Title: Transanal Endoscopic Microsurgery For Rectal Cancer: A Clinical and Cost Effectiveness Review

Date: 03 April 2008

Context and policy issues:

Most rectal cancers are adenocarcinomas which are classified according to the TNM system of primary tumor stages.\(^1\) Tis tumours (also referred to as T0) are carcinomas \textit{in situ} and have not spread to neighbouring tissue whereas stages T1 – T4 have invaded surrounding tissues.\(^1,2\) A T1 rectal tumour has invaded the submucosa.\(^1\) Low risk T1 rectal cancers can be described as well, or moderately differentiated adenocarcinoma, with no vascular or lymphatic invasion and not close to the muscularis layer.\(^2\) Tumours that are close to the muscularis layer are referred to as T1sm3 and are considered high risk.\(^2\)

Early rectal cancers are relatively uncommon in the West.\(^2\) The incidence of malignant colorectal polyps as a proportion of all adenomas removed varies between 2.6 and 9.7 \%, with an average of 4.7 \%. About 3\% to 8.6\% of all resected adenocarcinomas are stage T1.\(^2\)

There are three major surgical curative options for early rectal cancer: local excision (LE), sphincter-preserving abdominal surgery (low anterior resection or LAR), and abdominal perineal resection (APR).\(^1\) Local excision methods include excision through the anus (transanal excision), by division of the anal sphincter (transsphincteric or York-Mason procedure), or through a posterior parasacral approach (Kraske resection).\(^1\) The traditional transanal approaches to local excision is limited to low and midrectal lesions within 10 cm of the anal verge.\(^1\) The depth of tumour invasion into the rectal wall, the presence or absence of regional lymph node metastases, the size and macroscopic appearance of the cancer, and tumour location are all critical in determining the best surgical option.\(^1\)

Transanal endoscopic microsurgery (TEM) is a type of LE. Minimally invasive endoscopic techniques such as TEM have expanded the possibility of transanal excision to otherwise inaccessible lesions that are within reach of the endoscope (up to 18 cm from the dentate line).\(^1\)
TEM uses a set of endoscopic surgical instruments that can reach further into the rectum than other forms of local excision, along with a form of enhanced or assisted vision (usually stereoscopic). This magnified three-dimensional image allows an optimal view of the tumour and thus facilitates an extremely precise dissection. It usually involves dilation of the anal sphincter to a large-diameter (4 cm) and operating sigmoidoscope to accommodate optics, suction, and ports for dissecting instruments. Insufflation of the rectum is used to improve the field of vision and access.

One of the disadvantages with the TEM procedure is that it does not provide information on lymph node status. The rate of nodal metastases in selected early rectal cancers (T1 tumours with good differentiation) is low (around 3%; although it can go up to 25% in tumours with poor differentiation): this may be a factor in local recurrence rates. It is necessary to review the evidence on the use of TEM to determine whether this technique should be implemented for the treatment of early rectal cancer.

Research question:

1. What is the clinical effectiveness of transanal endoscopic microsurgery versus conventional transanal excision or radical excision in patients with rectal cancer?

2. What is the cost effectiveness of transanal endoscopic microsurgery versus conventional transanal excision or radical excision in patients with rectal cancer?

Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 1, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2003 and February 2008, and are limited to English language publications only. No filters were applied to limit the retrieval by study type.

Summary of findings:

There were no health technology assessments or randomized controlled trials (RCTs) identified on the topic of TEM for rectal cancer. There was one systematic review, 8 observational studies (5 case-control, and 3 case series) and 1 economic study.

Systematic review

Middleton et al. summarized one RCT, two non randomized studies (1 in Hungarian) and 55 case series in a systematic review of TEM in patients 18 years or over, with or without previous surgery from 1980 to August 2002. The systematic review had clear search terms, a PICO format, two independent reviewers who resolved differences by consensus. The RCT and non-randomized study examined adenoma recurrence, carcinoma recurrence, and safety of TEM for adenomas and carcinomas. These four outcomes were not reported by every case series.

Adenoma Recurrence. For benign tumours, the comparative interventions were anterior resections (AR) or LE in the RCT. The RCT survival results at follow-up were not given for the adenoma patients. The LE technique of the perianal submucosal excision (PSE) group had a
significantly higher rate of local recurrence (20/90; 22 %) than the TEM group (6/98; 6 %) [relative risk (RR), 0.28; 95 % confidence interval (CI), 0.12–0.66] (unstated follow-up period). This finding remained robust even after a worst-case, intention-to-treat analysis. In the case series, the median local recurrence rate after TEM was 5.1 percent, ranging from 0 percent to 15.8 percent (24 studies).

**Carcinoma Recurrence.** In the RCT, TEM was compared with AR (APR, posterior proctectomies (PP), or LE). The survival graphs for TEM vs. AR showed no differences at follow-up of nearly four years, with a hazard ratio of dying after TEM of 1.02 (CIs not reported). In the case series, longer-term survival differed according to the cancer stage. The median local recurrence rate was 8.7 percent, ranging from 0 percent to 50 percent (31 studies). A median 6.7 percent of patients needed immediate conversion to radical resection (mostly because of under-staging).

**Safety for adenoma treatment.** In the RCT, there was no discernible difference in the early complication rate between TEM (10.3 %; 10/98) and PSE (17%; 15/90) (RR, 0.61; 95 % CI, 0.29–1.29), nor could any differences be detected for individual complications except mean blood loss that was less in the TEM groups (101 mL for TEM vs 115 mL for PSE). The ten complications in TEM patients were two cases of rectal bleeding, three cases of leakage or suture dehiscence, two perforations, and three cases of disrupted micturition. Unfortunately, many of the larger case series did not report complication rates for adenomas and carcinomas separately, but a typical complication rate extrapolated from the case studies for adenomas ranged from 3 percent to 7 percent. Five perioperative or early deaths out of a total of 1,046 patients could be clearly identified in the case series that reported on safety of TEM in adenomas.

**Safety for carcinoma treatment.** No perioperative deaths were reported in the RCT, but the authors did not state whether there were any longer-term mortalities in either the TEM or PSE group. At just under four years mean RCT follow-up (45.8 months for AR and 40.9 months for TEM), there was one death in each group (1/28 in the AR group and 1/25 in the TEM group). The death in the AR group was due to distant metastasis, and it was not clear whether the death in the TEM group was related to the primary cancer. No difference could be detected between TEM (20 %; 5/25) and AR (35.7%; 10/28) for the overall early complication rate (RR, 0.56; 95% CI, 0.22–1.42) and there were no clear patterns of differences for individual complications except mean blood loss that was less in the TEM groups (143 mL for TEM vs 745 mL for AR). In the TEM group, there was one case of rectal bleeding, one perforation, one ischemic compartment syndrome, and two cases of disrupted micturition. In the case series, forty-seven deaths (including late deaths) out of a total of 599 patients could be clearly identified in carcinoma patients undergoing TEM. Fifteen of these deaths were reported to be not cancer related. Of the remaining deaths, 13 patients had been treated palliatively. No death was clearly reported as a perioperative death. On the basis of results from only seven case series, complication rates ranged from 0 percent to 28 percent with a median of 19 percent.

As to the study quality, Middleton noted that the RCT was underpowered and the case series were often poorly reported and did not give separate results for adenomas and carcinomas. Although the author was able to conclude that TEM does appear to result in less local recurrence than other methods of direct LE, it was not possible assess the recurrence rate for TEM when compared to radical resection (for either adenomas or carcinomas) because the RCT did not provide AR data.
Case-control studies

There were five case-control studies in a total of 187 TEM patients (89 adenomas, 98 carcinomas). Two studies were in T1 patients only.\textsuperscript{5,6} The controls varied: two of the studies had historical controls which is a weak study design,\textsuperscript{7,8} one study had internal controls,\textsuperscript{9} while the other studies’ controls were patients with either radical resection procedures or local excision. The TEM recurrence rate varied from none\textsuperscript{7} to 11\%\textsuperscript{8} for adenomas and from 5.1\%\textsuperscript{5} to 14\%\textsuperscript{8} for carcinomas. In one study, the radical resection local recurrence rate was significantly different at 1.4\% for AR compared to 5.1\% for TEM;\textsuperscript{5} the difference was thought to be from lymphatic removal in the resection group. There was no difference in overall survival in the TEM group compared to the control group.\textsuperscript{5,7} In the two studies that discussed bowel function, they found that bowel function recovered after TEM with time.\textsuperscript{6,9} The complications included blood loss, urinary retention, sepsis and dehiscence and one study reported that higher complications occurred in the radical resection groups compared to the TEM group.\textsuperscript{5} Another study reported a higher complication rate in the TEM group compared to the LE group, and suggested the effect of the learning curve was responsible for the higher complication rate.\textsuperscript{8} The median follow-up periods ranged from 6 weeks to 44 months in the case-controlled studies. Details of the case-control studies are described in Table 1.

### Table 1: Summary of case-control studies

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Design/Participants</th>
<th>Intervention/Comparator</th>
<th>Outcome</th>
<th>Comments/Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ptok, 2007\textsuperscript{5}</td>
<td>Prospective multicentre observational study in 282 hospitals. 479 pts with low risk T1 treated for cure. 85 (17.7%) conventional transanal approach (no microsurgery), 35 (7.3%) TEM, 359 (74.9%) radical resection (anterior/low anterior or APR).</td>
<td>Transanal approach and TEM vs radical resection</td>
<td>Local recurrence TEM vs. radical resection: 5.1% vs 1.4%; median 19 months. 5 year local recurrence rate for limited resection: 6.0% vs 2.0% (p=0.049). No difference in tumour -free and overall survival.</td>
<td>No significant differences in intraoperative complications. Radical resection significantly increased general and specific postoperative complications and hospital stay compared to TEM (all p&lt;.001). 90% follow up. Median follow-up time 44 mo (1-65). The authors concluded that the significant increase in risk of local recurrence after LE needs to be weighed against the significantly higher postoperative morbidity of radical resection. Appropriate patient selection is critical.</td>
</tr>
<tr>
<td>Doornebosch, 2007\textsuperscript{5}</td>
<td>TEM group: n=31 Controls group: age and sex matched: 31 had total mesorectal excision (TME) and 31 healthy community controls.</td>
<td>TEM, TME and community controls.</td>
<td>NR</td>
<td>Quality of life questionnaires showed TEM patients had less defecation problems compared to TME patients (P &lt; 0.05). TEM time period 1996 - 2003, controls time period 1997-2002. The median time interval between the operation and the questionnaire mailing was 28 months (range: 5–91 months). Response rate 86%. There was no difference in impact on quality of life after TEM and TME. Defecation problems after TEM are less frequent than after TME.</td>
</tr>
<tr>
<td>Author/Year</td>
<td>Study Design/ Participants</td>
<td>Intervention/ Comparator</td>
<td>Outcome</td>
<td>Comments/Conclusions</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------------------</td>
<td>--------------------------</td>
<td>---------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Mihai, 2005&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Cases: 22 consecutive unselected TEM patients (18 adenoma, 4 carcinoma). Controls: matched for age, sex and ASA class. There were 2 controls for each TEM pt.</td>
<td>TEM/ Anterior resection, perianal procedures (Parks), transanal resection (TAR).</td>
<td>No recurrences during the period of study. 3 invasive carcinomas would have been missed during TAR.</td>
<td>NR</td>
</tr>
<tr>
<td>Cataldo, 2005&lt;sup&gt;9&lt;/sup&gt;</td>
<td>41 prospective TEM patients: 14 malignant lesions, 27 benign lesions. Each person served at his or her own control (i.e., preoperative function was compared with postoperative function).</td>
<td>TEM</td>
<td>NR</td>
<td>No statistical difference in urgency before and after surgery. No significant differences were identified in quality of life scores. Complications developed in 4/41 (9.8 %): 1 urinary retention, 2 intraperitoneal sepsis at 2 and 4 days following surgery, 1 dehiscence.</td>
</tr>
<tr>
<td>Dafnis, 2004&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Cases: 58 consecutive TEM patients. Controls: 80 transanal excision patients and 12 York Mason’s procedure patients for recurrence rates.</td>
<td>TEM compared to other procedures.</td>
<td>The recurrence rate was 11% (5/44) for adenomas, and 14% (2/14) for carcinomas. The T1 recurrence rate: 1/10 (10%). Lower proportion of adenoma recurrence in the York Mason group and in the TEM group than in the transanal group (P = 0.042). The TEM intra-operative complication rate was 3%. In 6 patients, the blood loss was &gt; 500 mL. TEM postoperative complications were seen in 3 (5%) patients: chest pain, neuralgia of the perineum, dehiscence of the suture line. Long-term complications were seen in 8 (14%) patients: incontinence, stricture, urgency, neuralgia of the perineum. 2/3 patients reported that the TEM procedure had had no impact on continence.</td>
<td>Study period 1996-1999. TEM introduced in 1996. The study found low morbidity, no 30-day mortality, and a low rate of recurrence with TEM compared to the recurrence rate of transanal excision. Operating time and blood loss decreased by increased experience of the surgeons. A positive correlation between operating time and impairment of continence as well as recurrence rate was found. The authors concluded that the functional outcome was acceptable.</td>
</tr>
</tbody>
</table>
Case series

There were three case series chosen because they are recent and provide information on 548 patients (423 adenomas, 83 T1 carcinomas). Two studies included patients with both adenomas and carcinomas, while the third study was in adenoma patients. The intervention was TEM only. Based on the case series, the recurrence rate of adenomas ranged from 4.8% to 30%. Recurrence rate was significantly associated with either involved surgical resection margins in 2 studies or piecemeal removal. There was no recurrence in low risk T1 tumours. Complications were the focus of one study. The commonly reported complications included bleeding that may be related to location of lesion and require transfusion. Other complications included: perforation, urinary retention or dysuria, and temporary incontinence. The minimum median time follow up time was 39 months. Details for the case series are described in Table 2.

Table 2: Summary of TEM case series studies

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Design/ Participants</th>
<th>Outcome</th>
<th>Comments/Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speake, 2008&lt;sup&gt;11&lt;/sup&gt;</td>
<td>117 consecutive pts (80 benign, 37 malignancy: 31 stage T1 disease and 6 T2.</td>
<td>Adenomas There were no recurrences with clear margins. Recurrence rates are significantly higher with involved surgical resection margins (10%) or when tumour excision is piecemeal (36%)(P = 0.001). Time to recurrence was 3–35 months (median 10.5 months). Carcinomas No low risk T1 (T1sm1 and T1sm2) developed recurrent cancer.</td>
<td>Adenomas Complication rate was 2.5% (2/80); perforation, stricture. There were no postoperative deaths. Carcinomas Not noted</td>
</tr>
<tr>
<td>Kreissler-Haag, 2008&lt;sup&gt;12&lt;/sup&gt;</td>
<td>288 prospective patients over 16 years of age: 200 adenomas, 52 T1 carcinoma, 24 T2 carcinoma, and 12 T3 carcinomas</td>
<td>NR Overall surgical complications: OR 7.0 (1.5–45.5); p&lt;0.01 Bleeding OR 222 (82 – 14316); p&lt;0.01 Complications correlated with the localization of the neoplasm on the lateral wall of the rectum. A tumour</td>
<td>Time period: 1988-2004. Patients with adenomas were followed for 394 ± 530 days (i.e., 215 ± 290 patient-years). Patients with carcinomas were followed for a mean of 1,306 ± 1,156 days (i.e., 314 ± 278 patient-years). The authors concluded that the risk of bleeding is higher with tumours on the lateral</td>
</tr>
</tbody>
</table>
**Economic studies**

There was one economic study\(^4\) with three studies including a costing section.\(^3,4,13\) Two of the studies contained the same information\(^4,13\) and therefore only one is summarized.\(^4\) Each of the studies noted a cost saving, primarily because of the shorter surgeon’s time and shorter hospital stay.

Maslekar examined National Health Service (NHS) mean reference costs for major large intestinal surgery, intensive care unit/high dependency unit and hospital accommodation for each procedure. Stapling devices, disposable instruments, suture materials and all other consumables were costed and included in the study. The costs of the staff, investigations and medications were not considered because they were uniform in both series.\(^4\)

Each additional inpatient day over and above the standard duration was calculated at the NHS rate of £233. The cost of TEM for each patient included £521 for the inpatient stay and £46 for disposables resulting in a total cost of £567. The cost of open operations included £424/£644 for disposables in case of AR and APR, respectively, £3711 for inpatient stay and £1968.11 for ileostomy closure. The total cost of high anterior resection thus worked out to be £4135 and that of low anterior resection £6323 and is therefore higher compared with £567 for the TEM procedure.\(^4\)

About 70% of those patients undergoing TEM excision would have otherwise required high anterior resection and around 30% would have required low anterior resection with protective ileostomy, as determined by their distance from anal verge and their radiological findings. With a difference of around £3568 - £5756 for each patient without or with ileostomy, the total cost difference for the series, including rectal adenomas is £525 576.\(^4\)
Although the initial capital cost of the TEM equipment is high at approximately £40 000 and using the reference cost scenario, the equipment costs are amortized by the time 11.2 operations have been undertaken. Fifteen TEMs completed would result in cost savings within the first 10 months.4

Middleton notes some US costs as follows:3 For Adenomas. The base case cost of treating an adenoma with TEM was calculated to be US$2,081 per patient, compared with US$3,309 for treatment with the comparator (LE/AR). With a lower recurrence rate and a lower cost, TEM dominated LE/AR. In a sensitivity analysis, TEM costs were still less than comparator costs, with hospital stays of up to 6.5 days for TEM. For Carcinomas. The base case cost of treating a carcinoma with TEM was calculated to be US$2,542 per patient compared with $5,679 for treatment with the comparator (AR/APR). Because the effectiveness of TEM for carcinomas could not be determined, it is not clear whether TEM is cost-effective in comparison with AR/APR. In a sensitivity analysis, TEM costs were still less than comparator costs, even when TEM hospital stay was increased from three days to eight days. The economic evaluation showed TEM to incur approximately two-thirds the recurrent cost of the alternative standard procedures for adenomas, and approximately one-half the recurrent costs for carcinomas. Middleton adds that further details of an Australian costing analysis can be found at at the Medical Services Advisory Committee (MSAC) Web site: http://www.msac.gov.au/reviews.htm.

Limitations

No RCTs were identified on the topic of TEM for rectal cancer; observational studies do not control for potential selection bias. Furthermore, case series are a weak study design as there is no comparison group. There were only three cost studies identified and they were not Canadian. It is therefore unclear whether these costs would be generalizable to the Canadian health care setting.

The complications were often not reported separately for adenomas and carcinomas and therefore it was unclear if the complications occurred in both the adenomas and carcinomas. Some of the studies used historical controls which is a weaker study design. The time period for one study5 was unclear while for other studies the study duration ranged from 6 weeks to 44 months. One study had a considerable difference in the median follow up time between the TEM group (shorter mean time 8 months) and the other study group (18 months),6 the authors did not discuss reasons for the difference in follow-up time. The effect of the surgeons experience and learning curve was only discussed in one study6 and this issue was not clearly addressed in the other studies. One study had few carcinoma cases, so the rates of recurrence would be less reliable in this study6 as the authors noted. One study had significantly more proximal tumour sites in the radical resection group than the TEM group.5 Two studies did not provide carcinoma staging and the numbers of patients in each staging group was unknown.7,9

Conclusions and implications for decision or policy making:

The evidence from the studies suggests that TEM is effective and safe in removing adenomas and T1 carcinomas when compared to local or radical resection. One study noted the local recurrence rate was higher for TEM compared to resection,5 possibly because of lymphatic involvement; however, there was no difference in long term survival between TEM and resection.5 Overall, the recurrence rates for adenomas and carcinomas were low, provided the resection margins are clear and the lesions are not removed in a piecemeal fashion. The most common complications include bleeding (may be related to lesion location and surgeon...
experience), urinary retention and incontinence that resolves. There was an overall good bowel function response with TEM as shown by the two functional quality studies.\textsuperscript{6,9} The TEM costing studies have shown it to be a cost-saving procedure when compared to radical resection, primarily because of the shorter procedure time and hospital stay.

Prepared by:

Elizabeth Keay, MD FRCPC MHSc MPA
Kelly Farrah, MLIS, Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
References:


