIS when followed by cTME, specifically focusing on surgical and oncological outcomes.

Method

All operations were performed in the ETZ (Elisabeth-TweeSteden Hospital) in Tilburg, the Netherlands, which is a large teaching hospital.

Indications for TAMIS were: early stage rectal cancer defined as well-differentiated T1 cancers, tumour size < 30 mm without lymph node, (lympho)vascular or perineural involvement on MRI. Furthermore, TAMIS was performed in patients with a radiological response after chemoradiation (yc1-2), to prove or disprove pathological complete response (ypT0). Patients were excluded if they had previously undergone conventional transanal excision (e.g. with a Lonestar retractor or Parks speculum). All patients were assessed preoperatively with digital rectal examination, flexible colonoscopy, tumour biopsy and rigid rectoscopy; the latter to determine the height and location of the lesion. Patients were also staged preoperatively with pelvic MRI to evaluate invasion (T-stage) and lymph node involvement (N-stage). All TAMIS procedures were full-thickness resections performed under general anaesthesia, as described earlier [18].

The decision to perform cTME surgery after TAMIS was based on tumour invasion beyond the muscularis propria (> T1), lymphovascular or perineural involvement, poor tumour differentiation and cases with incomplete resection margins. The decision to perform initial TAMIS and cTME was made during multidisciplinary team meetings and after extensive shared decision-making with the patient at the outpatient clinic (Fig. 1).

A minimum convalescence period of 6–8 weeks was maintained in order to facilitate safe secondary surgery.

Follow-up was carried out in accordance with Dutch national guidelines on colorectal cancer [19].

Primary end-points are surgical outcomes defined as total procedure time, intra-operative blood loss, peri- and postoperative morbidity and mortality. Secondary end-points are oncological outcomes defined as mesorectal integrity of the resected specimen, local and distant recurrence and disease-free survival. All resection specimens were sent fresh (without fixation) to pathology. Mesorectal integrity was judged by the pathologist according to the Quirke classification [20].

Statistical analysis

Every patient in the cTME group was matched with two patients who underwent pTME surgery during the same time period and at the same hospital. We case-matched patients on the basis of age, American Society of Anesthesiologists classification, gender, body mass index, distance of the tumour from the anal verge, tumour size, clinical T-stage (cT/TNM stage) and whether or not they underwent neoadjuvant chemoradiotherapy.

Descriptive statistics were expressed as median and range (minimum, maximum) for continuous variables. Differences between groups were calculated using the Mann–Whitney *U*-test for continuous variables. The Pearson chi-square test or Fisher's exact test, if appropriate, were used for categorical variables. We used Kaplan–Meier analyses to calculate the estimated survival rates. Differences in recurrence rates were analysed by using the log-rank test. Statistical significance was considered at $P < 0.05$. Statistical analyses were performed by IBM SPSS Statistics v.19 (IBM Corp, Armonk, New York, USA) and SAS v.9.4 (SAS Institute, Cary, North Carolina, USA).

Results

From October 2011 to October 2017, 130 patients underwent a TAMIS procedure. Of these patients, 20 (15.4%) [female:male 30%:70%; median age 70 (range 46–84) years] patients underwent cTME surgery after previous TAMIS. Detailed patient characteristics are summarized in Table 1.

During the primary TAMIS procedure, the peritoneal cavity was entered inadvertently in three patients (15%), in two of these endoluminal closure was possible and in one case the defect was closed laparoscopically due to an unstable pneumorectum. Four patients (20%) encountered postoperative complications within 90 days after TAMIS: in one case a rectal stricture which could be dilated endoscopically formed at the location of the TAMIS resection, two patients developed fever for which they were treated with oral antibiotics and one

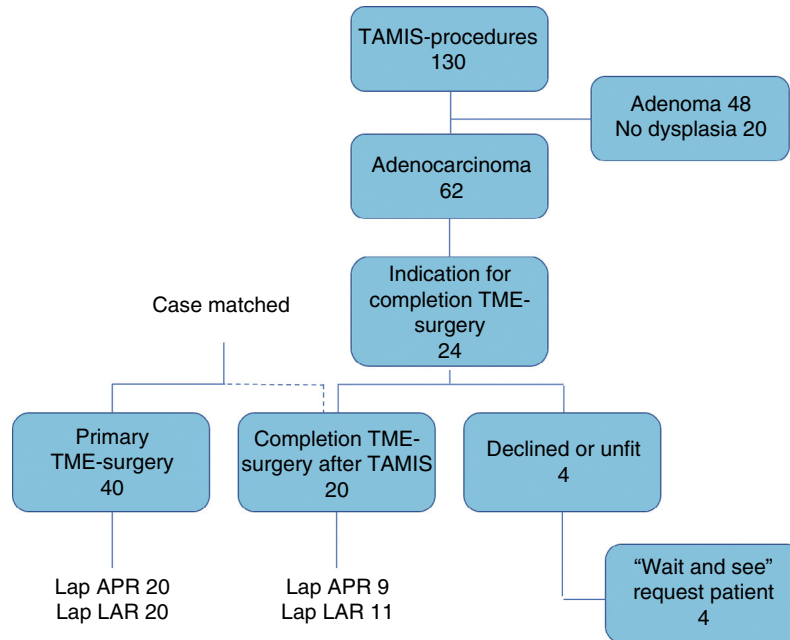


Figure 1 Study design (TAMIS, transanal minimally invasive surgery; TME, total mesorectal excision).

Table 1 Patient characteristics.

	cTME (n = 20)	pTME (n = 40)	P-value
Age (years), median ± SD [range]	70 ± 9.9 [46–84]	73 ± 8.3 [54–87]	0.11
Gender, n (%)	F = 6 (30), M = 14 (70)	F = 16 (40), M = 24 (60)	0.457
ASA grade, n (%)			
I	6 (30)	11 (27.5)	0.327
II	7 (35)	26 (65)	
III	6 (30)	2 (5)	
IV	1 (5)	1 (2.5)	
BMI (kg/m ²), median ± SD [range]	25.3 ± 3.5 [21.3–33.2]	25.8 ± 3.1 [22.0–32.8]	0.249
Distance from anal verge (mm), median ± SD [range]	85.0 ± 37.3 [20–140]	80.0 ± 35.7 [20–110]	0.058
< 50 mm	6 (30)	17 (42.5)	
60–100 mm	6 (30)	17 (42.5)	
> 110 mm	8 (40)	6 (15.0)	
Tumour size (mm ²), median ± SD [range]	39.0 ± 12.6 [20–65]	33.0 ± 12.4 [10–55]	0.062
T-stage			
Scar, n (%)	0 (0)	0 (0)	0.312
T1, n (%)	1 (5)	3 (7.5)	
T2, n (%)	17 (85)	32 (80)	
T3, n (%)	2 (10)	5 (12.5)	
Neoadjuvant radiation therapy, n(%)	4 (20)	15 (37.5)	0.152
Follow-up (years), median [range]	2.5 [1.1–6.3]	3.22 [1.6–7.6]	0.057

ASA, American Society of Anesthesiologists; BMI, body mass index; cTME, completion TME; pTME, primary TME; TAMIS, transanal minimally invasive surgery; TME total mesorectal excision.

patient developed urinary retention for which a urethral catheter was inserted.

The median time to cTME was 8 (range 6–16) weeks. In the present cohort, one completion TME procedure was performed after 11 weeks and one after

16 weeks. In both cases, patients needed more time to decide whether or not they wanted to undergo the cTME procedure.

Procedural features are summarized in Table 2. The control group consisted of 40 patients [female:male

16:24; median age 73 (range 54–87) years] who underwent pTME surgery for rectal cancer within the same time frame. There were no statistically significant differences at baseline between the groups.

All patients in both groups underwent laparoscopic TME surgery. The decision to perform an APR in nine patients (45%) was based on distal tumour location diagnosed on preoperative work-up. No statistically significant differences were found concerning mean operation time and intra-operative blood loss. In the cTME group two patients (10%) endured an intra-operative complication, in the pTME group such complications occurred in three patients (7.5%) ($P = 0.069$). In both groups, one conversion to conventional open anterior resection was necessary. In the cTME this was a reactive conversion due to a retroperitoneal haematoma (puncture of the abdominal aorta) that occurred after open insertion of Hasson trocar. The conversion to open surgery in the pTME group was an early strategic conversion due to obesity of the patient.

Postoperative outcomes are summarized in Table 3. Complications occurred in 9 (45%) of the cTME cases and 22 (55%) of the pTME cases ($P = 0.473$). No statistically significant differences could be discerned for wound infection, anastomotic dehiscence, pelvic abscess or sepsis between the groups. There was no difference in the severity of complications according to the Clavien–Dindo severity index. A higher incidence of readmissions was noted in the cTME group [6 (30%) *vs* 4 (10%), $P = 0.032$]. Surgical site infections and perineal wound dehiscence were the main reasons for readmittance in both groups. We found a 2.5% mortality rate (one patient) within 90 days after pTME surgery.

This patient developed severe sepsis on the basis of bowel perforation. Reoperation was performed with resection of the perforated bowel segment and extensive rinsing of the abdominal cavity with saline solution. The patient was admitted to the ICU but died of irreversible multiple organ failure at the third postoperative day. No mortality was observed in the completion group during the study period ($P = 0.317$). Furthermore, there was no statistically significant difference in hospital stay. After pTME patients stayed for a median of 6 days while after cTME patients stayed for a median of 5 days ($P = 0.988$).

Mesorectal integrity was judged by the pathologist according to the Quirke classification. Breach of the mesorectal fascia was found in three (15%) of the cTME cases. All defects in the mesorectal fascia were found at the previous TAMIS site; these resection specimens were classified as Quirke 2 (moderate) and 100% mesorectal integrity (Quirke 1) was found in the pTME group ($P = 0.083$). No residual tumour was found in four patients (20%) in the cTME group. It is noteworthy that no residual tumour was found in all cases where the mesorectal fascia was breached. None of the patients with an inferior resection specimen developed local or distant metastasis.

Median follow-up was 36 (13–91.2) months. No local recurrences were observed in either group. Three patients in the cTME group and one patient in the pTME group (15% *vs* 2.5%, $P = 0.069$) developed distant metastases. In the cTME group, this included one patient (ypT2N1) with lung and liver metastases, discovered after 6 months' follow-up. Additional resection of both metastases was performed successfully. Two

Table 2 Procedural results.

	cTME (<i>n</i> = 20)	pTME (<i>n</i> = 40)	<i>P</i> -value
Type of procedure, <i>n</i> (%)			
APR	9 (45)	20 (50)	0.720
LAR	10 (50)	15 (37.5)	
LAR-i	1 (5)	5 (12.5)	
Interval between TAMIS and TME (weeks), mean [range]	8.0 [6–16]	NA	
Operative time (min), mean ± SD [range]	238 ± 69.6 [143–369]	226 ± 67.0 [105–377]	0.531
Intra-operative blood loss (ml), mean ± SD [range]	137 ± 248.4 [0–1000]	158.33 ± 259.0 [0–1000]	0.883
Intra-operative complications, <i>n</i> (%)	2 (10)	3 (7.5)	0.069
Bleeding	1	1	
Iatrogenic bowel perforation	2	2	
Conversion to open surgery, <i>n</i> (%)	1 (5)	1 (2.5)	1
Obesity	0	1	
Bleeding	1	0	

APR, abdominoperineal excision; cTME, completion TME; LAR, low anterior resection; LAR-i, low anterior resection with protective ileostomy; pTME, primary TME; NA, not applicable; TAMIS, transanal minimally invasive surgery; TME, total mesorectal excision.

Table 3 Postoperative outcomes.

	cTME (<i>n</i> = 20)	pTME (<i>n</i> = 40)	<i>P</i> -value
TAMIS complication*	6 (30)	NA	
Morbidity [†]	9 (45)	22 (55.0)	0.473
Arrhythmia	3 (15)	0 (0)	0.011
Urinary retention	4 (20)	1 (2.5)	0.079
Perineal wound dehiscence	4 (20)	3 (7.5)	0.746
Superficial wound infection	3 (15)	2 (5)	0.193
Ileus	1 (5)	6 (15)	0.370
Bowel ischaemia	0 (0)	2 (5)	0.317
Sepsis	0 (0)	2 (5)	0.317
Pneumonia	0 (0)	4 (10)	0.148
Anastomotic dehiscence	3 (15)	4 (10)	0.291
Pelvic abscess	3 (15)	6 (15)	1
High-output ileostomy	1 (5)	3 (7.5)	0.216
Haemorrhage	1 (5)	1 (5)	0.484
Bowel evisceration	0 (0)	1 (5)	0.312
Clavien–Dindo grade			
I + II	8 (40)	14 (35)	0.646
IIIa	1 (5)	2 (5)	1
≥ IIIb	4 (20)	12 (30)	0.192
30-day mortality	0 (0)	1 (2.5)	0.317
Hospital stay (days), mean [range]	5.0 [3–21]	6.0 [2–33]	0.998
Readmission	6 (30)	4 (10)	0.032

Values are number (%) unless otherwise stated.

cTME, completion TME; NA, not applicable; pTME, primary TME; TAMIS, transanal minimally invasive surgery; TME, total mesorectal excision.

*Initial TAMIS procedure.

[†]Number of procedures (%) with postoperative complications.

Bold values are statistically significant.

patients (ypT2N1 and yT3N0) developed liver metastases after 3 and 4 months, respectively, for which they underwent successful additional resection as well.

In the pTME group, one patient (ypT3N2) developed liver metastases at 7 months of follow-up. Additional liver resection was performed successfully. All patients with metastases were alive at the time of preparation of this manuscript.

Patients after cTME surgery had 1 and 5-year disease-free survival of 85%. Patients in the pTME group had 1 and 5-year disease free survival of 97.5% ($P = 0.062$, log rank). The overall survival for patients undergoing cTME was 100% at 1 and 5 years. Overall survival in the pTME group was 100% at 1 year and 86% at 5 years.

Oncological outcomes are summarized in Table 4 and Fig. 2.

Discussion

Local excision is considered by many surgeons to be the gold standard for the treatment of selected and early stage low-risk neoplasms in the lower two-thirds of the

rectum [5,21]. Techniques such as TAMIS are associated with low morbidity and are considered as curative treatment in case of pT1 early rectal cancers without unfavourable characteristics [10,22]. However, these treatment modalities require careful patient selection and detailed preoperative radiological staging to meet the criteria for treatment with TAMIS. Imaging tools like endorectal ultrasound and MRI are indispensable in preoperative staging and analysing tumour invasion of the rectal wall [23,24], nonetheless there is often a discrepancy between preoperative T-stage and the definitive T-stage after pathological examination [25,26]. This discrepancy results in up to 23% of the patients requiring a cTME procedure [27]. In our analysis, 12.3% of patients underwent cTME surgery after primary TAMIS.

With the increasing incidence of early stage rectal cancer and a trend towards organ-preserving surgery, it is likely that the total amount of cTME surgery is going to increase drastically. Furthermore, the benefits of adjuvant chemoradiotherapy or intensive watch and wait protocols after local excision are under investigation [28].

Table 4 Oncological outcomes.

	cTME (<i>n</i> = 20)	pTME (<i>n</i> = 40)	<i>P</i> -value
Definitive tumour stage*			0.359
Complete regression	4 (20)	0 (0)	
I	9 (45)	32 (80)	
IIa	4 (20)	2 (5)	
IIb	0 (0)	1 (2.5)	
IIIa	3 (15)	5 (12.5)	
Mesorectal integrity	17 (85)	40 (100)	0.083
Length of specimen (cm), mean ± SD [range]	37.9 ± 53 [9–225]	26.7 ± 35.1 [7–195]	0.383
Harvested lymph nodes, <i>n</i> ± SD [range]	15 ± 6 [2–30]	18 ± 6.8 [5–33]	0.060
Local recurrence	0 (0)	0 (0)	NA
Metastasis	3 (15)	1 (2.5)	0.069

Values are number (%) unless otherwise stated.

cTME, completion TME; pTME, primary TME; TAMIS, transanal minimally invasive surgery; TME, total mesorectal excision.

*American Joint Committee on Cancer staging system.

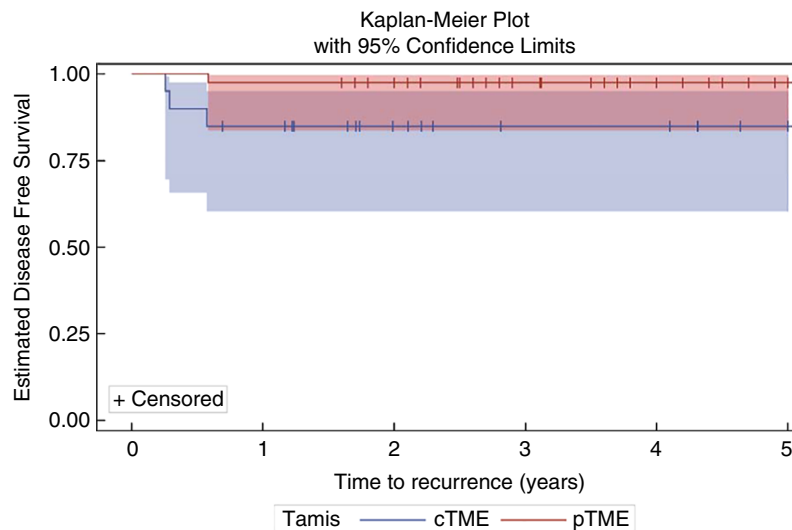


Figure 2 Disease-free survival. Kaplan–Meier curves for 5-year estimated disease-free survival with strata comparison completion TME (cTME) versus primary TME (pTME) ($P = 0.0618$, log-rank test). Survival probability at 5 years was 85% (cTME) and 97.5% (pTME).

Completion TME surgery after primary local excision is considered by many surgeons to be a challenging procedure, with high incidence of APR [13,14,16,17,29–31]. Dissection is considered to be more difficult due to fibrotic changes to the bowel wall after primary full thickness resection which tend to obscure the normal pelvic dissection planes. These anatomical changes could potentially lead to difficult surgery (e.g. increased blood loss, increased morbidity) but could also affect oncological results due to increased risk of violating surgical dissection planes and making radical surgery more difficult. Interestingly, the present data do not support this perception of difficulty. Operating time is not significantly

longer, no increase in perioperative complications is observed and no difference in blood loss is encountered. We can only surmise that the complexity of cTME is mainly subjective.

Few studies have evaluated the surgical and oncological outcomes of cTME surgery after previous TEM. Morino *et al.* [17] retrospectively analysed patients who underwent laparoscopic cTME after TEM; they found a significantly longer procedural time and a significantly increased APR rate in the cTME group (intra-operative difficulties due to severe inflammation were the reason to convert to APR). In contrast, Levic *et al.* [31] showed a shorter total operation time for the cTME

group. Morbidity rates were 52% for both groups. APR was required in 44% of patients in both groups. An intra-operative perforation rate of 20% was reported, all at the previous TEM site. Even though intra-operative rectal wall perforation is one of the most important risk factors for local and distant recurrence in radical rectal surgery [32,33] no local recurrences and only one distant metastasis were reported during a median of 25 months of follow-up. The study by Hompes *et al.* [29] shows similar surgical outcomes to Levic *et al.* [31]. They suggest that mesorectal integrity during cTME is the most important predictor for disease-free survival. The largest study by van Gijn *et al.* [16] retrospectively compared 59 patients undergoing cTME after TEM with 881 pTME procedures. They report a colostomy rate of 50.8% in the cTME group versus 45.9% in the pTME group. In the cTME group 10.2% of patients developed local recurrence compared with 5.2% in the pTME group. Even though the present study identified the same difference in mesorectal integrity, this difference did not reach statistical significance. Moreover, it did not translate to an increased incidence of local recurrences. It has to be noted, however, that follow-up of the present series is relatively short.

In our cTME surgery group we did not find a higher APR rate (45% in the cTME group versus 50% in the pTME group, $P = 0.720$). None of the APRs in the cTME group were performed due to mesorectal fibrosis or perforation of the resection specimen during dissection. All APRs in the cTME group were planned preoperatively based on the height of the tumour from the anal verge. On the other hand, in cases where cTME surgery is warranted, we postulate that a certain percentage of the APRs are performed in order to ascertain complete and oncologically safe resection, since no surgeon is willing to run the risk of needing to perform a third operation. Moreover, it is possible that the decision to proceed with initial local excision by whatever means can be influenced by the eventual ablative procedure. In patients in whom APR would be necessary, both surgeon and patient will be more likely to choose primary local resection in order to prevent a definitive stoma.

The 1- and 5-year disease-free survival of 85% after completion surgery in this patient population is comparable to the disease-free survival in patients after pTME surgery when compared with the literature [29]. There were no statistically significant differences in the overall survival between both groups. The disease-free survival in this study is determined solely by distant metastatic disease. The increased incidence of distant metastases in the cTME group is a matter for concern. This phenomenon was also encountered by

Levic *et al.* [31] and Doornebosch *et al.* [34] in their cTME groups. They postulated that completion therapy should therefore be upgraded by adding neoadjuvant radiotherapy and/or adjuvant chemotherapy in an effort to improve oncological outcomes. Currently there are no data on neoadjuvant radiotherapy and/or adjuvant chemotherapy in relation to cTME, so the potential benefit on disease-free survival remains hypothetical [28].

As mentioned before, pathological analysis in the present study revealed three cTME cases that showed violation of the mesorectal fascia versus no mesorectal fascia breaches in the pTME group. Similar observations were done made Hompes *et al.* [29]. Whether an inferior resection specimen will result in increased metastatic disease remains unanswered based on our analysis, since we found no recurrent disease in those patients with an inferior resection specimen. Recently two studies have suggested using the transanal TME (TaTME) technique for cTME surgery after local excision [30,35]. Both studies show significantly better-quality resection specimen compared with standard 'top-down' cTME. Unfortunately, both studies lack long-term follow-up and oncological results. Long-term follow-up needs to be awaited in order to prove that mesorectal integrity plays a role in disease-free survival after cTME.

To our knowledge, this is the only published study on patients undergoing cTME surgery after TAMIS. The foremost limitation of this study is the small study population. This could result in statistical bias of the surgical and oncological results. The limitation of the relatively small group is that statistics are relative; even though no statistically significant differences can be shown it is not fully clear whether there are no differences or whether the relatively small groups contribute to apparent equality. Due to the absence of local recurrences in this study, no multivariate analysis for prognostic factors could be performed. Furthermore, the shorter follow-up time for the cTME group and the retrospective nature of the collection of the control group in this study are considered to be limitations.

Conclusion

Laparoscopic cTME surgery after TAMIS is feasible. In the present study, cTME surgery after TAMIS is not associated with increased morbidity and mortality when compared with pTME surgery, neither are local recurrence rates influenced. However, the suggestion that patients have an increased risk of developing distant metastasis necessitates vigilance and further investigation.

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Conflicts of interest

The authors report no conflicts of interest.

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