The outcome of rectal cancer after early salvage surgery following transanal endoscopic microsurgery seems promising

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ABSTRACT

INTRODUCTION: Transanal endoscopic microsurgery (TEM) allows locally complete resection of early rectal cancer as an alternative to conventional radical surgery. In patients with unfavourable post-TEM histology, salvage surgery can be performed. The aim of this study was to evaluate the results of early radical surgery after TEM for rectal cancer.

MATERIAL AND METHODS: From 1997 to 2010, 86 TEM procedures were performed in 79 patients due to rectal cancer. Early salvage surgery was performed in 25 patients. Data were obtained from the patients' charts and reviewed retrospectively. Perioperative data and oncological outcome were analysed.

RESULTS: No patients received preoperative chemotherapy. The median time to salvage surgery was 37 days. Five patients underwent laparoscopic surgery. The median operative time was 165 min (range 101-341 min, 95% confidence interval (CI): 156-214 min) and the median blood loss 275 ml (range 0-1,275 ml, 95% CI: 232-530 ml). The 30-day mortality was 8% (95% CI: 1-19%, n = 2). Intra-operative perforation occurred in 20% (95% CI: 3-37%, n = 5). The median number of harvested lymph nodes was 12 (range 3-25, 95% CI: 9-14) and the median circumferential resection margin (CRM) was 10 mm (range 0-20 mm, 95% CI: 5-12 mm). Only one patient (4%, 95%CI: 1-12%) had a positive CRM. The median follow-up time was 25 months (range 3-80 months). There was no local recurrence. Distant metastasis occurred in 4% (95% CI: 1-12%, n = 1).

CONCLUSION: Early salvage surgery after TEM seems to be safe despite a high risk of specimen perforation during the operation.

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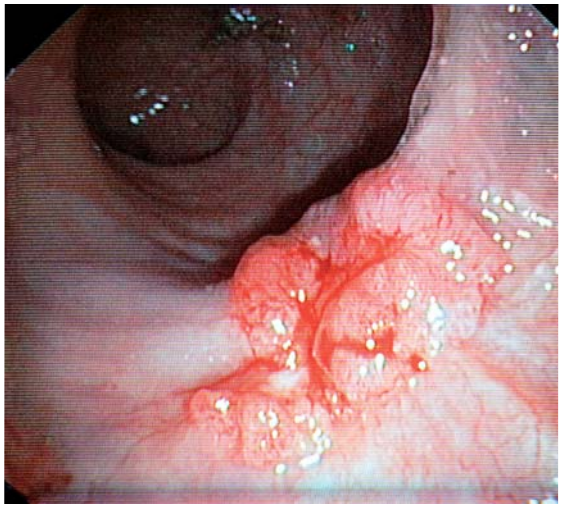

Endoscopic view of early rectal cancer.

ORIGINAL ARTICLE

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Total mesorectal excision (TME) is the gold standard in treatment of rectal cancer [1, 2]. Due to the morbidity and mortality rates associated with TME, transanal endoscopic microsurgery (TEM) has become a frequent choice of procedure in the treatment of early rectal cancer T1-T2-N0, especially in elderly and/or frail patients [1, 3, 4].

TEM is associated with reduced hospital stay and lower morbidity and mortality [5-7]. The major problems with TEM in the treatment of early rectal cancer are non-radical resection in up to 24% [3] and local recurrence in up to 21% in T1 cancers [1] and up to 29% in T2 cancers [8]. The increased use of TEM in the treatment for rectal cancer has led to discussions and studies comparing TEM with radical surgery [5-7]. Salvage surgery intended to eradicate all remaining tumour in patients with unfavourable histology (non-radical resection or advanced cancer stage) and/or local recurrence after TEM can be performed. Salvage surgery is required in 4-23% of patients following TEM [4, 9]. However, there is inconsistency in the literature regarding the results of salvage surgery following local excision [6-8, 10-14].

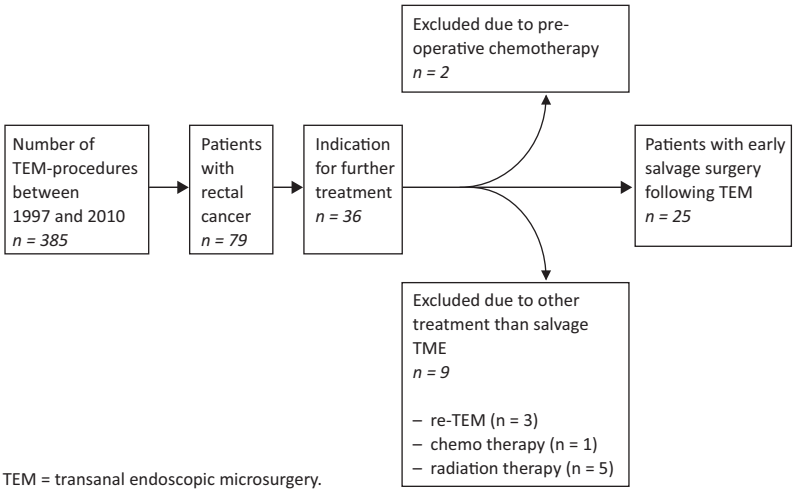
In the present study, we present the outcome in patients undergoing early salvage surgery following TEM.

MATERIAL AND METHODS

From January 1997 to December 2010, 385 TEM-procedures were performed in our institution. A total of 86 TEM-procedures (22%) with curative intention were performed in 79 rectal cancer patients. Cancer was suspected in 61% (n = 48), adenoma in 38% (n = 30) and the pre-operative evaluation was unclear in one patient. A total of 27 of these patients (34%) underwent early radical surgery following the TEM-procedure due to non-

FIGURE 1

Flow chart demonstrating the inclusion criteria of the study.



TEM = transanal endoscopic microsurgery.

radical resection or more advanced cancer stage than anticipated (T1sm1). The rest were followed-up according to the guidelines of the Danish Colorectal Cancer Group (DCCG).

Nine of the remaining 52 patients were treated with chemo- or radiation therapy or re-TEM due to lymphatic or vascular invasion (n = 6) or local recurrence (n = 3): Six patients received adjuvant chemo- or radiation therapy instead of TME. One patient had metastasis of the liver. One patient was offered salvage surgery, but declined. Four patients received radiation therapy due to substantial co-morbidity preventing them from undergoing major surgery (n = 3) or as decided at the multidisciplinary team (MDT) conference (n = 1). Three patients received re-TEM after local recurrence due to co-morbidity preventing major surgery (n = 2), or because the patient declined major surgery (n = 1).

All patients had been discussed at the MDT conference before early salvage surgery was offered. Two of the 27 patients were excluded from this study due to pre-operative chemotherapy, which left a total of 25 patients who underwent early TME following TEM (**Figure 1**). None of the 25 patients received pre-operative chemo- or radiotherapy. A total of 17 of the 25 salvage surgeries (68%) were performed after the year 2006, which has an effect on the follow-up time.

We performed a retrospective analysis of collected data including patient characteristics, perioperative data and 30-day mortality. Transrectal ultrasound was used in patients when adenocarcinoma was suspected. The patients were followed-up with rectoscopy every three months in the first post-operative year, colonoscopy three months after the operation (clean colon) and then on the third and fifth year postoperatively. Thoracoabdominal computed tomography was performed in the first and third year postoperatively. Local recurrence was defined as histopathologically confirmed recurrence of cancer in the rectum, at or near the previous TEM site.

Trial registration: not relevant.

RESULTS

Patient and tumour characteristics are shown in **Table 1**.

Patient selection

There was no indication for pre-operative chemo- or radiotherapy for the 25 patients. Twenty-two of the 25 patients (88%) underwent salvage surgery following TEM due to non-radical or unclear resection margins and/or due to lymphatic or venous invasion. Three patients (12%) with negative resection margins and no invasion of lymph nodes or venous tissue underwent TME for the following reasons: One patient with a T2 tumour underwent TME as decided at the MDT conference at the time. The tumour of one patient was located 10 mm from the anal verge, and the patient underwent abdominoperineal resection (APR). Although one patient with familiar adenomatous polyposis had rectal adenocarcinoma excised with clear margins by TEM and no presence of lymphatic or venous invasion, she was considered at high risk due to previous development of several adenomas in succession within a short period.

Five patients had clear resection margins. Lymphatic or venous invasion in the TEM specimen was found in six patients; four patients had venous invasion, one patient had involvement of a lymph node, and one had a micrometastasis in one lymph node.

Perioperative data of total mesorectal excisions

The median time from TEM to TME was 37 days (range 14-90 days) after the exclusion of four patients with a prolonged interval (> 90 days): two patients chose to postpone salvage surgery for personal reasons; and in two patients the reason for the prolonged interval was unknown. With these patients included, the median time from TEM to TME was 41 days (range 14-183 days).

Table 2 shows procedure details for TME. Five patients (20%) underwent laparoscopic surgery.

Intraoperative complications occurred in 20% (95% confidence interval (CI): 3-37%, n = 5) and comprised the following: perforation of the remaining tumoural tissue (n = 2) and perforation into the peritoneal cavity at the site of previous TEM resection (n = 3). The operative method for the patients with perforation into the peritoneal cavity was APR in two patients and low anterior resection in one patient, all three by conventional open surgery.

TABLE 1

Patient and tumour characteristics.

Male/female, n	15/10
Age, median (range), years	73 (40-84)
ASA-score, median (range)	2 (1-3)
BMI, median (range), kg/m^2	25.2 (18.4-33.4)
Tumour distance from anal verge[a], n (%)	
≤ 5 cm	12 (48)
6-10 cm	5 (20)
≥ 11 cm	8 (32)
Tumour size, median (range), cm	3 × 3.5 (1 × 1.5-7 × 7)
Tumour size, median (range), cm^2	8.5 (1.5-49)

ASA = American Society of Anesthesiologists; BMI = body mass index.
a) Median range 9 cm (range 1-14 cm)

TABLE 2

Procedural details and perioperative data for salvage surgery with total mesorectal excision.

Blood loss, median (range), ml	275 (0-1,275)
Operating time, median (range), min	165 (101-341)
Procedure, n (%)	
LAR-I	4 (16)
LAR	7 (28)
APR	10 (40)
HO	3 (12)
TP	1 (4)
Intraoperative complications, n (%)	5 (20)
Postoperative complications,[a] n (%)	14 (56)
Hospital stay, median (range), days	9.5 (4-22)
30-day mortality, n (%)	2 (8)
Complications, n	
Perineal wound dehiscence	3
Superficial wound infection	3
Urinary tract infection	3
Stoma necrosis	1
Stoma retraction	1
Anastomotic leakage	1
Ileus	1
Sepsis	1
Urinary retention	1
Arrhythmia	1
Late complications	4
Total	20

APR = abdominoperineal resection; HO = Hartmann's operation; LAR = low anterior resection; LAR-I = low anterior resection with protective ileostomy; TP = total proctocolectomy.
a) 14 patients with 20 complications.

Postoperative complications (Table 2) occurred in 56% of the patients (95% CI: 35-77%, n = 14). Major complications were anastomotic leak (n = 1), small bowel obstruction (n = 1), sepsis and multiorgan failure (n = 1) after an anastomotic leak. Superficial perineal wound dehiscence occurred in three patients who underwent APR (12%). Four of the complications occurred after 30 days: small bowel obstruction (n = 1), parastomal hernia (n = 2) and stoma prolapse (n = 1).

The 30-day mortality was 8% (95% CI: 1-19%, n = 2). The first patient was an 83-year-old woman who developed signs of small bowel obstruction eight days after TME. She was unable to recover following an urgent laparotomy due to progressive cardiovascular failure and died 21 days after TME. The second patient was a 73-year-old woman developing multiorgan failure following anastomotic leakage on the eighth day after TME.

TABLE 3

Oncological outcome.

No residual tumour, n (%)	13 (52)
Staging[a], n	
Stage I	4
Stage II	3
Stage IIIa	1
Stage IIIb	1
Stage IIIc	3
Radical resection, n (%)	24 (96)
Harvested lymph nodes, median (range), n	12 (3-25)
CRM, median (range), mm	10 (0-20)
DRM, median (range), mm	27.5 (0-110)
MRF: C/NC/IC, n	10/2/7
Adjuvant chemotherapy, n (%)	4 (16)
Local recurrence, n	0
Distal metastasis, n (%)	1 (4)

C = complete; CRM = circumferential resection margin; DRM = distal resection margin; IC = incomplete; MRF = mesorectal fasciae; NC = nearly complete.
a) American Joint Committee on Cancer staging system.

Oncological results

Oncological details are presented in **Table 3**. There was no residual tumour in 52% (95% CI: 31-73%, n = 13). However, two of these patients had positive lymph nodes. The completeness of the mesorectal fascia (MRF) was not described in the histological examination in six patients (24%). Of the remaining 19 patients, the MRF was complete or nearly complete in 63% (95% CI: 39-87%, n = 12). Only one patient (4%, 95% CI: 1-12%) had a positive circumferential resection margin (CRM), staged as IIa adenocarcinoma. This patient had a prolonged period from TEM to TME (183 days) and perforation of the remaining tumoural tissue occurred during her salvage surgery with APR. She declined further treatment or follow-up.

Four patients (16%) received adjuvant chemotherapy due to lymph node involvement (n = 2), venous invasion (n = 1) and perforation of the remaining tumoural tissue (n = 1). The median follow-up time was 25 months (range 3-80 months). No local recurrence was observed.

One patient (4%, 95% CI: 1-12%) with a radically resected stage III adenocarcinoma developed liver metastases four months after TME and was referred to liver resection. Six patients (24%) died during the observation period.

DISCUSSION

Non-radical resection and unfavourable histological criteria such as poor tumour differentiation and lymphatic or vascular invasion may lead to recurrence and careful selection of patients and correct pre-operative staging is therefore crucial. Following a non-radical resection or in cases with unfavourable histology, salvage surgery is considered amenable, but it is controversial whether this provides results equivalent to those of primary radical surgery [1, 5, 8, 11-13].

Of the 25 patients in this study, two patients had lymphatic invasion and four patients had vascular invasion after TEM. After salvage surgery with TME, the final histological examination revealed that five patients (20%) had a stage III cancer. Similar numbers were reported in a study by Baron et al [10], where 23% of the patients had lymphatic or vascular involvement after immediate salvage surgery following transanal excision.

A total of 13 patients (52%) had no residual tumour at the histological examination following salvage surgery. Non-radical resection after TEM, which may lead to major surgery with considerable morbidity, can be avoided if a wide resection margin is secured. Since TEM is widely used for excision of rectal adenomas (which sometimes turn out to be carcinomas), creation of a wide resection margin (1 cm) should always be aimed for. Positive resection margin rates will decrease if the surgeon supposes that lesions are malignant and uses appropriate resection techniques. Furthermore, correct specimen handling is important, since poor pinning of the tumour specimen and tumour fixation with formalin can damage the relationship between the tumour and the healthy margin [4]. A concern with early salvage surgery after TEM is that the patients will undergo two surgical procedures within a short period of time which may cause increased morbidity [15]. In this study, the post-operative morbidity was 56% which is comparable to the morbidity after primary radical surgery [5-7].

No compromise in outcome has been reported when immediate radical operation followed local treatments of rectal diseases such as transanal excision [10, 13]. However, only a few studies have addressed the outcome of early surgery following TEM procedure. In patients who underwent radical surgery within four weeks of TEM, Borschitz et al [8, 11] found a local recurrence rate of 5% for T1 cancers, 12% for T2 cancers and distant metastases in 12%. In a multicentre study, Bach et al [4] analysed 63 patients who underwent early salvage surgery following TEM and found no local recurrences for the T1 and T2 cancers. It was reported that one patient with a T3 cancer developed a local recurrence, while three patients developed distant metastases. If salvage surgery is performed after the local recurrence has presented, the results may not be equivalent to those of primary radical surgery [1, 12, 14]. However, TEM was used as the primary treatment in only one of these studies [1]. This indicates that the time interval between TEM and salvage surgery is of major importance.

In the conversion procedure from TEM to TME due to insufficient clearance margins or unfavourable histology, the mesorectal fascial plane may be compromised by tumour implantation, which may result in TME resection with positive margins and therefore a higher risk of local recurrence. Furthermore, the rectal wall may be weakened if reconstitution with suturing is not used at the end of the TEM procedure [4, 13]. These factors could result in an inadequate CRM, which is important with a view to minimizing local recurrence in rectal cancer. With a CRM > 1 mm, the recurrence rate after TME is 5%, but when CRM ≤ 1 mm, the local recurrence rate is 20% [16].

Previous studies have not reported any episodes of local recurrence, but it is not mentioned if intra-operative perforation occurred [8, 11]. A recent study from the DCCG showed that inadvertent rectal perforation occurred in 10% (a total of 1,125 patients) operated with APR [17]. The literature reports a perforation rate during APR of 8-24%, which is higher than that observed for anterior resection [17-19]. Several studies have demonstrated that iatrogenic intra-operative rectal perforation is one of the most important risk factors for both local and distant recurrence and impaired survival [17-20]. In the present data, intra-operative perforation occurred in five patients (20%), including two cases of perforation of the remaining tumoural tissue, all located at the site of the previous TEM resection. The surgeon can reduce the perforation risk by paying more attention to this complication in patients who have previously undergone a TEM procedure.

The resection margins were positive in only one of the patients with perforation of the remaining tumoural tissue, and the median CRM was 10 mm in this series. In our study, which comprised only a limited number of patients, there was only one non-radical resection, no local recurrences and a median CRM of 10 mm. Therefore, the increased risk of compromising the mesorectal fascia and weakening the rectal wall seems not to compromise safety after radical surgery regarding margin clearance and recurrence. It seems that our results support those of other studies reporting no negative influence of TEM on local recurrence and survival concerning radical sur-

gery following TEM for resected lesions with bad prognostic factors or after local failure [6, 11]. However, there is a high risk of type II error in this patient population. The main limitations of this study is the follow-up time and that it is a retrospective study with a limited number of patients, which possibly undermines the results concerning low rates of local recurrence and metastases. An aggressive approach towards early rectal cancer and the controversies of treating early malignant lesions with the TEM procedure may be an explanation for the small sample size in our study and an elderly patient population with relatively short expected life time explains the short follow-up time.

CONCLUSION

Early salvage surgery following TEM seems to be safe with low rates of recurrence and metastases despite a high risk of intra-operative specimen perforation. The surgeon must be aware of the perforation risk in radical cancer surgery following TEM. However, there is a need for comparative studies based on robust data in the future.

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