

## Transanal Endoscopic Microsurgery (TEM) Following Neoadjuvant Chemoradiation for Rectal Cancer: Outcomes of Salvage Resection for Local Recurrence

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### ABSTRACT

**Background.** Transanal endoscopic microsurgery (TEM) has been considered an alternative for selected patients with rectal cancer following neoadjuvant chemoradiation (CRT). Immediate total mesorectal completion for all patients with unfavorable pathological features would result in unnecessary proctectomies in a significant proportion of patients. Instead, salvage total mesorectal excision (TME) could be restricted for patients developing local recurrence. The aim of the present study is to determine oncological outcomes of salvage resection for local recurrences following CRT and TEM.

**Methods.** Consecutive patients undergoing TEM following neoadjuvant CRT for rectal cancer were reviewed. Patients with “near” complete response to CRT ( $\leq 3$  cm; ycT1-2N0) were offered TEM. Salvage surgery was attempted in the event of a local recurrence.

**Results.** A total of 53 patients were managed by CRT followed by TEM. Unfavorable pathological features were present in 36 patients (68 %). None of the patients underwent immediate completion TME. There were 12 patients who developed local recurrence resulting in a 2-year local recurrence-free survival of 77 % (95 % CI, 53–100 %). Of these patients, 9 developed exclusively local recurrences, and all had at least 1 unfavorable pathological feature in the specimen after TEM (100 %). Eight patients (8 of 9)

underwent salvage resection (abdominoperineal resection [APR] in 87 %) with CRM+ in 7 of 8 patients (87 %). Four patients developed local re-recurrence after a median 36 months of follow-up. The 2-year local re-recurrence free survival was 60 %.

**Conclusions.** Salvage resection for local recurrence following CRT and TEM is associated with high rates of R1 resection (CRM+) and local re-recurrence. Immediate completion of TME should be considered for patients with unfavorable pathological features after TEM.

Neoadjuvant chemoradiation (CRT) may result in tumor regression in a significant proportion of patients.<sup>1</sup> In this setting, organ-preserving strategies have been considered in selected patients in order to avoid the functional consequences of total mesorectal excision (TME) depending on baseline staging and response to CRT.<sup>2–5</sup>

Full-thickness local excision with the use of transanal endoscopic microsurgery (TEM) after CRT has become an attractive option since it provides a more appropriate specimen for pathology examination when compared with standard transanal approaches.<sup>6</sup> However, in a significant proportion of patients initially considered to be ideal candidates for TEM following CRT, the presence of unfavorable pathological features at the TEM specimen may ultimately be revealed. In the presence of such features, the risk of residual mesorectal metastases may be quite significant, increasing substantially the risk of local recurrence.<sup>7,8</sup> Therefore, in the presence of unfavorable pathological features, patients could be offered immediate prophylactic TME and proctectomy (also known as completion TME).<sup>9,10</sup> However, a number of patients may have

no residual mesorectal disease, despite the presence of unfavorable pathological features, suggesting that completion TME and proctectomy would be unnecessary.

Alternatively, even patients with unfavorable pathological features in the TEM specimen could undergo strict follow-up instead of prophylactic or completion TME. In this case, patients who eventually develop local recurrences would then be managed by salvage TME resection at the time of recurrence detection. This strategy could avoid a significant number of unnecessary proctectomies. On the other hand, some patients would be at risk for developing unresectable local recurrences or R1 salvage TME specimens after late local recurrence.

In this setting, we decided to study the surgical and oncological outcomes of patients managed by salvage TME resection at the time of local recurrences following CRT and TEM.

## PATIENTS AND METHODS

All patients in a single-center institution (Angelita and Joaquim Gama Institute) with nonmetastatic distal rectal adenocarcinoma located no more than 7 cm from the anal verge were eligible for the study. Patients were clinically assessed (digital rectal examination and rigid proctoscopy) by two experienced colorectal surgeons and radiologically staged at baseline using high-resolution magnetic resonance (MR) or endorectal ultrasound (ERUS). All patients with cT2-4N0-2M0 underwent neoadjuvant chemoradiation. Specifically, patients with cT2N0 only received neoadjuvant CRT if otherwise abdominal perineal excision or ultralow anterior resection was required. Briefly, neoadjuvant CRT consisted of 50.4–54 Gy of radiation delivered in a 6-week period and concomitant 5FU-based chemotherapy. Following at least 8 weeks from CRT completion, patients were reassessed for tumor response both clinically and radiologically using identical studies used at baseline assessment.<sup>11</sup>

Patients with clinical and radiological evidence of complete clinical response to CRT were offered no immediate surgery and strict follow-up (watch and wait strategy).<sup>11</sup> These patients were excluded from the study and are reported elsewhere.<sup>12,13</sup>

Patients with incomplete clinical response but with small residual suspicious lesions of  $\leq 3$  cm in diameter, restricted to the bowel wall after radiological assessment (ycT1-2), no evidence of nodal metastases (ycN0), and otherwise requiring APR or ultralow anterior resection were offered full-thickness local excision using TEM.

Patients with incomplete clinical responses ( $\geq 3$  cm in diameter) or radiological evidence of transmural invasion (ycT3 or more) or nodal metastases (ycN+) were recommended radical surgery including total mesorectal excision.

## Surgery

Resections were performed under general anesthesia exclusively by two colorectal surgeons together. Resection limits were based on the residual mucosal abnormality (not on the original lesion) with marking of a 1-cm margin laterally prior to incision. Depth of resection always attempted to reach the mesorectal fascia in order to achieve maximal radial margin clearance. Closure of the rectal defect was always attempted as described elsewhere.<sup>8</sup>

## Pathology

All specimens were fixed on a cardboard with clear indication of laterality and sent to two dedicated gastrointestinal pathologists. Specimens were colored for individual margin examination (lateral and radial) and then sliced into 5-mm sections for microscopic examination. Pathological features were annotated following a standardized checklist including ypT status, maximal diameter, closest lateral margin, radial margin, tumor grade, lymphovascular invasion, perineural invasion, and tumor regression grade (Dworak's TRG classification system).

## Management and Follow-up

Unfavorable pathological features at TEM specimen included those associated with a greater risk of nodal or mesorectal disease: ypT2 or ypT3, poor differentiation (tumor grade), lymphovascular invasion, or perineural invasion.

Patients with any unfavorable pathological feature at TEM specimen were fully informed of the risk of residual mesorectal disease (even after an R0 resection) and were offered prophylactic radical completion TME. They were also aware of the risk of a negative specimen (no residual cancer) after completion TME. Patients that refused radical proctectomy in this setting were managed by strict follow-up and were fully advised regarding the considerably high risks of local recurrence and requirement for salvage radical resection.

None of the patients were offered adjuvant chemotherapy following TEM.

Follow-up included regular 3-month interval visits for the first 2 years and 6-month interval visits thereafter. Digital rectal examination (DRE), rigid proctoscopy, and carcinoembryonic antigen (CEA) levels were performed on every visit. Radiological imaging including high-resolution pelvic MR and abdominal/chest CT scans were performed every 6 months for the first 2 years and yearly thereafter.

Local recurrences were defined as the presence of adenocarcinoma within the rectal wall or mesorectum. Pelvic recurrences were defined as radiological masses within the

pelvis outside the rectal wall or mesorectum. Systemic recurrences were defined as radiological evidence of recurrent disease outside the pelvis.

Patients with exclusively local recurrences were offered radical salvage resection including completion of TME. Patients with concomitant unresectable metastatic disease were managed palliatively with systemic chemotherapy. In the event of concomitant resectable disease (both locally and systemically), radical salvage resection was offered for both sites after multidisciplinary discussion.

Local re-recurrence was defined as pelvic or perineal local recurrence following salvage resection.

### Statistical Analysis

Local recurrence and local re-recurrence free survival were calculated using Kaplan–Meier actuarial curves. A  $p$  value  $\leq .05$  was considered statistically significant.

## RESULTS

Overall, 53 patients underwent TEM following CRT between 2009 and 2014. Baseline and final pathological findings are available in Table 1. A total of 36 patients (68 %) had at least 1 unfavorable pathological feature at TEM specimen. None of the specimens had positive resection margins. All patients opted for strict follow-up instead of immediate completion TME following TEM after thorough discussion with surgical team. After a median follow-up of 36 months, 12 patients developed local recurrence. The 2-year local recurrence-free survival was 77 % (95 % CI, 53–100 %) (Fig. 1). Of these, 9 patients developed exclusively local recurrence deemed resectable by radiological imaging. The 2-year local recurrence-free (for exclusive local recurrences) survival was 83 % (95 % CI, 61–100 %) (Fig. 1). One of these patients was medically unfit for salvage resection after developing a nodal mesorectal recurrence after 52 months from original TEM for a ypT3 tumor. The remaining 8 patients (8 of 9; 89 %) underwent successful salvage resection after a median 7 months from original TEM resection. Operative procedures and final pathological features of salvage TME specimens are available in Table 2. Markedly, 7 patients (87.5 %) underwent APR for salvage. Of nine patients, 7 were radiologically staged as cT3 (77.8 %), and only 1 as cN+ (11.1 %) at baseline. Circumferential resection margins were positive in 7 of 8 patients (87.5 %), all patients had ypT3 (100 %), and only 2 patients had ypN+ (25.0 %) at final pathology.

Curiously, specific pathological features were observed at original TEM specimens from patients with exclusively local recurrences. There were 8 patients (of 9, 89 %) who

**TABLE 1** Baseline and TEM pathological features

N	53 (100 %)
Gender (male–female)	32–21 (60.4–39.6 %)
Age (years)	61.0 $\pm$ 12.5
Initial size (mm)	37.6 $\pm$ 12.7
Distance from anal verge (cm)	3.5 $\pm$ 1.5
Initial staging <sup>a</sup>	
cT2	21 (40.4 %)
cT3	31 (59.6 %)
cN +	7 (13.5 %)
Tumor size (after TEM) (mm)	19.7 $\pm$ 12.6
Tumor stage	
ypT0	9 (17.0 %)
ypT1	9 (17.0 %)
ypT2	23 (43.4 %)
ypT3	12 (22.6 %)
Poor differentiation	3 (5.7 %)
Lymphovascular invasion	4 (7.8 %)
Perineural invasion	8 (15.7 %)
Any unfavorable pathological feature	36 (67.9 %)
Tumor regression grade	
0	6 (11.8 %)
1	18 (35.3 %)
2	14 (27.5 %)
3	4 (7.8 %)
4	9 (17.6 %)

TEM transanal endoscopic microsurgery

<sup>a</sup> One patient did not have baseline staging information available

had ypT  $\geq$  2 (4 ypT2 and 4 ypT3 tumors), and at least 1 unfavorable pathological feature (ypT  $\geq$  2, lymphovascular invasion, perineural invasion, or poor differentiation) was present in all patients (9 of 9, 100 %).

### Re-recurrence Following Salvage

Overall, 4 patients (of 8) developed local re-recurrence after salvage resection following CRT and TEM after a median 9.5 months of follow-up. Curiously, the only patient with a negative CRM at salvage did develop local re-recurrence. The remaining 3 patients with local re-recurrence all had CRM+ specimens at salvage TME resection (75 %). Actuarial 2-year local re-recurrence free survival following salvage therapy was 60 % (95 % CI, 30–90 %) (Fig. 2).

## DISCUSSION

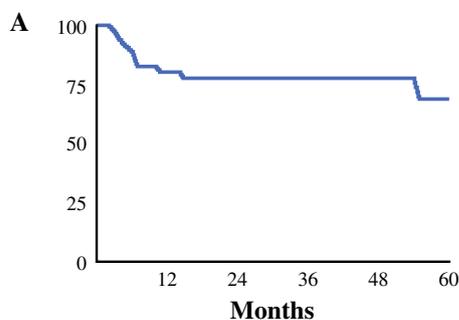
The most relevant finding of the present study is related to the results of salvage resection in patients with local

recurrence following CRT and TEM. In the present series, TME performed at the time of a local recurrence was frequently associated with CRM positivity (87.5 %). In addition, local re-recurrence rates following salvage resection were quite significant, resulting in a 2-year local re-recurrence free survival of 60 %.

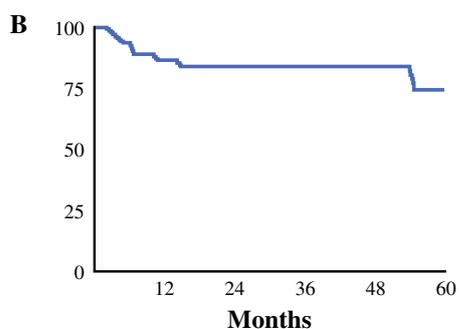
In a similar study, outcomes of patients undergoing RT or CRT followed by local excision were also analyzed. In

those who refused immediate TME completion and eventually developed local recurrences, salvage TME resulted in a R1 resection in only 12.5 % (1 of 8).<sup>10</sup> However, it should be noted that an additional four patients in that series refused or were unfit for salvage resection. In addition, re-recurrence rates were not reported.

Considering the poor outcomes of salvage for local recurrences following CRT and TEM, one could suggest the alternative of performing immediate prophylactic completion TME in the setting of unfavorable pathological features at the TEM specimen. Two case-matched studies compared TEM followed by immediate completion TME to primary TME alone (Table 3). None of the patients received preoperative CRT, and completion TME was performed only for patients with unfavorable pathological features. Results showed no differences in terms of quality of the specimen or oncological outcomes, except for the fact that previous TEM was an independent predictor for the need of APR.<sup>14,15</sup> In 1 of these studies, more than 50 % of patients undergoing immediate completion TME for unfavorable TEM pathology found no residual cancer.<sup>14</sup> Other prospective studies using RT or CRT followed by local excision and immediate TME completion of poor

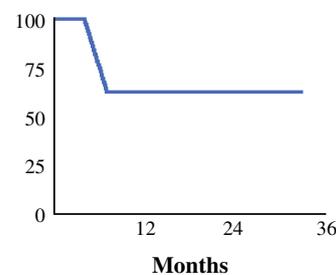


No. at risk 32 24 22 14 4



No. at risk 32 24 22 14 4

**FIG. 1 a** Local recurrence-free survival was 77 % at 2 years of follow-up (95 % CI, 53–100 %). **b** Exclusive local recurrence-free survival was 83 % (95 % CI, 61–100 %)



No. at risk 8 3 1

**FIG. 2** Local re-recurrence free survival was 60 % at 2 years of follow-up (95 % CI, 30–90 %)

**TABLE 2** Patients undergoing salvage resection for local recurrences following TEM and CRT

Patient No.	Initial staging	ypT (TEM)	LVI or PNI	Histological grade III	Any adverse feature	Interval for recurrence (months)	Path	Salvage procedure	CRM+	Re-recurrence	Interval for re-recurrence (months)
1	cT2N0	2	No	Yes	Yes	4	ypT3N0	LAR	Yes	Yes	12
2	cT3N0	2	No	No	Yes	55	ypT3N0	APR	Yes	No	–
3	cT3N0	2	Yes	No	Yes	7	ypT3N0	APR	Yes	Yes	7
4	cT3N0	1	Yes	No	Yes	7	ypT3N0	APR	No	Yes	34
5	cT3N1	3	Yes	Yes	Yes	4	ypT3N1	APR	Yes	No	–
6	cT3N0	3	Yes	No	Yes	5	ypT3N0	LAR/APR <sup>a</sup>	Yes	Yes	5
7	cT3N0	3	No	No	Yes	15	ypT3N0	APR	Yes	No	–
8	cT2N0	2	Yes	No	Yes	11	ypT3N1	APR	Yes	No	–

APR abdominoperineal resection, LAR low anterior resection, CRM circumferential resection margin, TEM transanal endoscopic microsurgery, LVI lymphovascular invasion, PNI perineural invasion

<sup>a</sup> One patient underwent LAR followed by APR due to poor functional outcome (fecal incontinence)

**TABLE 3** Reported outcomes of completion TME after local excision

Study	N	CRT	Path T stage	Type of local excision	Immediate TME completion (N/%)	No residual cancer	Positive margins (R1) (%)	Recurrence (%)
Hahnloser et al. <sup>21</sup>	37	No	pT1	Standard/polypectomy	37 (100 %)	30/37 (81 %)	NA	1
Baron et al. <sup>22</sup>	91	No	pT1-3	Standard/fulguration/polypectomy	21 (14.2 %)	5/21 (24 %)	5	21
Levic et al. <sup>15</sup>	25	No	pT1-3	TEM	25 (100 %)	10/25 (40 %)	4	4
Morino et al. <sup>14</sup>	17	No	pT1-3	TEM	17 (100 %)	9/17 (53 %)	0	NA
Pucciarelli et al. <sup>9</sup>	63	Yes	ypT1-3	Standard/TEM	11 (17.5 %)	5/11 (45 %)	NA	9
Bujko et al. <sup>10</sup>	89	Yes	ypT1-3	Standard/TEM/Kraske	8 (8.9 %)	3/8 (37.5 %)	NA	14

CRT chemoradiation therapy, TEM transanal endoscopic microsurgery, TME total mesorectal excision

responders also report no residual cancer in 37–45 % of patients (Table 3).<sup>9,10</sup> Therefore, routine completion TME after unfavorable pathological features at TEM resulted in a significant number of patients with potentially unnecessary proctectomies. In this setting, identification of predictors of local recurrence in the original TEM specimen, particularly after the use of neoadjuvant CRT, would be very helpful in identifying more accurately patients at higher risk and therefore minimizing the number of unnecessary TME completions. In our series, if patients with any unfavorable pathological feature would have undergone prophylactic completion TME, potentially all local recurrences could have been prevented. On the other hand, 27 of 36 patients (75 %) would also have undergone TME completions/proctectomies unnecessarily. Unfortunately, considering the limited sample sizes in all of these studies (including our series), a robust determination of pathological features predictive of local recurrence capable of identifying ideal patients for prophylactic completion TME is impossible.

Despite the frequent observation of no residual cancer in the resected specimen after prophylactic completion TME, oncological outcomes seem to be similar to primary TME. Positive CRM of the resected specimen is rarely observed in these patients.<sup>9,10,14,15</sup> On the contrary, salvage TME at the time of recurrence is performed for the removal of macroscopic recurrent disease in a setting where the mesorectal fascia is already disrupted due to previous TEM. This anatomical disruption caused by previous TEM may have significant clinical consequences during completion TME. A previous study has indicated that the quality of TME specimen that resulted from completion TME was significantly inferior following TEM.<sup>16</sup> Altogether, the findings of the present study indicate that performance of salvage TME after local recurrence following CRT and TEM is associated with high rates of R1 resections and poor local control rates. In this setting, one could argue that prophylactic completion TME is probably justified even if more than 50 % of immediate TME

completions result in no residual cancer at specimens. On the other hand, long-term results of TEM followed by immediate TME completion will not necessarily be associated with improved local disease control since there is a high risk for mesorectal disruption during the original TEM procedure and an optimal TME specimen (grade I) is unlikely during TME completion.<sup>16</sup>

In the present series, the majority of patients with local recurrence developed no concomitant systemic metastases. All of these patients had potentially resectable exclusively locally recurrent disease, and those medically fit for an operation actually underwent salvage resection. As previously reported, patients undergoing completion of TME after a local excision (and particularly TEM) with or without CRT frequently requires an APR.<sup>10,14</sup> In our series, nearly 90 % of patients undergoing salvage resection required an APR.

Local recurrences after local excision in rectal cancer have been mainly attributed to nodal metastases.<sup>17</sup> Therefore, one would expect a high rate of nodal positivity among those patients with local recurrence after TEM undergoing salvage radical surgery. However, in the present series only 2 patients (25.0 %) had ypN+ in the salvage TME specimens and none of the patients had cancer cells exclusively within the mesorectum. In fact, in a Polish prospective study using preoperative RT (short-course) or CRT (long-course) followed by local excision, none of the patients with local recurrences managed by radical salvage TME had residual cancer exclusively within the mesorectum—there was always disease within the rectal wall.<sup>10</sup> This observation may suggest that other foci of micrometastases within the rectal wall or even the presence of a fragmented pattern of the primary tumor (also known as tumor scatter) following CRT may be involved in tumor recurrence after full-thickness local excision of the residual mucosal abnormality.<sup>18–20</sup>

Limitations of the present study include the small number of patients with local recurrence and a relatively short follow-up. In addition, potential selection bias is

inherent to the study design and cannot be ruled out. However, the risk of 87.5 % CRM positivity after salvage resection of local recurrence following CRT and TEM is quite significant and is an important message of our study. Still, in the setting of considerably poor pathological findings and oncological outcomes, TEM not followed by immediate TME completion among patients with unfavorable pathological findings should be strongly discouraged.

In conclusion, salvage TME after local recurrence in patients undergoing CRT followed by TEM may result in high rates of R1 resections (CRM+ specimens). Even if salvage resection is feasible, local re-recurrence-free survival is considerably low (60 % at 2 years). Patients with unfavorable pathological findings in the original TEM specimen should be strongly advised to undergo immediate TME completion despite the possibility of a negative specimen and potential unnecessary proctectomy.

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