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ORIGINAL ARTICLE

The outcome of rectal cancer after early salvage TME following TEM compared with primary TME: a case-matched study

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Abstract
Background Transanal endoscopic microsurgery (TEM) allows locally complete resection of early rectal cancer as an alternative to conventional radical surgery. In case of unfavourable histology after TEM, or positive resection margins, salvage surgery can be performed. However, it is unclear if the results are equivalent to primary treatment with total mesorectal excision (TME). The aim of this retrospective study was to determine whether there is a difference in outcome between patients who underwent early salvage resection with TME after TEM, and those who underwent primary TME for rectal cancer.
Methods From 1997 to 2011, early salvage surgery with TME after TEM was performed in 25 patients in our institution. These patients were compared with 25 patients who underwent primary TME, matched according to gender, age (±2 years), cancer stage and operative procedure. Data were obtained from the patients' charts and reviewed retrospectively. No patients received preoperative chemotherapy. Perioperative data and oncological outcome were analysed. The Mann–Whitney U-test and Fisher's exact test were used to compare the results between the two groups.
Results There was no significant difference between the two groups in median operating time ($P = 0.39$), median blood loss ($P = 0.19$) or intraoperative complications ($P = 1.00$). The 30-day mortality was 8 % ($n = 2$) among patients who underwent salvage TME after TEM, and no patients died in the primary TME group ($P = 0.49$). There was no significant difference between two groups of patients in the median number of harvested lymph nodes ($P = 0.34$), median circumferential resection margin (CRM) ($P = 0.99$) or the completeness of the mesorectal fascia plane. No local recurrences occurred among the patients with salvage TME, and there were 2 patients (8 %) with local recurrences among the patients with primary TME ($P = 0.49$). Distant metastasis occurred in one patient (4 %) after salvage TME and in 3 patients (12 %) with primary TME ($P = 0.61$). The median follow-up time was 25 months (3–126) for patients who underwent salvage TME and 19 months (3–73) for patients after primary TME.
Conclusions No difference was found in outcome between patients with rectal cancer undergoing salvage TME after TEM, those undergoing primary TME. In selected patients, TEM can therefore be chosen as a primary treatment, since failure of treatment and subsequent conventional resection appears not to compromise the outcome.

Keywords Rectal cancer · Transanal endoscopic microsurgery · Colorectal surgery · Operative outcomes · Local excision

Introduction

Total mesorectal excision (TME) is the gold standard in treatment for rectal cancer [1]. It is, however, associated with considerable morbidity and mortality [2, 3]. Transanal endoscopic microsurgery (TEM) was primarily developed as a procedure for local excision of rectal adenomas. Due

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to procedure-related morbidity and mortality associated with TME, TEM has been increasingly used for treatment of patients with early rectal cancer, especially in elderly and/or frail patients, although this indication is more controversial.

In patients with early rectal cancer (T1/T2-N0), TEM is an alternative treatment to TME. TEM is associated with low morbidity and mortality, and a shorter hospital stay [2–4], which seems appealing, considering that a majority of the patients treated for rectal cancer are elderly and often have significant medical comorbidities. However, the major problem with TEM in treatment for rectal cancer is non-radical resection in up to 24 % [5] and local recurrence in up to 29 % for T2 cancers [6].

Salvage surgery in the form of TME (sTME) is considered appropriate after failed local excision with TEM, when the patient presents with unfavourable histology and/or non-radical resection, and is required in 4–23 % of patients [7, 8]. Some studies indicate that the results after salvage surgery for rectal cancer are not equivalent to those of initial conventional radical surgery, and other studies have not shown differences in outcome if early salvage surgery is performed [6, 9–13]. There is no consensus regarding the definition of early/immediate salvage surgery following TEM. Early salvage surgery can typically be performed within 3 months [7], but there are also reports describing salvage surgery within 4 weeks following TEM [14]. It remains unclear whether the results of early sTME following TEM are similar to those of conventional primary radical surgery (pTME) as there are no studies comparing sTME following TEM with conventional primary radical surgery (pTME).

The aim of this case-matched study is to determine whether there is a difference in outcome between patients with early rectal cancer who undergo early radical resection with sTME after TEM and those who undergo pTME.

Materials and methods

From January 1997 to December 2011, 386 TEM procedures were performed at our institution. Of these, 87 (23 %) were performed in 80 patients with rectal cancer, including 27 patients (34 %) undergoing sTME after a primary TEM procedure. Two patients were excluded from this study: one due to preoperative chemotherapy and one with familial adenomatous polyposis (FAP) undergoing total colectomy, leaving 25 patients who underwent early sTME after TEM. These patients were compared with 25 patients with a primary TME and matched according to gender, age (±2 years), operative procedure and cancer stage according to The American Joint Committee on Cancer (AJCC) staging system. None of the patients included in this study underwent preoperative chemo- or radiation therapy. The data obtained from the patient charts included patient characteristics, histopathological features, perioperative data, adjuvant radio- or chemotherapy and 30-day mortality. Preoperative assessment and tumour staging included digital rectal examination, proctoscopy, endorectal ultrasound, abdominal ultrasound and thoraco-abdominal computerized tomography (CT) scans. Pelvic magnetic resonance imaging was carried out after 2002.

Three of the 27 patients treated with TEM had partial thickness excision. Adenoma was suspected in all 3 patients prior to the TEM procedure. These 3 patients underwent sTME due to positive resection margins. The remaining 24 patients all had full-thickness excision.

Indications for salvage TME are shown in Table 1.

In 23/25 patients (92 %), the indication for sTME was non-radical or unclear resection margins and/or lymphatic or venous invasion. Seventeen patients had either positive or unclear resection margins. Two patients had lymph node involvement, which in one case was micrometastasis. Venous invasion was found in 4 patients and 3 of these patients also had unclear resection margins.

One of the remaining 2 patients underwent TME, because of a T2 tumour, and one patient underwent abdominoperineal resection (APR) because the tumour was close to the anal verge as decided at the Multidisciplinary Team (MDT) conference. None of the sTMEs were

Table 1 Staging and indication for TME in the salvage TME group

Pre-TEM evaluation (*n*)	Adenocarcinoma	11	Adenoma	14
TEM staging (*n*)	Stage I	7	Stage I	10
	Stage II	3	Stage II	2
	Uncertain	1	Uncertain	2
Indication for sTME (*n*)	Positive/unclear margins	6	Positive/unclear margins	11
	Venous invasion	2	Venous invasion	2
	Lymphatic invasion	2	Lymphatic invasion	0
	Other[a]	1	Other[b]	1
Final histological evaluation (*n*)	Stage I	1	Stage I	3
	Stage II	2	Stage II	1
	Stage IIIa	0	Stage IIIa	2
	Stage IIIb	1	Stage IIIb	0
	Stage IIIc	2	Stage IIIc	1
	No residual tumour	5	No residual tumour	7

[a] T2 tumour

[b] Close to anal verge

TME total mesorectal excision; *TEM* transanal endoscopic microsurgery

sTME salvage TME; *pTME* primary TME

performed due to recurrence. The pathologist could not estimate the ingrowth of the tumour in 3/25 patients, and thus the tumour staging in these patients was uncertain, but all 3 had unclear resection margins, and it was therefore decided to perform early salvage surgery.

All patients were followed up according to the guidelines of Danish Colorectal Cancer Group (DCCG) with digital rectal examination, proctosigmoidoscopy, colonoscopy and thoracoabdominal CT scans [15]. Colonoscopy was carried out 3 months after the operation (clean colon) and then at 3 and 5 years postoperatively. Thoracoabdominal CT scan was performed at 3 and 5 years postoperatively.

Local recurrence was defined as histopathologically confirmed recurrence of cancer in the rectum, at or near the previous TEM site. Distant metastasis was defined as recurrent disease outside of the pelvis.

Statistical analysis

Data are expressed as median and percentages.

Statistical differences were analysed by Fisher's exact test when the variables were categorical and the Mann–Whitney U-test when data was continuous. A P value < 0.05 was considered statistically significant. All calculations were made using the statistical package IBM® SPSS® Statistics version 20.0 for Windows.

Results

The patient and tumour characteristics for the two groups are shown in Table 2.

According to DCCG guidelines, there was no indication for preoperative chemo- or radiotherapy in any of the 25 patients who underwent sTME after TEM.

In these 25 patients, the median time from TEM to sTME was 37 days (range 14–90 days) after exclusion of 3 patients with an interval >90 days. Two patients chose to postpone salvage surgery for personal reasons, and the reason for the prolonged interval was unknown in the third case. With these patients included, the median time from TEM to sTME was 39 days (range 14–183 days).

Procedural details and perioperative data are summarized in Table 3.

Of the 25 patients who were operated on using sTME after TEM, 6 patients (24 %) underwent laparoscopic surgery and 2 patients from the pTME group were operated laparoscopically ($P = 0.25$). In the pTME group, one laparoscopic operation was converted to an open Hartmann's procedure due to perforation of the colon and limited exposure of the operative field in the pelvis. There was no significant difference between the two groups of patients regarding operating time ($P = 0.39$) and estimated blood loss ($P = 0.19$).

Table 2 Patient and tumour characteristics

	sTME	pTME	*P* values
Number of patients	25	25	
Median age, years (range)	73 (48–84)	71 (48–85)	0.98[a]
Gender (M/F)	14/11	15/10	1[b]
Median BMI kg/m^2 (range)	25,2 (18,4–33,4)	25.9 (17.4–32.1)	0.75[a]
Median ASA score	2 (1–3)	2 (1–3)	0.64[b]
ASA 1 (*n*) (%)	6 (24)	8 (32)	
ASA 2 (*n*) (%)	13 (52)	14 (56)	
ASA 3 (*n*) (%)	6 (24)	3 (12)	
Median tumour distance from anal verge cm (range)	9 (1–14)	6 (1–15)	0.31[a]
≤5 cm (*n*) (%)	12 (48)	12 (48)	
6–10 cm (*n*) (%)	5 (20)	6 (24)	
≥11 cm (*n*) (%)	8 (32)	7 (28)	

sTME salvage TME, *pTME* primary TME, *BMI* body mass index (kg/m^2), *ASA* American Society of Anesthesiologists score

[a] Mann–Whitney test

[b] Fisher's exact test

The difference in the incidence of intraoperative complications between the two groups of patients was similar.

Five patients (20 %) had intraoperative complications during sTME, and they were perforation of the remaining malignant lesion ($n = 2$) and perforation into the peritoneal cavity at the site of previous TEM resection ($n = 3$). The surgical technique used for the patients with perforation into the peritoneal cavity was APR in 2 patients and low anterior resection (LAR) in one patient. All three were open procedures. In the 2 patients with perforation of the remaining malignant lesion, there was significant fibrosis of the area around the remaining tumoural tissue and perirectal tissue. The surgical technique used in these 2 patients was APR: one open and one laparoscopic procedures.

Five patients (20 %) in the pTME group had intraoperative complications: These consisted of iatrogenic perforation of the bowel wall ($n = 2$) tumour perforation ($n = 1$), perforation of anal canal during the perineal dissection stage in APR ($n = 1$) and an intraoperative lesion of the bladder and ureter ($n = 1$).

There was no difference in the number of postoperative complications in the two groups (Table 3). The late complications were small bowel obstruction ($n = 1$), parastomal hernia ($n = 2$) and stomal prolapse ($n = 1$) in the sTME group, and parastomal hernia ($n = 2$) and incisional hernia ($n = 1$) in the pTME group.

Two patients in sTME group died within 30 days after surgery (Table 3). One was a 73-year-old woman who developed multi-organ failure following anastomotic

Table 3 Procedural details and perioperative data

	sTME	pTME	P values
Procedure (*n*) (%)			1[b]
LAR-i	4 (16)	4 (16)	
LAR	7 (28)	7 (28)	
APR	11 (44)	11 (44)	
HO	3 (12)	3 (12)	
Median OR time min (range)	165 (101–341)	193 (113–361)	0.39[a]
Median estimated blood loss mL (range)	225 (0–1275)	410 (0–2800)	0.19[a]
Median length of hospital stay days (range)	10 (4–22)	10 (4–33)	0.61[a]
Intraoperative complications (*n*) (%)	5 (20)	5 (20)	1[b]
Morbidity (*n*)[a] (%)	13 (52)	13 (52)	1[b]
Perineal wound dehiscence	3	3	
Stoma necrosis	1	2	
Anastomotic leakage	1	1	
Ileus	1	1	
Faecal incontinence	0	1	
Small bowel fistula	0	1	
Superficial wound infection	3	2	
Urinary tract infection	3	0	
Sepsis	1	0	
Pneumonia	0	1	
Pelvic abscess	0	1	
Urinary retention	1	1	
Arrhythmia	1	0	
Late complications	4	3	
TOTAL	19	17	
30-day mortality (*n*) (%)	2 (8)	0 (0)	0.49[b]

sTME salvage TME, *pTME* primary TME, *LAR-i* low anterior resection with protective ileostomy, *LAR* low anterior resection, *APR* abdominoperineal resection, *HO* Hartmann's operation, *TC* total colectomy, *OR time* total procedure time, *Morbidity* number of patients with one or more complications

[a] Mann–Whitney test

[b] Fisher's exact test

leakage after TME, and the second was an 83-year-old woman who was reoperated on for small bowel obstruction and developed progressive cardiovascular failure.

The oncological results are shown in Table 4. Unfortunately, the completeness of the mesorectal fascia (MRF) was not described in the histological report of 6 patients (24 %) with sTME and in 4 patients (16 %) with pTME. More patients with pTME had a complete or nearly complete mesorectal fascia than those with sTME (16 vs. 11), but the difference was not statistically significant ($P = 0.31$). Defects of mesorectal fascia in the sTME group were probably related to previous TEM procedure as expected. TEM causes increasing fibrosis, inflammatory reaction in the perirectal tissue or tearing of the rectal wall down to the mucosa during the radical procedure. No residual tumour was found in 12 patients (48 %) following TEM, but 2 of these patients had metastatic lymph nodes.

One patient with sTME (4 %) had a positive circumferential resection margin (CRM) with no lymph node involvement. Therefore, the cancer was staged as IIa adenocarcinoma. This patient had a prolonged time from TEM to TME (183 days), due to initial refusal of treatment, and a perforation of the remaining malignant lesion occurred during her salvage APR. She also refused further treatment or follow-up. There was also only one patient with a positive CRM (0.5 mm) in the pTME group.

There was no significant difference in adjuvant chemotherapy, local recurrence or number of distant metastases. During the follow-up period, there were no local recurrences among the patients treated with sTME, whereas 2 patients in the pTME group developed local recurrence following surgery at 13 and 31 months, respectively. This difference was not statistically significant ($P = 0.49$). Distant metastases were observed in only one patient with sTME, who had a stage IIIa adenocarcinoma and developed liver metastases 4 months after surgery. Three patients (12 %) who underwent pTME developed distant metastases in the follow-up period; in one patient (stage IIIa), a liver metastasis was discovered a month after surgery, one (stage IIa) developed both lung- and liver metastases 13 months after surgery, and one (stage IIIa) developed local recurrence and synchronous lung metastases 31 months postoperatively. All 3 patients were treated with chemotherapy. Beside these 3 patients in the pTME group, one patient was treated with adjuvant chemotherapy due to lymph node involvement and another

Table 4 Oncological outcome

	sTME	pTME	P values
Median harvested lymph nodes (*n*) (range)	12 (3–25)	10 (3–22)	0.34[a]
MRF (*n*)			0.37[b]
C	9 (36)	15 (60)	
NC	2 (8)	1 (4)	
IC	8 (32)	5 (10)	
Median CRM mm (range)	10 (0–20)	6 (0.5–25)	0.99[a]
Median DRM mm	27,5 (0–110)	25 (0–95)	0.48[a]
Staging * (*n*) (%)			0.12[b]
Stage I	4 (16)	13 (52)	
Stage II	3 (12)	7 (28)	
Stage IIIa	2 (8)	2 (8)	
Stage IIIb	1 (4)	3 (12)	
Stage IIIc	3 (12)	0 (0)	
Postoperative chemo- or radiation therapy (*n*) (%)	4 (16)	5 (20)	0.99[b]
Local recurrence (*n*) (%)	0 (0)	2 (8)	0.49[b]
Distant metastasis (*n*) (%)	1 (4)	3 (12)	0.61[b]
Median follow-up months (range)	25 (3–126)	19 (3–73)	0.26[a]

* American Joint Committee on Cancer staging system

MRF mesorectal fascia, *C* complete, *NC* nearly complete, *IC* incomplete, *CRM* circumferential resection margin, *DRM* distal resection margin, *TME* total mesorectal excision, *sTME* salvage TME, *TME* primary TME

[a] Mann–Whitney test

[b] Fisher's exact test

one who developed local recurrence 13 months postoperatively received chemoradiation therapy. Four patients (16 %) with sTME received adjuvant chemotherapy due to lymph node involvement ($n = 2$), venous invasion ($n = 1$) and perforation of the remaining tumoural tissue ($n = 1$), and the difference in adjuvant treatment between the two groups was not statistically significant ($P = 0.99$).

The median follow-up time was similar in the two groups (Table 4).

Discussion

TEM is a safe technique associated with low morbidity and recurrence rates, and it is an effective curative treatment for pT1 sm1 early rectal cancers [16, 17]. Ramirez et al. [18] concluded that TEM is an adequate treatment for T1 low-risk tumours, and no additional measures are required in a prospective study. Although TEM remains the treatment of choice for stage T1 low-risk rectal cancers, patients with T1 sm2, 3 and T2 low-risk tumours should be considered high-risk cases if treated only by TEM [17, 18]. Comparative studies of TEM versus TME showed no difference in local recurrence or survival rates in patients with early rectal cancer. sTME was typically performed within approximately 3 months of the completion of local treatment [4, 19]. Early sTME can be offered to patients, in whom local treatment for early rectal cancer has failed. In our study, the median time between TEM and sTME was 37 days, which is similar to results of previous reports. Longer intervals occurred primarily due to patient-related factors.

Only a few studies evaluated the results of rectal surgery after transanal excision (TAE) and showed that TAE did not result in a worse outcome than primary radical resection [9, 12] However, to the best of our knowledge, there are no comparative studies evaluating outcome of sTME following TEM.

The patients with inadequate resection margins after TEM surgery and thus failure to eradicate the tumour or with unfavourable histological criteria should be offered radical sTME. Careful selection of patients who meet the criteria for treatment with TEM is therefore of great importance. Preoperative staging with transrectal ultrasound (TRUS) and MRI of the rectum should be used to evaluate the T stage and the CRM. TRUS has a sensitivity of 90 % for accurate T-staging [20] and is superior to MRI for accurate preoperative T-staging [21]. In contrast, MRI is the preferred modality when it comes to predicting CRM involvement [22]. Due to our patient material reaching over 15 years, with some patients treated in the late 1990s, not all patients received preoperative TRUS and/or MR scanning. This could explain why some of the specimens were found to be a more advanced cancer stage than anticipated.

Histological examination of the TME specimens of the 25 patients in our study, who underwent sTME, revealed that 6 patients (23 %) had stage III cancer. Baron et al. [9] report similar numbers in a study of TAE and polypectomy, where 23 % of the patients had lymphatic or vascular involvement after salvage surgery following local treatment.

Insufficient margin clearance was the main reason why the patients in our study underwent salvage surgery after TEM. However, 13 patients (50 %) did not have a residual tumour at the final histological examination following salvage surgery. Two of these patients had tumour invasion of the lymph nodes. Non-radical resection after TEM leading to salvage surgery with considerable morbidity can be avoided if a wide resection margin is secured during TEM. Rectal cancer is sometimes misdiagnosed for rectal adenoma, for which TEM is widely used as a treatment. Creation of a wide resection margin (10 mm) should therefore always be attempted. Positive resection margin rates will decrease if the surgeon supposes the lesions to be malignant and uses appropriate resection techniques [7].

When TEM fails as a definite treatment for early rectal cancer, it is controversial whether sTME following TEM provides results equivalent to primary TME [2, 6, 10, 23].

The time from local treatment for rectal cancer to salvage surgery may have an influence on outcome in these patients, as it was reported that there is no compromise in outcome when immediate radical operation followed local treatments, such as TAE [9, 12]. However, only a few studies address the outcome of salvage surgery following TEM. Borschitz et al. [6, 10] found a local recurrence rate of 5 % for T1 cancers, 12 % for T2 cancers and distant metastases in 12 % of patients who underwent radical surgery within 4 weeks of TEM. In a study by Bach et al. [7], none of the 63 patients who underwent early salvage surgery after TEM developed local recurrences for T1 and T2 cancers. One patient with T3 cancer developed a local recurrence, and 3 patients developed distant metastases in that study.

If salvage surgery is performed after the local recurrence has presented, the results may not be equivalent to those of primary radical surgery [11, 13, 23]. However, in only one of these studies [23] was TEM used as the primary treatment.

One concern with salvage surgery after TEM is that the patients will undergo two surgical procedures within a short period of time, which could cause higher morbidity rates [24]. Our study shows no significant difference in preoperative or postoperative surgical complications between the two groups, and the postoperative morbidity after sTME is comparable with that reported in other studies [2–4].

Another concern is that salvage surgery with TME may lead to compromise of the mesorectal fascial plane by tumour implantation, and this may result in sTME resection with positive margins and an inadequate CRM and therefore a higher risk of local recurrence.

TEM for rectal cancer results in defects in both the rectal wall and the mesorectum. The risk of weakening of the rectal wall is more obvious if repair with suturing is not used at the end of the TEM procedure [7, 12]. These defects heal after TEM and are replaced by a fibrous and fragile granulation tissue, even after suturing of the defect. In addition, traction on the rectum during pelvic dissection may cause tearing of the bowel wall in patients in whom the rectal wall has been traumatizes by a previous TEM procedure. This may increase the difficulty of pelvic dissection and may lead to an increased risk of intraoperative perforation. It was shown in a study from the DCCG that inadvertent rectal perforation occurred in 10 % (a total of 1125) of patients who underwent APR [25]. Perforation during APR is reported in 8–24 % of patients in the literature [25–27]. Iatrogenic intraoperative rectal perforation is one of the most important risk factors for both local and distant recurrence and impaired survival [25–28]. A difference between the two groups in intraoperative perforation of tumour or bowel was not seen in our study, and the rates of intraoperative perforation do not exceed those reported in other studies. All of the perforations that occurred during sTME occurred at the site of the previous TEM resection. Reduction in perforation can be achieved by awareness of and increased focus on this possible complication in patients who have previously undergone TEM.

Balch et al. [29] reported that with CRM >1 mm, the recurrence rate after TME is 5 %, but when CRM ≤1 mm, the local recurrence rate is 20 %. The risk of weakening the rectal wall and compromising the mesorectal fascia after a previous TEM procedure can lead to an increased risk of positive CRM, compromising oncological safety. There was only one non-radical resection and a median CRM of 10 mm in the sTME group, which in spite of the risks mentioned above, seemed not to compromise oncological safety in sTME following TEM in our study.

The small number of patients in this study may result in an overestimation of the results and an increased risk of type II errors. Other limitations of our study are the follow-up time and the retrospective nature of the study. An aggressive approach towards early rectal cancer and the controversies of treating early malignant lesions with TEM explain the small sample size in our study, and the elderly patient population can explain the short follow-up time.

Conclusions

We found no significant difference in surgical or oncological outcome between patients who underwent early sTME after TEM and patients with pTME. Early salvage surgery after TEM seems to be oncologically safe, but the surgeon must be aware of the perforation risk in TME following TEM.

Conflict of interest The authors declare that they have no conflict of interest.

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