Title: Submucosal Dissection Has Advantages Over Full-Thickness Transanal Endoscopic Microsurgery In Selected Rectal Lesions

Running title: Submucosal TEM

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Abstract

Aim: To establish the incidence of unsuspected malignancy in lesions excised via transanal endoscopic microsurgery and examine the justification for full thickness excision of all lesions thought to be benign preoperatively.

Methods: Demographic, operative and pathology data of all patients undergoing TEM at a single institution were collected in a prospectively maintained database. Follow-up data were collected with a focus on polyp recurrence rates and outcome in patients found to harbour malignancy. For lesions thought to be benign preoperatively, a submucosal excision was routinely performed.

Results: TEM was attempted in 156 cases between June 1999 and April 2013. Mean (SD) patient age was 66.8(2.1) years, with 111 males. Mean tumour size was 4.1 (1.6) cm, and mean height from anal verge was 10.4 (2.1) cm. In 9 cases, the procedure was unable to be completed and in 8 cases a deliberate full thickness excision was performed. In 139 patients with a presumed benign lesion, mean operating time was 53.4 minutes. Seventeen (12.2%) were found to harbour an unsuspected malignancy. Recurrent polyp was seen in 14 (11.7%) of 122 cases of benign pathology (mean follow-up 24.5 months) and was managed by endoscopic means in 10 patients. Mean length of stay was 1.2 days and complications

occurred in 7% of cases. No patient with an unsuspected malignancy has developed recurrent disease (mean follow-up 43 months).

Conclusion: Submucosal TEM can result in low complication rates, short duration of surgery, short hospital stay and satisfactory recurrence rates when performed for presumed benign rectal tumours.

INTRODUCTION

Transanal endoscopic microsurgery (TEM) is a minimally invasive technique first introduced 30 years ago [1]. Stereoscopic imaging with magnified views and rectal insufflation enables precise local excision of rectal lesions up to 20 cm from the anal verge not accessible via traditional trans-anal methods and at the same time allows the resection of large or sessile lesions not amenable to routine endoscopic removal.

Although developed and initially used primarily for rectal adenomas, TEM is also being considered as a minimally invasive alternative for early (T1/2) rectal cancers. However, there is still debate as to whether TEM alone provides similar outcomes to the current gold standard for rectal cancers, which is total mesorectal excision (TME). Evolving evidence suggests that with careful selection and possible incorporation of neoadjuvant or adjuvant chemoradiotherapy this may be the case [2]. The minimally invasive approach of TEM with decreased operative time and post-operative stay with low complication rates suggests many advantages to TME, which is associated with considerable morbidity and mortality. Nevertheless, until there is more conclusive evidence defining the role of TEM in early rectal cancers, many surgeons choose to use TEM generally for the treatment of rectal adenomas.

With respect to the treatment of benign adenomatous lesions, some controversy exists as to whether to perform a submucosal or full thickness TEM excision. Proponents quote the incidence of unrecognised malignancy as justification for full thickness excision in all cases

thought preoperatively to be benign [3], but it seems likely that this is associated with a longer hospital stay and complication rate when compared to submucosal excision [4,5]

This study aims to establish the incidence of unsuspected malignancy in lesions excised via transanal endoscopic microsurgery and to examine the justification for full thickness excision of all lesions thought to be benign preoperatively by examining the outcome following submucosal excision of such lesions.

METHODS

Patients referred for consideration of TEM excision of rectal lesions were seen by a single surgeon to assess suitability. Patients were assessed by history, examination and rigid sigmoidoscopy (to determine lesion level and quadrant, macroscopic appearance and to assess sphincter integrity). All patients underwent full colonoscopy and biopsy of the index rectal tumour. Initially, patients also underwent ERUS by an experienced colorectal surgeon but this practice was ceased later in the series. MRI staging was not routinely used if the lesion was thought benign. If there was clinical, biopsy or ERUS suggestion of malignancy, the preferred management was for referral for radical surgery, except in very high risk patients. This series therefore largely represents patients thought to harbour benign tumours suitable for local excision.

All procedures were performed by a single consultant colorectal surgeon based at a major tertiary hospital. All patients underwent mechanical bowel preparation and received prophylactic intravenous antibiotics at induction. Initially, procedures were performed with the patient positioned such that the lesion was placed dependently but after the first year, all procedures (irrespective of lesion quadrant) were performed in the prone position due to the more stable pneumo-rectum so produced. A standardised microsurgical technique based on the original method described by Buess et al [1] was performed using diathermy dissection in the submucosal plane with a macroscopically clear margin of normal mucosa. Identification of the plane was aided by submucosal injection of adrenaline in saline (1;100,000). . Procedures were planned as overnight stay only with discharge planned on the first

postoperative day. All patients were reviewed in the clinic at 3 months to assess continence and to perform rigid sigmoidoscopy to exclude early recurrence. They were then referred back to the referring practitioner for endoscopic follow-up according to their preferences.. The last date of endoscopic assessment that could be documented was regarded as the last point of follow-up. No assumptions regarding absence of disease were made beyond this point. All patients with malignancy were followed up according to a unit specific protocol (3 monthly CEA for 2 years, six monthly thereafter, CT chest abdomen and pelvis at 12 and 24 months postop, colonoscopy at 12 months and 4 years postop).

A prospective database of all patients undergoing TEM for any indication was maintained from 1999 to 2014. Data collected included patient demographics, tumour level and quadrant, whether the tumour was index or recurrent, operative details, postoperative complications and length of stay. Practitioners responsible for follow-up were contacted in late 2014 for details of endoscopy outcomes during follow-up, in particular evidence of local recurrence of the index polyp. Where required, a retrospective review of patient records was performed to populate all data.

Statistical analysis was performed using GraphPad Prism (Version 6.02, GraphPad Software Inc. La Jolla, California, USA). Data is presented as mean (± SEM). Comparative statistical analysis was performed using the independent t-test or Fisher's Exact Test as appropriate. Significance was set at the conventional 5% level.

RESULTS

A total of 156 TEM were attempted on rectal lesions between June 1999 and April 2014. The mean age of patients was 66.8 (2.1) years, with 111 males.. Twenty eight patients had a history of prior polyp disease elsewhere in the colon and in 34 cases, the lesion in the rectum was a recurrent index polyp. Pre-operative ERUS was performed in 53 (29%) patients. The lesion was not seen at ERUS in 10 cases, was thought to be uT0 in 41 and uT1 in 2 cases. All tumours were located in the mid or upper rectum. In 8 cases, deliberate full thickness local excisions were performed (small cancer n = 3, scar excision for malignant polyp n = 1, carcinoid tumour n = 4). In 9 cases the procedure was unable to be completed (internal prolapse making the lesion impossible to visualise n= 6, hitherto unsuspected cancer n = 1, lesion deemed too large and proceeded to radical surgery, n = 1 and early intraoperative perforation requiring open surgery, n = 1). This left a group of 139 patients who underwent TEM excision of their rectal tumour for presumed adenomata which forms the study group of interest. This group was analysed both as a total group (n =139) and as those with confirmed adenomata on histology post TEM and those in whom histology revealed an unsuspected carcinoma.

Demographic and tumour details for these groups are shown in Table 1. There were no significant differences between those patients with adenomata or those with unsuspected malignancy. Operative details are given in Table 2. Mean duration of procedure was 53.4 (45) minutes and specimens were considered completely excised histologically in 39.5 % of cases. New post-operative faecal incontinence was noted in 6 patients (4.3%).

One hundred and twenty two of the 139 patients with presumed adenomata were discharged without complication on day one postoperatively. Mean length of stay was 1.2 (0.1) days with a median of 1.0 days. Complications occurred in 8 patients (chlorhexidine anaphylaxis n=1, intraoperative perforation successfully sutured n = 2, postoperative myocardial infarction n=1, urinary retention n=1, reactionary bleed n = 2, a 6 day delay in discharge due to social reasons n = 1) . Including the case of early intraoperative perforation mentioned above, the overall complication rate was 7%. Only one patient required return to theatre (one of the patients with reactionary bleed). There was one patient who developed a mild rectal stenosis at 12 months after excision of a 7 cm mid rectal polyp but this was managed conservatively and did not require endoscopic or surgical intervention.

Histopathology of the TEM specimens revealed benign pathology in 122 cases, comprising tubulovillous adenoma (TVA) in 87 cases,, tubular adenoma (TA) in 10 cases, villous adenoma (VA) in 21 cases and serrated adenoma or hyperplastic polyp in 4 cases. Mean follow-up for this group was 24.5 months (range 3 – 144 months) with 2 patients lost to follow-up. Adenomatous tissue recurred at the site of TEM excision in 14 (11.7%) of cases. Recurrent adenoma was managed by colonoscopic excision in 7 cases, redo TEM in 3 cases and required either low anterior or ultra low anterior resection in 2 cases. In one case with a recurrent polyp in a rectal stump post Hartmann procedure, recurrence post TEM excision was thought to best be managed with a completion proctectomy (APR). In one other case,

recurrent polyp with significant incontinence attributed to radiation injury post treatment for prostate cancer necessitated APR. None of these cases have required further intervention.

Preoperatively unrecognised carcinoma was found in 17 of the 139 presumed adenomata (12.2%). Of these, 8 patients were deemed to have had appropriate treatment (resection margins greater than 2 mm, no high risk features such as poor differentiation or lymphvascular invasion) and were managed conservatively. The remaining 9 patients were thought to require and underwent radical surgery (6 positive or suspected positive margins, two SM 2 or 3 invasion with or without lymphovascular invasion and one poorly differentiated cancer). No patient undergoing salvage radical surgery had an intraoperative specimen perforation at the TEM site (or elsewhere). Pathology details and follow-up of these patients is outlined in Table 3. At a mean follow-up of 42.7 months with no patients lost to follow-up, no patient with unsuspected carcinoma in the TEM specimen has developed recurrent disease (polyp or cancer, local or distant)

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DISCUSSION

These results suggest that submucosal TEM for the treatment of rectal adenomas is a relatively quick, safe method for rectal tumour excision with low complication rates, short hospital stay, and low recurrence rates. These results are congruent with other published case series which have been reviewed recently [4,5]. An increasing focus is the incidental finding of occult adenocarcinomas in presumed benign lesions, which range from 2.6% to as high as 18.8% [3, 5,6]. This study reports within this range (12.2%). Some previous studies have had a relatively high incidence of T2 and T3 lesions but no T3 lesions were found in our cohort, and the incidence of T2 lesions was low (5.8%) suggesting some differences in selection. There is clearly some selection bias involved in this study in the sense that patients with lesions thought to be malignant on preoperative assessment by an experienced colorectal surgeon were not managed with TEM . The observation that there were no significant differences in tumour height, size or duration of procedure between benign and malignant cases suggests that this cohort were selected similarly and the incidence of malignancy probably reflects that to be achieved in a group thought preoperatively benign.

When confronted with a rectal tumour with histologic evidence of invasive malignancy, a decision must be made as to whether the lesion might be suitable for local excision and if so, in most cases a full thickness local excision would be regarded as the standard of care. Full thickness excision, whether by standard transanal means or by TEM allows accurate assessment of the level of invasion and aids in further decision making re salvage radical surgery. However the approach to presumed benign lesions requires a balancing of the risk of

malignancy and any negative outcomes that may ensue from inadequate excision at the time of primary surgery against the potential benefits from a perhaps less morbid procedure (in this case submucosal excision) and the consequences of overtreating a significant number of patients. Submucosal TEM in this study was associated with a low (7%) rate of postoperative complications and a short length of stay (median 1 day) comparable to that reported in other studies using submucosal dissection [7,8]. This is to be compared to published studies using full thickness excision [3,9,10,11,12] where complication rates are higher (often related to sepsis and pain associated with suture line dehiscence) and length of stay is correspondingly longer. TEM full thickness excision has been reported to be more likely associated with other local complications such as intra-operative perforation [13] and post-operative rectal stenosis [11]. The risk of malignancy in this study (12.2%) means that fully 87.8% of patients would arguably have been overtreated by full thickness excision and exposed to an unnecessary rate of complications and extended hospital stay.

Recurrence of benign adenoma occurred in 11.7% of cases which is higher than that reported in many series, particularly those using full thickness excision [9,10] It is clear that the specimen produced with a submucosal excision is more fragile and fragments more easily (confirmed complete excision only seen in 39.5% of cases in this study). Despite this, the majority of recurrences could be successfully managed by local (endoscopic or TEM) reintervention. Importantly, of cases with an unsuspected cancer, no patient has recurred on extended follow-up. This is consistent with reports of the safety of early salvage surgery after TEM for rectal cancer [14,15]

One of the weaknesses of this study is the variability of the use of preoperative staging by either ERUS or MRI. It must be remembered that this is a selected group of patients with lesions thought to be benign on endoscopy by an experienced colorectal surgeon. The universal application of ERUS and or MRI to all such patients is neither practicable nor desirable in the Australian healthcare setting because of cost constraints. While both ERUS and MRI are useful tools in assessing more advanced T stage, the inability of either to reliably differentiate between T0 and early and more advanced T1 lesions means that such routine use can be called into question in this setting. A submucosal excision specimen will however often allow such distinctions to be made. It might be argued that that selection for submucosal versus full thickness excision should be done on the basis of ERUS to exclude small volume invasion. It seems illogical to the authors to treat lesions in the colon thought on clinical grounds at the time of colonoscopy to be benign by submucosal resection (polypectomy) but to treat rectal lesions similarly thought on clinical grounds to be benign in a different manner and require routine imaging.

Full thickness excision also has important implications for salvage surgery. Full-thickness excision may potentially produce weakening of the rectal wall with a compromised mesorectal plane, and increased fibrosis at the site of excision with inflammation in the peri-rectal tissue. This increases the likelihood of perforation at the site of previous TEM, reported as high as 20% [14, 15] and may be associated with poorer oncologic outcomes [14,16]. It is argued that submucosal dissection of the index polyp minimises this risk. Furthermore, full-thickness excision TEM has been associated with a higher rate of APR as salvage surgery, whereas case-matched patients were more likely to undergo sphincter-sparing procedures if

they had been offered TME in the first place [17]. In this study where lesions were treated with submucosal dissection, we report a low intra-operative perforation rate during TEM (2.1%) despite the majority (74%) of lesions being located in the antero-lateral rectum and 50% of lesions in the upper rectum (e 10cm from anal verge), which are factors associated with a higher rate of perforation [13]. Importantly, no perforations were caused during salvage surgery. There was a low rate of APR (1.4%) which was not performed in the cancer subgroup.

Full thickness excision is not without its advantages. It is useful in ensuring adequate removal in low-risk rectal cancers. However, the role of TEM in the curative management of T1/T2 rectal cancer is still not clearly defined. A review of the literature comparing TEM to primary TME in the management of T1/T2 rectal cancer suggests a higher risk of local recurrence with TEM alone [18], and recurrence rates for TEM alone have been reported as high as 20.5% for T1 [19] and 35% for T2 cancers [20]. Local excision methods such as TEM are generally not recommended for T2 and more invasive cancers, although the use of neoadjuvant/adjuvant therapy is being explored [2]. With T1 lesions however, it has been proposed that predictors of lymph node involvement and recurrence such as depth of submucosal invasion, differentiation grade, and lymphovascular invasion can be used to distinguish between low risk lesions suitable for TEM alone, and higher risk lesions requiring further treatment post TEM [21-23]. In this study of lesions thought preoperatively to be benign , only 8 very selected lesions in which malignancy was detected were treated by submucosal excision alone and the presence of adverse features (inadequate margins, lymphovascular invasion, poor differentiation) led to radical surgical management. At this

stage it seems that until the role of TEM in the treatment of rectal cancer can be conclusively defined, many incidental malignancies found after routine TEM will likely proceed to salvage surgery.

An alternative approach to TEM for lesions thought to be benign is endoscopic mucosal resection (EMR). This of course is another submucosal resectional technique and has gained popularity for the management of large polyps elsewhere in the colon. Recurrence rates following EMR have been reported [24] at a similar rate to that experienced in this study and a prospective comparison of TEM and EMR [25] is underway but no results have been forthcoming. Our preference remains to use TEM for large rectal polyps not amenable to standard endoscopic techniques given the precision that a two handed technique provides over EMR.

Based on this study, we advocate a submucosal rather than full thickness excision for lesions considered preoperatively to be benign, which facilitates short operating time, post-operative stay, and a low risk of intra-operative perforation with satisfactory local recurrence rates. Importantly, in patients with incidental finding of adenocarcinoma that proceed to salvage surgery, submucosal dissection appears not to influence oncologic outcome. Full thickness excision should be reserved for lesions thought malignant and likely to be treated by TEM alone, although case selection and pre-operative staging needs to be optimised.

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Table 1

Patient demographics and tumour characteristics

	Presumed adenoma pre TEM	Confirmed adenoma post TEM	Unrecognised cancer post TEM	P =
	N = 139	N = 122	N = 17	
Age	67.7 (0.9)	68.4 (1.0)	62.9 (2.7)	0.06 [1]
Sex (M :F)	101 : 38	88 : 35	13 : 4	1.0 [2]
Size (cm)	4.1 (0.3)	4.1 (0.1)	4.5 (0.4)	0.34 [2]
Level (cm)	10.4 (0.3)	10.5 (0.2)	10.3 (0.6)	0.84 [2]
Quadrant				
Ant	53	48	5	
Left	28	24	4	0.87 [2]
Post	38	33	5	
Right	20	17	3	

[1] Independent t-test

[2] Fisher's Exact Test

Table 2.

Operative details

	Presumed adenoma pre TEM	Confirmed adenoma post TEM	Unrecognised cancer post TEM	
	N = 139	N = 122	N = 17	
Duration (min)	53.8 (3.3)	54.2 (3.5)	51.5 (6.4)	
Complete excision (n)	55	49	6	
Complications				
Medical	4	3	1	
Surgical	4	3	1	

Table 3.

Outcome of patients found to harbour unrecognised carcinoma in TEM specimen

	Conservative treatment	Radical Surgery
	N = 8	N = 9
Stage		
T1Nx	8	
T1N0		6
T1N1		2
T2N1		1
Follow-up (months)	43.1 (11.0)	42.3 (6.4)
Recurrence (any)	0	0