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Purpose

This study was undertaken to assess the short-term outcomes of neoadjuvant short-course radiation therapy (SCRT) followed by transanal endoscopic microsurgery (TEM) for T1-T2 N0 extraperitoneal rectal cancer. Recent studies suggest that neoadjuvant radiation therapy followed by TEM is safe and has results similar to those with abdominal rectal resection for the treatment of extraperitoneal early rectal cancer.

Methods and Materials

We planned a prospective pilot study including 25 consecutive patients with extraperitoneal T1-T2 N0 M0 rectal adenocarcinoma undergoing SCRT followed by TEM 4 to 10 weeks later (SCRT-TEM). Safety, efficacy, and acceptability of this treatment modality were compared with historical groups of patients with similar rectal cancer stage and treated with long-course radiation therapy (LCRT) followed by TEM (LCRT-TEM), TEM alone, or laparoscopic rectal resection with total mesorectal excision (TME) at our institution.

Results

The study was interrupted after 14 patients underwent SCRT of 25 Gy in 5 fractions followed by TEM. Median time between SCRT and TEM was 7 weeks (range: 4-10 weeks). Although no preoperative complications occurred, rectal suture dehiscence was observed in 7 patients (50%) at 4 weeks follow-up, associated with an enterocutaneous fistula in the sacral area in 2 cases. One patient required a colostomy. Quality of life at 1-month follow-up, according to European Organization for Research and Treatment of Cancer QLQ-C30 survey score, was significantly worse in SCRT-TEM patients than in LCRT-TEM patients (P=.0277) or TEM patients (P=.0004), whereas no differences were observed with TME patients (P=.604). At a median follow-up of 10 months (range: 6-26 months), we observed 1 (7%) local recurrence at 6 months that was treated with abdominoperineal resection.

Conclusions

SCRT followed by TEM for T1-T2 N0 rectal cancer is burdened by a high rate of painful dehiscence of the suture line and enterocutaneous fistula, compared to TEM alone and TEM following LCRT, which forced us to stop the study.

Summary
In a pilot study, patients with T1-T2 N0 rectal adenocarcinoma underwent irradiation of 25 Gy in 5 fractions followed by transanal endoscopic microsurgery 4 to 10 weeks later. We observed a 50% rate of complete dehiscence of the suture, with severe pain and impairment of quality of life in 2 cases associated with an enterocutaneous fistula in the sacral area that forced us to stop the study.

Introduction

With the widespread introduction of population-based screening programs, the rate of rectal cancers diagnosed at an early stage has progressively raised during the last 2 decades, leading to an increasing debate around the potential role of local treatment of early rectal cancer (1). In 1983, Buess et al (2) introduced a novel surgical approach for the resection of large rectal adenomas, namely transanal endoscopic microsurgery (TEM). Since its introduction, many centers have adopted TEM as the new standard surgical approach to treating both large rectal adenomas and early rectal cancer (3). Supporters of the TEM technique praise the excellent exposure of the rectum and the minimal invasiveness, as opposed to conventional surgical techniques (1). In addition, recurrence rates after TEM appear to be lower than with conventional surgical transanal excision (4). The TEM technique has been shown to be highly effective in several retrospective and prospective case series with reported recurrence rates of 0% to 19% and complication rates of 2% to 21% 5, 6, 7, 8, 9 and 10.
Even if TEM provides excellent outcomes, diffusion of the technique among colorectal surgeons has been limited by the considerable cost of the instrumentation and the steep learning curve required to master the TEM technique. In 2007, the transanal endoscopic operation device was introduced (Karl Storz GmbH, Tuttlingen, Germany), and 2 years later, the device for transanal minimally invasive surgery was introduced, adopting the use of a simplified rectoscope in the first case and use of a disposable, single-port device in the second case, with the intent of making this technique available to a wider population of surgeons (11).
More recently, TEM has been proposed in a multimodality treatment strategy of highly selected T2 N0 rectal cancers. In these series, including a randomized controlled trial (12), patients underwent neoadjuvant long-course chemoradiation therapy: 50.4 Gy in 28 fractions associated with a continuous infusion of 5-fluorouracil, 200 mg/m^2/day. Although this schedule showed great efficacy in terms of control of the disease, it is quite uncomfortable for patients, who often are elderly. Moreover, there are concerns regarding the wound healing process after neoadjuvant long-course chemoradiation therapy 13 and 14.
Two randomized European clinical trials have shown that short-course preoperative radiation therapy (SCRT) reduces local recurrence and improves survival in locally advanced rectal cancer 15 and 16. In selected T1-T2 N0 rectal cancers it could represent a more comfortable alternative therapy, ensuring results comparable to long-course chemoradiation therapy in terms of control of the disease.
The aim of this pilot study was to assess short-term outcomes of SCRT followed by TEM for selected T1-T2 N0 extraperitoneal rectal cancers.

Methods and Materials

Study design

The study is a prospective case series pilot study including consecutive patients undergoing neoadjuvant SCRT followed by TEM (SCRT-TEM) for T_1 to T_2, N_0, or G_{1-2} rectal cancer. Preoperative results, morbidity, quality of life (QoL), and oncologic outcomes of SCRT-TEM patients were compared with the outcomes of patients who had undergone TEM following 46-Gy long-course radiation therapy (LCRT-TEM), TEM alone (TEM), or laparoscopic rectal resection

with total mesorectal excision (TME) for extraperitoneal rectal cancer at the same stage of disease (T_1-T_2, N_0, G_{1-2}). For comparison, patients with that stage of disease who were treated at our institution since 1999 were selected. The study was approved by the Local Ethical Committee on May 30, 2011, and registered on Clinicaltrials.gov under identifier NCT02127645.

Study population

Patients affected by a sessile lesion of the rectum were eligible for this study when they met the following inclusion criteria: (*1*) largest diameter of >2 cm, estimated by an endoscopic snare; (*2*) lower and upper borders of the rectal neoplasm within 2 and 12 cm from the anal verge, respectively, estimated by rigid rectoscopy; (*3*) preoperative histology on biopsy samples showing G1-G2 adenocarcinoma; (*4*) endoscopic ultrasonography showing tumor invasion of the submucosa of >1 mm (uTsm2 or uTsm3) or of the muscular layer (uT2) with no perirectal lymph nodes of >1 cm; (*5*) pelvic magnetic resonance imaging (MRI), or computed tomography (CT) when MRI was contraindicated, showing no evidence of perirectal lymph nodes of >10 mm or of >5 mm with suggestive features (ie round shape, indistinct border, signal heterogeneity) (17); (*6*) CT scan showing no evidence of distant metastases; (*7*) American Society of Anesthesiologists score of I to III; and (*8*) no previous anorectal surgery.

Outcomes

The tentative primary endpoint was the incidence of local recurrence at 36 months. Local recurrence of cancer was defined as the presence of histologically proven neoplastic tissue in either visible recurrent lesions or in random biopsies.
Additional outcome measures were complications, QoL, and anorectal function. Complications were divided into those that were procedural, if observed during treatment, and delayed when observed after the end of the TEM procedure and classified according to Dindo et al (18). Measurement of generic and disease-specific health-related QoL was planned at baseline, 4 weeks; 3 months; 6 months; and 1 and 3 years; follow-up, using European Organization for Research and Treatment of Cancer version 3.0 QLQ-C30 questionnaire raw scores (19) and Wexner score (for incontinence) (20). Anorectal manometry to evaluate functional outcome was also planned before RT and at 3 months after surgery.

Recruitment of patients

The original intent was to recruit at least 25 consecutive patients eligible for this study from June 1, 2011. A physician informed those patients fulfilling the above-mentioned criteria about the study. After informed consent was given, Internet web-based central data acquisition took place, and patients were treated according to the study protocol. Patients unable or unwilling to enter the study were treated according to the current clinical guidelines for rectal cancer. A single proctologist performed all rectal examinations by rigid rectoscopy. A single expert in endorectal ultrasonography performed all rectal examinations by rigid probe.

Intervention strategies

Preoperative RT was carried out with image guided intensity modulated radiation therapy high-energy photons through a single arc volumetric modulated arc therapy technique from a linear accelerator (Axesse; Elekta, Crawley, UK). Patients were placed in the supine position. Fixation was accomplished by using a knee-foot immobilization device, and a radiopaque marker was placed at the anal verge during CT simulation. We included in the clinical target volume (CTV) the macroscopic visible tumor (gross tumor volume [GTV]), the whole mesorectum (defined as the

adipose tissue, with lymphovascular and neural structures, encapsulated by the mesorectal fascia), and internal iliac nodes with presacral space. The lower limit of CTV was extended at least 2 cm below the lowest part of visible tumor and included the pelvic floor for distal tumors with lower limit up to 5 cm from anal verge. The upper limit was typically 2.5 to 3 cm above the tumor. The posterior border of the CTV covered the presacral nodes and excluded the sacral bone; anteriorly it was sufficiently ventral to cover the entire mesorectum, whereas laterally it covered regional nodes. A nonuniform planning target volume (PTV) was generated by adding a margin of 10 mm in all directions, except for the posterior addition of 8 mm. This was applied to take into account systematic and random errors. Normal structures identified included the proximal femora and bladder. Patients underwent daily image guidance using an integrated CT modality and were repositioned after coregistration of these images with the planning CT scan.
The dose was administered to the PTV according to International Commission on Radiation Units (ICRU) guidelines. A total dose of 25 Gy in 5 daily fractions over 1 week would be delivered, administering 1 fraction per day, 5 Gy per fraction. Radiation therapy usually started on Monday and finished on Friday. We reported to the ICRU reference point the maximum dose and the minimum dose to the PTV. The treatment plan was specified with the 95% isodose line encompassing the PTV and no more than +7% and −5% inhomogeneity within the target volume (21). We examined the dose distribution in both coronal and sagittal views to ensure the optimal anatomical arrangement of isodoses. Further dose-volume requirements were provided for the PTV according to the guidelines for the planner (minimum PTV = D99% $\geq$ 95%; maximum PTV = D5% < 105%, and D2% of <110%).
TEM was performed between 4 and 10 weeks after the end of RT. All patients were asked to begin a low-fiber diet the week before TEM, and a rectal enema was performed 12 and 2 hours preoperatively. Intravenous antibiotics, such as a second-generation cephalosporin and metronidazole, were administered before insertion of the operative rectoscope and continued for 24 hours at 12-hour intervals. Deep venous thrombosis prophylaxis was administered. TEM was performed as described by Buess et al (2). With the patient under general anesthesia, a 7.5- or 15-cm transanal endoscopic rectoscope (Karl Storz GmbH Tuttlingen, Germany) was inserted through the anus and fixed to the operating table. The rectum was inflated with CO_2 to achieve stable distension of the rectal wall and appropriate visualization of the rectal tumor. The rectal lesion was dissected en bloc by means of a full-thickness rectal wall excision exposing the perirectal fat with at least 1-cm macroscopic disease-free lateral margins. The rectal wall defect was closed by 1 or more full-thickness inverting 3-0 polytrimethylene carbonate (Maxon suture; Covidien, Mansfield, MA) running sutures secured with dedicated silver clips (Richard Wolf GmbH, Knittlingen, Germany).

Pathology

Resected specimens were stretched and pinned on a cork plate and sent to pathology for examination under vacuum seal. After standard processing, the resection specimen underwent transection of each millimeter for evaluation by a single gastrointestinal pathologist, expert in large bowel neoplasms and RT effects. The lateral and deep resection margins were evaluated. Resections were considered R0 if at least 1 mm of tissue free of disease was detectable on each margin. Tumour regression grading (TRG) was assessed as a measurement of response to neoadjuvant RT according to Mandard et al (22).

Follow-up

During each surveillance endoscopy, planned at 3, 6, 12, 18, 24, and 36 months, local recurrence was defined by criteria of Higaki et al (23). Targeted biopsy samples were taken for histological confirmation; in case of an apparently healed normal scar without macroscopic evidence of recurrence, biopsy samples were taken from the basis and from the edges of the scar to detect occult

recurrent cancer. MRI, or CT scan when MRI was contraindicated, was planned at 6, 12, 24, and 36 months to detect extralumenal recurrences. Distant metastases were investigated as usual.

Data analysis

SCRT-TEM patients' characteristics and outcomes were compared with those of 3 historical groups of patients treated for similar indications, such as LCRT-TEM, TEM, and TME patients. Patients for comparison were selected as those treated at our institution for extraperitoneal rectal cancer preoperatively staged as T1 to T2, N0, and G1 to G2 between 1999 and the date the study began. Two-sample Wilcoxon rank-sum (Mann-Whitney U) test and Fisher exact test or Pearson χ^2 test were used for comparative analyses between the prospective group and each of the retrospective groups for some of the variables and to compare patients with and without complications. Morbidity and mortality rates according to Dindo et al (18) were compared in the same manner. All analyses were carried out primarily on an intention-to-treat basis.

Results

Recruitment of consecutive patients eligible for this study started on June 1, 2011. The study was interrupted in January 2014 after enrolment of 14 SCRT-TEM patients for the high rate of complications observed.
Although no preoperative complication was reported, 7 patients (50%) showed a complete dehiscence of the suture line at endoscopy 4 weeks after surgery. All 7 patients with suture dehiscence presented with severe pelvic pain within 2 weeks after surgery. This was treated in all cases with 10% iodine solution enemas, and in 4 cases oral antibiotics were administered. Despite this, 2 patients developed enterocutaneous fistulas in the sacral areas 6 weeks after surgery (Fig. 1). Patients were given intravenous antibiotics and a total parenteral nutrition regimen. In 1 case, a colostomy was performed to control sepsis, whereas in the other case complete healing was observed 12 months after surgery (Table 1).

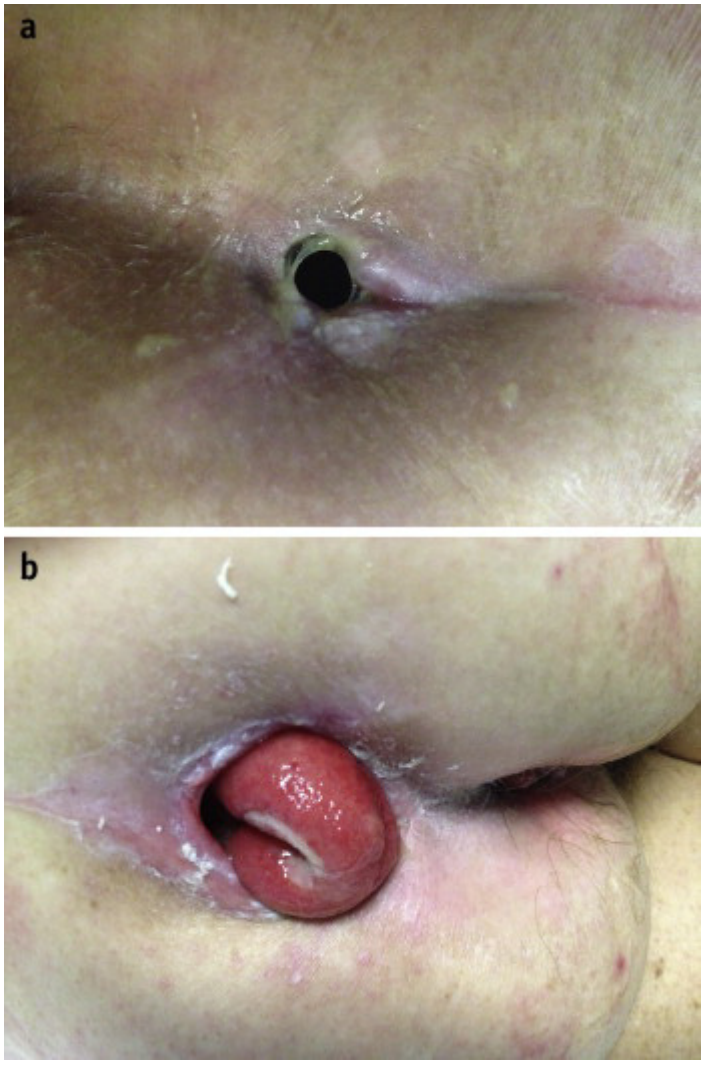

Fig. 1.
Rectal suture dehiscence complicated by an enterocutaneous fistula in the sacral area, 30 days (a) and 90 days (b) after surgery, requiring a colostomy to control sepsis.

Table 1.
Management and outcome of postoperative dehiscence

Patient	Dehiscence	Management	Outcome
5	Minor	10% iodine solution enemas	Complete healing
6	Enterocutaneous fistula	10% iodine solution enemas; i.v. antibiotics; total parenteral nutrition	Chronic enterocutaneous fistula, which healed 12 months later
8	Enterocutaneous fistula	10% iodine solution enemas; i.v. antibiotics; ostomy	Chronic enterocutaneous fistula; ostomy
9	Minor	10% iodine solution enemas; oral antibiotics	Complete healing
10	Minor	10% iodine solution enemas	Complete healing
12	Minor	10% iodine solution enemas; oral antibiotics	Complete healing
14	Minor	10% iodine solution enemas	Complete healing

Abbreviation: i.v. = intravenous.

The median time between SCRT and surgery was 7 weeks (range: 4-10 weeks). The sudden interruption of the study prevented analysis of the primary endpoint, the incidence of local recurrence at 36 months, although follow-up of patients continued.
Table 2 summarizes SCRT-TEM patients' characteristics. No significant differences were observed between SCRT-TEM patients and LCRT-TEM patients, TEM patients, and TME patients. Pretreatment endoscopic ultrasonography staging was uT1N0 in 2 cases and uT2N0 in 12 cases. All but 1 patient had R0 resection.

Table 2.
Patient characteristics

Characteristic	Therapy			
	25-Gy RT + TEM (SCTR-TEM)	**46-Gy RT + TEM (LCTR-TEM)**	**TEM**	**TME**
No. of patients	14	10	32	33
Sex, M:F	7:7	8:2	16:16	16:17
Median age (range), y	67 (39-81)	70 (39-88)	72 (38-91)	65 (34-90)
No. of comorbidities (range)	1 (0-3)	1 (0-3)	2 (0-4)	1 (0-2)
Median distance from the anal verge (range), cm	6 (2-12)	6 (3-9)	6 (3-11)	5 (1-12)
Median tumor diameter (range), cm	3 (1-5)	2.5 (1-5)	3 (1-4)	4 (2-6)
No. of tumor sites (% of total)				
Anterior	2 (14%)	0	7 (22%)	6 (18%)
Lateral	4 (29%)	2 (20%)	21 (66%)	20 (61%)
Posterior	8 (57%)	8 (80%)	4 (12%)	7 (21%)

Abbreviations: LCTR = long-course radiation therapy; RT = radiation therapy; SCTR = short-course radiation therapy; TEM = transanal endoscopic microsurgery; TME = total mesorectal excision.

Preoperative data are reported in Table 3. Median duration of surgery was significantly shorter in the SCRT-TEM group than in the TEM and TME groups, as was median blood loss, although it was negligible in any case. Postoperative histology showed 6 cases of TRG0, 3 cases of TRG1, 1 case of TRG2, 1 case of TRG3, and 3 cases of TRG4. Restoration of bowel function occurred earlier in the SCRT-TEM group than in the TME group. The median length of hospital stay for the SCRT-TEM group was shorter than that for the TEM group and TME group. At 1 month after surgery, median EORTC QLQ-C30 score decreased 17.0 points (interquartile range [IQR]: −42 to −11) in the SCRT-TEM patients, 9.5 points (IQR: −11 to −5) in the LCRT-TEM patients (P=.0277), 7.5 points (IQR: −9.5 to −5) after TEM alone (P=.0004), and 15.0 points (IQR: −24 to −11) after rectal laparoscopic resection and TME (P=.6004). At 3 month after surgery, median EORTC QLQ-C30 score decreased to 14.0 points (IQR: −38 to −10), whereas at 6 months, it decreased to 12.0 points (IQR: −36 to −4) in the SCRT-TEM patients. The overall complication rate in the SCRT-TEM group was higher than in both the LCRT-TEM and the TEM groups, whereas no differences were

observed compared to the TME group. In particular, no dehiscence was observed in either the LCRT-TEM or TEM groups. One patient required a stoma in the SCRT-TEM group compared to all patients in the TME group, according to our standardized technique. Postoperative complications were classified according to Dindo et al (18) in Table 4.

Table 3.
Preoperative data

Parameter	Therapy					
	25-Gy RT + TEM (SCTR-TEM)	46-Gy RT + TEM (LCTR-TEM)		TEM		TME
No. of patients	14	10	*P* value	32	*P* value	33	*P* value
Median duration of surgery (IQR), min	47.5 (45-60)	50 (50-60)	.1453	195 (180-230)	.0032	90 (57.5-120)	.0000
Median blood loss (IQR), mL	15 (10-40)	26.5 (20-32)	.3111	30 (20-50)	.0473	100 (100-200)	.0000
Median no. of bowel movements (IQR)	2 (2-3)	3.5 (2-4)	.3715	3 (2.5-4)	.3865	3 (3-4)	.0075
Median length of hospital stay (IQR), d	4 (3-5)	5 (4-6)	.0854	5 (5-7)	.0022	10 (7-12)	.0000
Median quality of life (IQR)	−17 (−42 to −11)	−9.5 (−11 to −5)	.0277	−7.5 (−9.5 to −5)	.0004	−15 (−24 to −11)	.6004
No. of any complications (%)	7 (50%)	1 (10%)	.0448	5 (15.6%)	.0157	13 (39.4%)	.5058

Abbreviations: IQR = interquartile range; LCTR = long-course radiation therapy; RT = radiation therapy; SCTR = short-course radiation therapy; TEM = transanal endoscopic microsurgery; TME = total mesorectal excision.

Comparison with 25-Gy + TEM group. Two-sample Wilcoxon rank sum (Mann-Whitney U) test.

Table 4.
Postoperative morbidity

Morbidity	Therapy			
	25-Gy RT + TEM (SCRT-TEM)	46-Gy RT + TEM (LCRT-TEM)	TEM	TME
No. of patients	14	10	32	33
No. of postoperative complications (%)	7 (50%)†	1 (10%)	5 (16%)†	13 (40%)
Grade I	0	0	0	2 (6%)

Morbidity	Therapy			
	25-Gy RT + TEM (SCRT-TEM)	46-Gy RT + TEM (LCRT-TEM)	TEM	TME
Grade II	5 (36%)	1 (10%)	5 (16%)	1 (3%)
Grade III	1 (7%)	0	0	10 (30%)
Grade IIIa	1 (7%)	0	0	6 (18%)
Grade IIIb	0	0	0	4 (12%)
Grade IV	1 (7%)	0	0	0
Grade V	0	0	0	0

Abbreviations: LCTR = long-course radiation therapy; RT = radiation therapy; SCTR = short-course radiation therapy; TEM = transanal endoscopic microsurgery; TME = total mesorectal excision.

Classified according to Dindo et al (18).

†

$P < .05$

With an average follow-up of 10 months (range: 6-26 months), we observed 1 local recurrence at 6 months in the patient who underwent an R1 resection. This patient required an abdominoperineal resection for a pT4aNc1.

In order to determine potential risk factors for suture dehiscence, we observed that 6 of the 9 patients who had a posterior tumor experienced a dehiscence. Similarly the median distance of the tumor was 4 cm (range: 4-5 cm) in the group of patients who experienced a dehiscence and 7 cm (range: 4-8 cm) in those who did not. The average time elapsed between RT and surgery was 7 weeks (range: 4-10 weeks) for patients who experienced dehiscence and 6 weeks (range: 4-10 weeks) for those who did not. No differences were observed between the 2 groups in terms of sex, median age, comorbidities, duration of surgery, intraoperative blood loss, or tumor diameter, as shown in Table 5. None of the above-mentioned factors potentially influencing the risk of dehiscence resulted statistically significant.

Table 5.

Risk factors for suture dehiscence in the SCRT-TEM group

Factor	Suture dehiscence	Regular healing	*P* value
No. of patients	7	7	
Sex: M:F	4:3	3:4	1
Median age (IQR), y	80 (65-82)	69 (54-81)	.3062†
Median no. of comorbidities (IQR)	1 (0-1)	0 (0-1)	.4751†
Median distance from the anal verge (range), cm	4 (4-5)	7 (4-8)	.0916†
Median tumor diameter (range), cm	3 (2.5-3)	2 (2-4)	.3191†
No. of tumors at the site shown (%)			

Factor	Suture dehiscence	Regular healing	*P* value
Anterior	0	2	.135
Lateral	1	2	
Posterior	6	3	
Time elapsed between RT and TEM (range), wk	9 (5-9)	6 (4-8)	.1928†
Median operative time (IQR), min	60 (45-60)	45 (40-60)	.2953
Median blood loss (IQR), mL	20 (10-40)	10 (10-40)	.7317

Abbreviations: IQR = interquartile range; RT = radiation therapy; SCTR = short-course radiation therapy; TEM = transanal endoscopic microsurgery.

Fisher exact test.

† Two-sample Wilcoxon rank-sum (Mann-Whitney U) test.

Discussion

The introduction of colorectal cancer screening programs has led to an increased detection of early rectal cancers, which has stimulated research focused on assessing the most appropriate treatment in terms of efficacy, safety, and QoL. We recently reported our series of rectal cancers treated by TEM, which demonstrates once more that submucosal invasion when extended to >1 mm in depth is associated with a non-negligible risk of lymph node metastases and local recurrence (24). Several groups have shown that neoadjuvant LCRT protocols, associated in some cases with chemotherapy, followed by TEM, achieve distant recurrence rates and survival similar to those of radical surgery but with lower morbidity, mortality, and a better QoL. Complications of LCRT and TEM for rectal cancer are reported in 4 different series: Lezoche et al (25) reported a minor wound separation incidence of 12%; Marks et al (13) reported an incidence of 25.6%; Coco et al (26) reported an incidence of 22.7%; and Bujko et al (14) reported an incidence of 13.4%. Minor wound dehiscence is a common short-term complication after TEM, usually managed conservatively with a daily rectal enema with a solution of 10% povidone-iodine. Despite this, both Marks et al (13) and Bujko et al (14) reported an unexpected number of major wound dehiscence occurrences requiring further treatment such as a diverting colostomy for better local sepsis control and even 1 case of abdominoperineal resection. This prompts the suspicion that LCRT may be burdened by a high rate of complications, too.

We reported 2 major complications consisting of chronic trans-sacral enterocutaneous fistula requiring ostomy in 1 case. Another 5 patients presented with symptomatic wound dehiscence and severe sepsis, which impaired patients' QoL. We had never observed a similar rate of dehiscence and such severe symptoms of local sepsis after a TEM procedure. Although the hypothesis was to determine whether SCRT-TEM could provide an oncologic result similar to radical surgery with the benefit of a better QoL, our results suggest that QoL is probably equivalent to radical surgery if not worse.

At the same time, the evidence of oncologic equivalence is very weak. The technical advancements in RT led us to believe that RT might play a role not only in reducing local recurrence rates of locally advanced rectal cancer in combination with radical surgery but also in allowing less invasive local excision with curative intent for adenocarcinomas at an earlier stage. The effect of RT on pathologic findings and, consequently, on the occurrence of down-staging in rectal cancer depends on total dose, fraction size, and interval between the beginning of RT and the day of surgery, which

is called the overall treatment time. There are 2 schedules of preoperative RT in the treatment of rectal cancer: a conventional RT (50 Gy in 25-28 fractions twice a week) and a short-course RT (25 Gy in 5 daily fractions). The optimal fraction, timing of surgery, and best use of concomitant chemotherapy remain controversial 27 and 28. The schedule most commonly used in RT is 1.8 or 2 Gy given twice a week in 25 to 28 fractions or LCRT. On the other hand, as demonstrated by the Swedish rectal cancer trial, only SCRT (5 Gy in 5 daily fractions) was associated with improved disease-free and overall survival in addition to an increased local control. However, SCRT may induce higher early and late morbidity than LCRT (29). The Stockholm Colorectal Cancer Study Group completed a further multicenter randomized trial to address these issues (30). Patients with primarily resectable rectal cancer were randomized to receive SCRT followed by surgery within 1 week or after 4 to 8 weeks, or to receive LCRT followed by surgery after 4 to 8 weeks. Apparently both groups who underwent surgery at least 4 weeks after RT had lower and comparable rates of complications and reoperations, whereas patients in the SCRT group who underwent surgery immediately had higher rates of complications. The conclusion is that the increased morbidity rate depends not on the way RT is administered but on the time lapsed between RT and surgery. This randomized trial as well as other nonrandomized studies (26) suggested that the rate of pathologically complete response observed after SCRT and delayed surgery is not significantly different compared to conventionally fractioned chemoradiation.

Conclusions

The present pilot study of SCRT followed by TEM aimed to verify at a minimum follow-up of 3 years the good oncologic results previously reported with LCRT followed by TEM, reducing discomfort for the patient. Unfortunately the very high complication rate, consisting of suture dehiscence and severity of 2 cases of enterocutaneous fistula, convinced us to stop the recruitment. The high complication rate severely affected QoL of patients whose QoL score was similar to that in TME and much worse than those in both the LCRT-TEM and TEM groups. Both posterior location and the proximity to the anal verge seem to be potential risk factors for dehiscence, although the difference was not statistically significant. Unfortunately, the small number of patients and the short follow-up do not allow any definitive conclusion regarding the correct timing.

References

1.

P.G. Doornebosch, R.A. Tollenaar, M.P. Gosselink, *et al.*

- Quality of life after transanal endoscopic microsurgery and total mesorectal excision in early rectal cancer
- Colorectal Dis, 9 (2007), pp. 553–558

2.

- G. Buess, F. Hutterer, J. Theiss, *et al.*
- A system for a transanal endoscopic rectum operation
- Chirurg, 55 (1984), pp. 677–680 [in German]

3.

- T.J. Saclarides
- TEM/local excision: Indications, techniques, outcomes, and the future
- J Surg Oncol, 96 (2007), pp. 644–650

|

4.
- P.F. Middleton, L.M. Sutherland, G.J. Maddern
- Transanal endoscopic microsurgery: A systematic review
- Dis Colon Rectum, 48 (2005), pp. 270–284

5.
- F. Bretagnol, A. Merrie, B. George, *et al.*
- Local excision of rectal tumours by transanal endoscopic microsurgery
- Br J Surg, 94 (2007), pp. 627–633

6.
- H. Schafer, S.E. Baldus, A.H. Holscher
- Giant adenomas of the rectum: Complete resection by transanal endoscopic microsurgery (TEM)
- Int J Colorectal Dis, 21 (2006), pp. 533–537

7.
- M. Guerrieri, M. Baldarelli, M. Morino, *et al.*
- Transanal endoscopic microsurgery in rectal adenomas: Experience of six Italian centres
- Dig Liver Dis, 38 (2006), pp. 202–207

8.
- J.M. McCloud, N. Waymont, N. Pahwa, *et al.*
- Factors predicting early recurrence after transanal endoscopic microsurgery excision for rectal adenoma
- Colorectal Dis, 8 (2006), pp. 581–585

9.
- P.A. Whitehouse, H.S. Tilney, J.N. Armitage, *et al.*
- Transanal endoscopic microsurgery: Risk factors for local recurrence of benign rectal adenomas
- Colorectal Dis, 8 (2006), pp. 795–799

10.
- C. Cocilovo, L.E. Smith, T. Stahl, *et al.*
- Transanal endoscopic excision of rectal adenomas
- Surg Endosc, 17 (2003), pp. 1461–1463

11.
- B. Martin-Perez, G.D. Andrade-Ribeiro, L. Hunter, *et al.*
- A systematic review of transanal minimally invasive surgery (TAMIS) from 2010 to 2013
- Tech Coloproctol, 18 (2014), pp. 775–788

12.
- E. Lezoche, M. Baldarelli, G. Lezoche, *et al.*
- Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy
- Br J Surg, 99 (2012), pp. 1211–1218

13.
- J.H. Marks, E.B. Valsdottir, A. DeNittis, *et al.*
- Transanal endoscopic microsurgery for the treatment of rectal cancer: Comparison of wound complication rates with and without neoadjuvant radiation therapy
- Surg Endosc, 23 (2009), pp. 1081–1087

14.
- K. Bujko, P. Richter, M. Kołodziejczyk, *et al.*
- Preoperative radiotherapy and local excision of rectal cancer with immediate radical re-operation for poor responders
- Radiother Oncol, 92 (2009), pp. 195–201

15.
- E. Kapiteijn, E.K. Kranenbarg, W.H. Steup, *et al.*
- Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer. Prospective randomised trial with standard operative and histopathological techniques. Dutch ColoRectal Cancer Group
- Eur J Surg, 165 (1999), pp. 410–420

16.
- D. Petterson, B. Cedermark, T. Holm, *et al.*
- Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer
- Br J Surg, 97 (2010), pp. 580–587
-

17.
- R.G. Beets-Tan, G.L. Beets
- Local staging of rectal cancer: A review of imaging
- J Magn Reson Imaging, 33 (2011), pp. 1012–1019

18.
- D. Dindo, N. Demartines, P.A. Clavien
- Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey
- Ann Surg, 240 (2004), pp. 205–213

19.
- P.M. Fayers, N.K. Aaronson, K. Bjordal, EORTC Quality of Life Group, *et al.*
- The EORTC QLQ-C30 Scoring Manual
- (3rd ed.)European Organisation for Research and Treatment of Cancer, Brussels (2001)

20.
- J.M.N. Jorge, S.D. Wexner
- Etiology and management of fecal incontinence
- Dis Colon Rectum, 36 (1993), pp. 77–97

21

- International Commission on Radiation Units and Measurements
- ICRU report 83: Prescribing, recording, and reporting photon-beam intensity-modulated radiation therapy (IMRT)
- J ICRU, 10 (2010)

22

- A.M. Mandard, F. Dalibard, J.C. Mandard, *et al.*
- Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations
- Cancer, 73 (1994), pp. 2680–2686

23

- S. Higaki, S. Hashimoto, K. Harada, *et al.*
- Long-term follow-up of large flat colorectal tumors resected endoscopically
- Endoscopy, 35 (2003), pp. 845–849

24

- M. Morino, M.E. Allaix, M. Caldart, *et al.*
- Risk factors for recurrence after transanal endoscopic microsurgery for rectal malignant neoplasm
- Surg Endosc, 25 (2011), pp. 3683–3690

25

- G. Lezoche, M. Baldarelli, M. Guerrieri, *et al.*
- A prospective randomized study with a 5-year minimum follow-up evaluation of transanal endoscopic microsurgery versus laparoscopic total mesorectal excision after neoadjuvant therapy
- Surg Endosc, 22 (2008), pp. 352–358

26

- C. Coco, G. Rizzo, C. Mattana, *et al.*
- Transanal endoscopic microsurgery after neoadjuvant radiochemotherapy for locally advanced extraperitoneal rectal cancer: Short-term morbidity and functional outcome
- Surg Endosc, 27 (2013), pp. 2860–2867

27

- K. Bujko, M.P. Nowascki, A. Nasierowska-Guttmejer, *et al.*
- Sphinter preservation following preoperative radiotherapy for rectal cancer: Report a randomized trial comparing short-term radiotherapy vs conventionally fractionated radiochemiotherapy
- Radiother Oncol, 72 (2004), pp. 15–24

28

- B.D. Minsky, A.M. Cohen, N. Kemeny, *et al.*
- Combined modality therapy of rectal cancer: Decreased acute toxicity with the preoperative approach
- J Clin Oncol, 10 (1992), pp. 1218–1224

29

- E. Kapiteijn, C. Marijnen, I.D. Nagtegaal, *et al.*
- Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer
- N Engl J Med, 345 (2001), pp. 638–646

- 30
- D. Pettersson, B. Glimelius, H. Iversen, *et al.*
- Impaired postoperative leucocyte counts after preoperative radiotherapy for rectal cancer in the Stockholm III trial
- Br J Surg, 100 (2013), pp. 969–975