Original article

Multicentre study of short-course radiotherapy and transanal endoscopic microsurgery for early rectal cancer

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Background: **Organ-preserving treatment for early-stage rectal cancer may avoid the substantial perioperative morbidity and functional sequelae associated with total mesorectal excision (TME). The initial results of an organ-preserving approach using preoperative short-course radiotherapy (SCRT) and transanal endoscopic microsurgery (TEMS) are presented.**

Methods: **Patients with cT1–2N0 rectal cancers staged using high-quality MRI and endorectal ultrasonography received SCRT, with TEMS 8–10 weeks later, at four regional referral centres between 2007 and 2013. Patients were generally considered high risk for TME surgery (a small number refused TME).**

Results: **Following SCRT and TEMS, 60 (97 per cent) of 62 patients had an R0 resection. Histopathological staging identified 20 ypT0 tumours, 23 ypT1, 18 ypT2 and one ypT3. Preoperative uT category was significantly associated with a complete pathological response, which was achieved in 13 of 27 patients with uT0/uT1 disease and in five of 29 with uT2 ($P = 0{\cdot}010$). Acute complications affected 19 patients, the majority following TEMS. No fistulas occurred and no stomas were formed. Surveillance detected four intraluminal local recurrences at a median follow-up of 13 months, all in patients with tumours staged as ypT2. Salvage TME achieved R0 resection in three patients and a stent was placed in one patient owing to co-morbidities.**

Conclusion: **SCRT with TEMS was effective in the majority of patients considered high risk for (or who refused) TME surgery.**

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Introduction

Historically, only a minority of rectal tumours (less than 8 per cent) were detected at an early stage (T1–2 N0 M0), but introduction of bowel screening has resulted in a marked stage shift. By 2009, early-stage disease constituted 25 per cent of all newly diagnosed rectal cancers in the UK[1]. Standard total mesorectal excision (TME) surgery is an oncologically effective treatment for early-stage rectal cancer; only 2 and 12 per cent of patients experience local or distant failure respectively[2]. Unfortunately, treatment-related morbidity and mortality are substantial[3–6]. Early diagnosis through screening provides an opportunity to evaluate the role of potentially less harmful 'organ-sparing' treatments[7]. A key research question is whether standard TME for early rectal cancer can be replaced by a strategy of organ-preserving surgery, with salvage surgery reserved for episodes of pelvic relapse.

A number of transanal surgery platforms exist, such as transanal endoscopic microsurgery (TEMS) for precise local excision of small rectal cancers[8]. TEMS alone (without radiotherapy) is associated with reduced morbidity and mortality compared with radical surgery, but the risk of pelvic relapse is substantially higher[9–11]. Preoperative external-beam radiotherapy is proven to reduce the rate of pelvic tumour relapse when used in conjunction with radical surgery[12–14]. By combining external-beam chemoradiotherapy (CRT) with TEMS for early-stage disease, promising improvements in disease control have

been reported in non-randomized phase II studies[15–18], but CRT-related toxicity has proven problematic.

Two randomized trials[19,20] have shown no difference in the oncological effectiveness of short-course radiotherapy (SCRT) and CRT when using standard surgery to treat resectable rectal cancer. SCRT benefits from reduced acute toxicity compared with CRT and may be a more appropriate treatment for individuals with early-stage rectal cancer[19]. A recent single-centre cohort study[21] abandoned evaluation of SCRT and TEMS because of a high rate of rectal suture-line dehiscence (50 per cent), and perineal fistulation in two of 14 patients. Treatment-related complications are a particular concern in frail or elderly individuals who have diminished physiological reserve[3,22]. The present multicentre cohort study evaluated SCRT and TEMS in patients with early rectal cancer considered high risk for TME. The aim was to determine early clinical and histopathological outcomes following SCRT and TEMS.

Methods

Four tertiary regional referral centres participated in this retrospective cohort study (Queen Elizabeth Hospital, Good Hope Hospital and Heart of England Foundation Trust, Birmingham; Manchester Royal Infirmary, Christie Hospital, Manchester; Bradford Royal Infirmary, Leeds Teaching Hospital Trust, Leeds/Bradford; St Richard's Hospital, Portsmouth Hospital NHS Trust, Chichester). Patients referred for organ-preserving treatment were generally considered high risk for TME surgery owing to either frailty or co-morbidity. A small number of patients were fit but had refused TME. Patients were identified from prospectively collated TEMS registries at each site[9]. All eligible patients were included up to the point that the Cancer Research UK TREC (Transanal Endoscopic Microsurgery and Radiotherapy in Early Rectal Cancer) study opened[23]. Eligibility criteria comprised: biopsy-proven adenocarcinoma within 15 cm of the anal verge on rigid proctoscopy; clinical stage T1 or T2 N0 M0; maximum tumour diameter less 5 cm; multidisciplinary team considered patient high risk for standard TME surgery, or individual unwilling to consent to TME surgery; and treatment comprised SCRT (5 × 5 Gy) and delayed local excision, 8–10 weeks later with TEMS. Factors that precluded patients from either radiotherapy or TEMS constituted exclusions, such as previous pelvic irradiation.

Clinical staging

Staging investigations comprised digital rectal examination, proctoscopy, endorectal ultrasonography (ERUS), MRI, and CT of the chest, abdomen and pelvis[24]. In addition, tumour position was marked using an ink tattoo.

Radiotherapy

A total dose of 25 Gy was delivered in five fractions over 5 consecutive days, using a three- or four-field plan. Clinical target volume was determined by tumour position, but incorporated mesorectal, presacral, internal iliac and obturator nodes. The upper field border was between the S2/3 junction and the sacral promontory.

Surgical treatment

TEMS was recommended for all patients 8–10 weeks following completion of radiotherapy, allowing time for tumour regression (*Fig. 1*). TEMS was used to verify instances of complete clinical response. Supervising surgeons had performed more than 30 TEMS procedures for benign and malignant disease. TEMS aimed to remove the tumour or residual scar, with a 1-cm margin of normal mucosa. The full thickness of the bowel wall was excised incorporating a thin layer of mesorectal fat. The mesorectum was not formally resected. The surgical defect was irrigated using cetrimide and chlorhexidine gluconate or distilled water, and closed where achievable using a continuous absorbable suture.

Histopathology

Lesions were pinned out in the operating room, mucosal surface upwards, and then placed tissue down in formalin for 48 h. Margins were identified with ink/gelatin markers. The whole specimen was sectioned transversely into 3-mm slices and submitted for histology in sequentially labelled cassettes. Representative areas of the tumour were sampled with a minimum of five blocks. Tumour dimensions were measured on the slides. TNM version 5 staging was used[25]. Margin involved by cancer was defined as tumour within 1 mm of any surgical incision. If no residual tumour was recognized on microscopic examination of five tissue blocks at three levels, the whole tumour specimen was blocked for histology and three levels were taken from each block.

Surveillance

As patients were considered high risk for TME or had refused the procedure, histopathological stratification did not select for conversion to TME. Patients were observed following TEMS irrespective of histopathological findings. Follow-up aimed to deliver high-quality MRI of

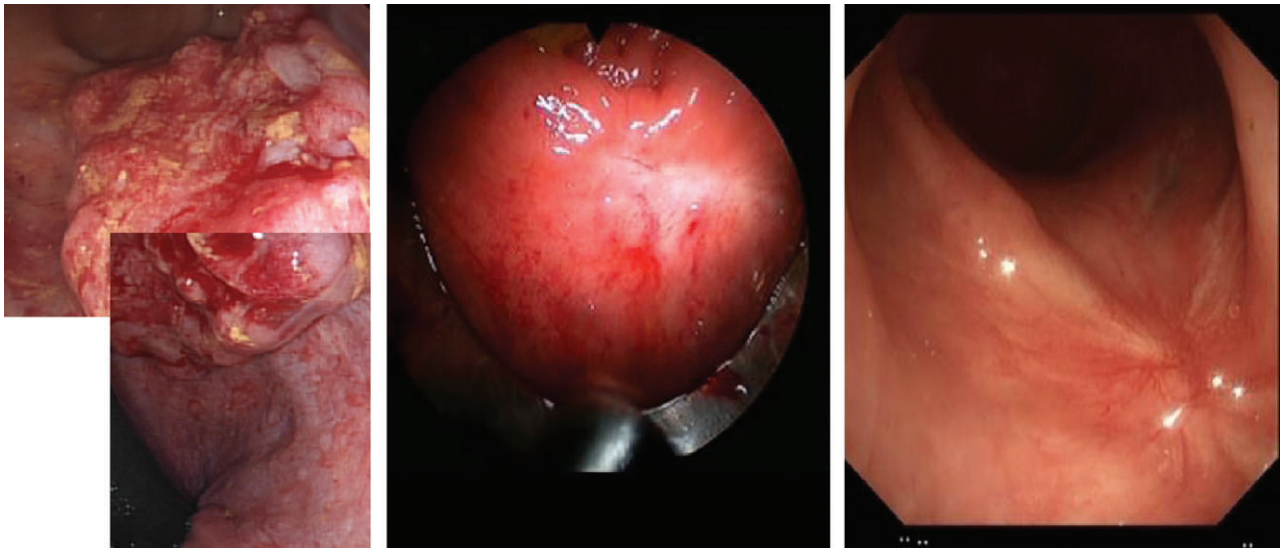

Fig. 1 Treatment of mrT2 low rectal cancer using 5 × 5-Gy radiotherapy followed by transanal endoscopic microsurgery (TEMS) 10 weeks later. **a** Retroflexed colonoscopic view of low rectal tumour. **b** Appearance 10 weeks after radiotherapy (before TEMS) showing resolution of all macroscopic tumour with a flat white scar (complete clinical response). **c** Appearance 1 year after TEMS (histology confirmed complete pathological response)

the pelvis combined with endoluminal assessment by flexible sigmoidoscopy every 6 months. By alternating these modalities, at least one assessment was made every 3 months. CT of the chest, abdomen and pelvis was performed annually in the first 2 years. Recurrence was defined as biopsy-proven adenocarcinoma or radiological evidence of systemic disease.

Results

A total of 62 patients (40 men and 22 women) with rectal cancer staged cT1–2 N0 received SCRT and TEMS between 2007 and 2013 (*Table 1*). Median age was 75 years, and 37 per cent of patients had an American Society of Anesthesiologists fitness grade of III or IV. Most patients were elderly and considered frail, although some were comparatively younger with substantial co-morbidity. Three patients were neither unfit nor frail but refused primary TME. It was on this basis that patients were referred to the regional units for consideration of SCRT and TEMS as an alternative to primary TME.

Preoperative clinical staging

Median maximum tumour diameter was 20 (i.q.r. 15–32) mm and median distance from the anal verge was 60 (40–80) mm. Imaging data were available for analysis in 60 patients (97 per cent). ERUS predicted that two tumours were uT0, 25 uT1, 29 uT2 and one uT3 (57 patients evaluated). MRI predicted that two tumours were mrT0, six mrT1, 45 mrT2 and three mrT3a (56 patients evaluated). No disease was assessed as T3 using both ERUS and MRI. Of 53 patients assessed jointly using ERUS and MRI, T category concurred in 26 of 53 tumours, of which 22 of 26 were cT2.

Delivery of organ-preserving treatment

The interval from completion of SCRT to TEMS was at least 8 weeks in 61 of 62 patients (range 4–14 weeks). One patient (the first to be treated) had a shorter planned interval of 4 weeks. Intercurrent illness caused postponement of TEMS until 14 weeks in one patient. TEMS was performed using general anaesthesia in 60 patients, whereas two received a spinal anaesthetic.

Acute treatment-related toxicity

Radiotherapy was well tolerated, with no deaths and no episodes of hospital admission. Three patients experienced persistent radiation-induced proctitis. In all, 19 patients (31 per cent) developed an acute complication of treatment. The majority of morbidity followed TEMS

Table 1 Patient demographics and tumour characteristics

	No. of patients* ($n = 62$)
Age (years)†	75 (51–94)
Sex ratio (M : F)	40 : 22
ASA fitness grade	
I	7 (11)
II	32 (52)
III	20 (32)
IV	3 (5)
Maximum tumour diameter (mm)†	20 (4–55)
Distance from anal verge (mm)†	60 (10–120)
ERUS T category	
uT0	2 (4)
uT1	25 (44)
uT2	29 (51)
uT3	1 (2)
Missing/not done	5
MRI T category	
mrT0	2 (4)
mrT1	6 (11)
mrT2	45 (80)
mrT3	3 (5)
Missing/not done	6

*With percentages in parentheses unless indicated otherwise; †values are median (range). ASA, American Society of Anesthesiologists; ERUS, endorectal ultrasonography.

surgery (*Table 2*). One patient experienced an intraoperative myocardial infarction. Symptomatic suture-line dehiscence occurred in eight patients, leading to severe urgency and frequency of defaecation. Symptoms typically lasted 8 weeks until healing occurred by secondary intention. Another 12 patients experienced looseness, urgency and soiling without evidence of suture-line dehiscence, whereas three complained of rectal pain. Most morbidity resolved with simple medical measures, including antidiarrhoeal agents and antibiotics for instances of suture-line dehiscence. No patient was returned to the operating theatre and no stomas were formed. There were no deaths within 30 days.

Chronic treatment-related toxicity

Long-term complications, beyond 12 months, occurred in six patients (*Table 2*). These included refractory radiation-induced proctitis, urgency, anorectal pain, non-compliant rectum with faecal soiling and persistent confusion. To date no patient has required a stoma.

Histopathological stage following radiotherapy and endoscopic microsurgery

Histopathological T category following SCRT and TEMS was ypT0 for 20 patients (32 per cent), ypT1 for 23 (37 per cent), ypT2 for 18 (29 per cent) and ypT3 for one patient (*Table 3*). R0 resection (tumour margin greater than 1 mm) was achieved in 60 patients (97 per cent). In two patients tumour encroached within 1 mm of the deep surgical margin. One patient demonstrated early T3 invasion with poor differentiation and intramural lymphatic invasion (MRI and ERUS had both indicated T2 disease). The patent was advised to consider low anterior resection, but instead opted for Papillion contact radiotherapy and died (disease-free) from myocardial infarction 14 months later.

Table 2 Treatment-related toxicities

	Acute toxicity	Chronic toxicity
Radiotherapy proctitis	3	1
Surgical		
Suture-line dehiscence	8	0
Soiling, urgency, diarrhoea	12	3
Anorectal pain	3	1
Medical		
Myocardial infarction	1	0
Confusion	0	1
Total no. of patients	19 (31)	6 (10)

Values in parentheses are percentages. Acute, measured up to 30 days; chronic, beyond 6 months.

Pretreatment stage and likelihood of pathological complete response

Preoperative uT category was significantly associated with a pathological complete response (pCR): 13 of 27 tumours classified as uT0/uT1 but only five of 29 classified as uT2 achieved a pCR ($P = 0{\cdot}010$, ANOVA). It was notable that mrT category was not associated with radiotherapy response ($P = 0{\cdot}130$).

Tumour recurrence

With median follow-up of 13 (range 2–48) months, a total of seven patients (11 per cent) were diagnosed with recurrent rectal cancer (*Table 3*). Local recurrence occurred in four patients (6 per cent), isolated in three and combined with liver metastases in one. All episodes of local recurrence were intraluminal. There were no instances of isolated mesorectal lymph node recurrence. All four local recurrences involved cT2 tumours that had not responded well to radiotherapy, whereas two of four displayed additional high-risk features: predominantly poor differentiation and R1 margin. Of six poorly differentiated tumours in this cohort, three recurred. Importantly no local recurrence developed in patients with ypT0 or ypT1 tumours. Three isolated systemic relapses occurred with no evidence

Table 3 Histopathological characteristics of transanal microscopic surgery specimens 10 weeks after short-course radiotherapy, and early patient outcomes

	Histopathological stage			
	pCR	ypT1	ypT2	ypT3
No. of patients	20 (32)	23 (37)	18 (29)	1 (2)
R1 resection	0	0	1	1
Local recurrence – isolated	0	0	3	0
Distant recurrence – isolated	1	1	1	0
Combined local and distant recurrence	0	0	1	0
Median follow-up (months)*	24 (2–48)	14 (5–30)	14 (4–48)	12

Values in parentheses are percentages unless indicated otherwise; *values are median (range). pCR, pathological complete response.

of pelvic recurrence on clinical examination, endoscopy or MRI.

Salvage surgery for local/luminal recurrence

Three of four patients underwent radical salvage surgery for local recurrence; one patient was considered unfit and received a stent. R0 resection was achieved in all three patients. One patient died in the perioperative period following cardiac arrest (ypT3 N0 R0). The remaining two (ypT3 N0 R0 and ypT3 N1 R0) each developed further metastasis, one local and the other distant.

Overall survival

At latest follow-up, 52 patients (84 per cent) remained alive; 48 (77 per cent) were disease-free and four (6 per cent) were alive with disease. Rectal cancer was not identified as a contributing factor in seven of ten deaths. Of three deaths attributed to rectal cancer, one patient died undergoing salvage TME surgery, one from complications of laparoscopic liver resection, and another from rapidly progressing local disease combined with pneumonia following stent insertion.

Discussion

A single-centre experience of CRT and TEMS for early-stage rectal cancer reported encouraging results[26], whereas two multicentre non-randomized phase II studies[15,16,27] reported unacceptable toxicities. American College of Surgeons Oncology Group (ACOSOG) Z6041[16,27] was abandoned as the oxaliplatin-containing CRT schedule led to 39 per cent grade 3 or higher complications. In the CARTS (Transanal Endoscopic Microsurgery After Radiochemotherapy for Rectal Cancer) study[15], two of 55 patients died as a result of CRT-related toxicity. In the present mixed population of mainly co-morbid and elderly, frail patients, SCRT and TEMS was well tolerated with no mortality. This is in contrast to the high mortality and morbidity reported for elderly patients following TME surgery[3], and a recent report[21] of SCRT and TEMS in 14 patients, where suture-line dehiscence affected 50 per cent of patients and two developed enterocutaneous fistula.

SCRT led to a pCR in one-third of patients, and a further third had minimal residual disease (ypT1). No local recurrence developed in this population, suggesting that an organ-preserving strategy may be safe. Patients were selected using tumour diameter and an absence of pathological nodes or T3 spread on MRI[28]. ERUS further refined this evaluation and was a better discriminator of cT1 *versus* cT2[29]. uT category therefore predicted pCR, whereas mrT category did not. Historical case series have generally suggested that salvage in this situation may be possible in only 50 per cent of patients[30], although a more recent study[31] suggested that salvage is generally feasible following watch and wait (as found here following TEMS).

Transanal local excision alone can cure the majority of patients with early-stage rectal cancer, with low complication rates, good postoperative bowel function and short hospital stay[9,32]. However, in all but the very earliest cancers local relapse rates are substantially higher than those after primary TME surgery[9,32,33]. External-beam radiotherapy is used in conjunction with TEMS to help combat the risk of occult mesorectal lymph node metastasis and to downsize the primary tumour, thereby diminishing the risk of tumour implantation during local excision. Selected patients may even demonstrate complete, sustained resolution of all tumour following radiotherapy alone[34,35]. Meta-analysis[36] suggests that pCR following CRT is stage-dependent, with 58 per cent of cT1, 28 per cent of cT2, 16 per cent of cT3 and 12 per cent of cT4 tumours obtaining a pCR.

Local excision with TEMS is one strategy to identify non-responders who may benefit from TME, and also to remove small pockets of residual disease that persist following external-beam radiotherapy. Brachytherapy boost is

an alternative strategy to ablate, rather than resect, residual disease. These approaches create different toxicities. Brachytherapy boost is associated with sustained bleeding at 24 months in more than 80 per cent of patients, faecal incontinence at 24 months in 25 per cent and substantial fibrosis that that can hinder salvage TME[31].

The present study suggests a benefit of SCRT and TEMS in patients at increased risk of adverse outcome from TME surgery. Looking forward it will be important to determine the risks and benefits of organ-preserving techniques in a fit patient population with early-stage rectal cancer. The phase II TREC study[23] will determine the feasibility of randomizing patients with cT1–2 N0 rectal cancer between primary TME surgery *versus* SCRT with a 10-week delay to TEMS. The new international STAR-TREC (Saving the rectum by active surveillance or TransAnal surgery after (chemo)Radiotherapy *versus* Total mesorectal excision for early Rectal Cancer) study will evaluate novel mesorectal radiation fields along with selective use of a watch-and-wait strategy as part of a three-arm design randomizing between TME surgery, and organ-preserving strategies incorporating either SCRT or CRT.

Disclosure

The authors declare no conflict of interest.

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