Current Colorectal Cancer Reports (2018) 14:98–105
https://doi.org/10.1007/s11888-018-0406-9

SURGERY AND SURGICAL INNOVATIONS IN COLORECTAL CANCER (S HUERTA, SECTION EDITOR)

Current Trends on the Status of Transanal Endoscopic Microsurgery

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Published online: 22 June 2018

Abstract

Purpose of Review Transanal endoscopic surgery (TES) is the standard of care for the local excision of large rectal adenomas and selected rectal cancers: an "en bloc" full-thickness local excision is performed, with limited risk of specimen fragmentation and positive resection margins, and subsequent significantly lower risk of recurrence and better survival than after conventional transanal excision with retractors. We perform a literature review aiming at assessing the current trends on the status of TES.

Recent Findings Patients undergoing TES report significantly lower rates of postoperative complications and better functional outcomes than patients who receive abdominal rectal resection with total mesorectal excision, with no adverse impact on long-term survival. To date, there are two different rigid platforms that are available to perform a TES procedure: the transanal endoscopic microsurgery (TEM) platform that was conceived by Buess in the early 1980s and the TEO (transanal endoscopic operation) platform. More recently, flexible platforms have been proposed as alternative to the rigid ones.

Summary Based on the current evidence, TEM and TEO represent the current standard of treatment for large rectal adenomas and selected rectal cancers. Large comparative studies are needed to assess the benefits of flexible platforms, considering that the wide adoption of flexible platforms might impair the quality of the local excision, mainly if performed in low-volume centers.

Keywords Transanal endoscopic microsurgery · Transanal endoscopic operation · Transanal minimally invasive surgery · Rectal adenoma · Rectal cancer · Full-thickness excision · Rectal wall defect · Peritoneal perforation · Neoadjuvant chemoradiation therapy · Survival · Recurrence · Quality of life

Introduction

Conventional transanal excision (TAE) with retractors has been considered the standard of care for the local excision of large rectal adenomas and selected rectal cancers until the 1990s, when the widespread diffusion of the concept of total mesorectal excision (TME) [1] and the implementation of new endoscopic rigid platforms, such as transanal endoscopic microsurgery (TEM) and transanal endoscopic operation (TEO), have raised several concerns regarding the oncologic safety of TAE.

Conceived by Buess in the early 1980s, the TEM platform has progressively replaced the use of TAE for the local excision of large adenomas and selected cancers of the rectum, since the quality of the excision performed with TEM is significantly better than with TAE, with subsequent lower rates of local failure and longer survival rates [2••]. Furthermore, TEM is favored by lower postoperative morbidity rates and is associated with better functional outcomes than abdominal rectal resection with TME [3]. More recently, the rigid TEO platform has been introduced, reporting similar outcomes when compared to the original rigid TEM platform [4•]. In 2009, a novel flexible platform has been developed with preliminary promising results as an alternative to the rigid platforms: the transanal minimally invasive surgery (TAMIS) [5].

The aim of this article is to revise the current status of transanal endoscopic microsurgery for the local treatment of large rectal adenomas and selected rectal cancers.

This article is part of the Topical Collection on *Surgery and Surgical Innovations in Colorectal Cancer*

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Literature Search

A critical appraisal of the literature was performed searching the electronic PubMed/Medline databases and the Cochrane Library for articles published in English language between January 1985 and March 2018. The following medical subject headings (MeSH) and free-text words alone or in combination were used: "transanal endoscopic microsurgery," "transanal excision," "full thickness excision," "rectal adenoma," "rectal cancer," "total mesorectal excision," "neoadjuvant chemoradiation therapy," "function," "quality of life," "peritoneal perforation," "Transanal Minimally Invasive Surgery," "TAMIS;" "Transanal Endoscopic Operations," "TEO," "sentinel lymph node."

Reference lists from the included articles were manually checked, and additional studies were included when appropriate.

Current Indications

Rectal Adenomas

The optimal treatment modality (endoscopic polypectomy, TAE, TEM) for the excision of rectal adenomas is controversial. Even though conventional endoscopic mucosal resection (EMR) is considered the standard of care for the treatment of colorectal adenomas, an *en bloc* resection is not technically feasible in the presence of large lesions, and the risk of incomplete or piecemeal resection is reported in up to 50% of EMRs [6]. As a consequence of a piecemeal resection, the subsequent pathologic evaluation of the resection margins is very challenging and the rates of local recurrence are high [7]. In addition, a submucosal dissection is not performed during EMR; therefore, if a polyp is found to contain malignancy, an accurate assessment of the colorectal wall invasion is not feasible.

During the last decade, the endoscopic submucosal dissection (ESD) technique has been developed aiming at overcoming the drawbacks of EMR, thus letting the endoscopist do an *en bloc* resection of the adenoma, especially in the presence of lesions with a diameter greater than 2 cm [8]. Even though ESD has a low morbidity and low local relapse rates [9–11], it is a technically demanding procedure characterized by a steep learning curve, and the operative time is longer than conventional EMR [9, 12]. As a result, transanal surgical excision is still considered the treatment modality of choice in patients with large rectal adenomas in the Western world, where ESD has not been widely adopted.

Many efforts have been made during the last 10 years to compare the effectiveness of EMR and TEM for large rectal benign lesions. However, most of the current evidence emanates from case series. In 2011, Barendse et al. [13] analyzed both the safety and clinical effectiveness of these two procedures. They evaluated the outcomes reported in 20 EMR case series and 48 TEM case series. Early morbidity rates were significantly lower after EMR than TEM: 3.8 vs. 13.0% ($p < 0.001$). At latest follow-up, the risk of local recurrence did not significantly differ between EMR and TEM patients: 1.5 vs. 3.0% ($p = 0.29$). More recently, the same group published the results of the first randomized controlled trial comparing EMR and TEM for large rectal adenomas: the TREND study [14••]. Patients affected by rectal adenomas with a diameter of 3 cm or larger, with no preoperative suspicion of malignancy, were randomized in a one-to-one fashion to EMR or TEM. Primary outcomes were local recurrence within 24 months after the procedure (aiming at demonstrating non-inferiority of EMR) and the number of recurrence-free days and out of the hospital. A total of 204 patients were enrolled in 18 hospitals; 27 of them, with definitive pathology positive for cancer, were excluded from the analysis. Overall recurrence rate was not significantly different: 15% in the EMR group and 11% in the TEM group ($p = 0.23$). Complication rates were similar, even though major complications occurred numerically more frequently after TEM (8 vs. 1%; $p = 0.064$); however, this difference did not reach the statistical significance. According to the cost analysis, EMR resulted about 3000 € cheaper than TEM. The authors concluded that EMR might be considered the primary treatment option for large rectal adenomas, since there was a trend towards less complications and lower costs. However, the financial evaluation needs a careful interpretation since TEM cases were mostly performed under general anesthesia. To date, it has been demonstrated that a TEM procedure can be safely performed under spinal anesthesia [15, 16•, 17•], with shorter operating room occupancy, earlier patient mobilization and resumption of oral intake, and shorter hospital stay. There is no added intraoperative morbidity or need for conversion to general anesthesia and postoperatively no patient usually requires opioids [17•, 18•].

Since the rate of unexpected malignancies in rectal polyps is as high as 13% [14••], a surgical procedure that allows to perform a full-thickness local excision should be preferred to achieve an accurate tumor local staging. Several studies comparing conventional TAE with TEM have reported significantly better oncologic outcomes after TEM. For instance, de Graaf et al. [19] reported the largest retrospective comparative study on this topic. Their data showed negative resection margins in 88% of specimens removed with TEM and 50% removed with TAE ($p < 0.001$); specimen fragmentation occurred in 1.4% of TEM procedures and 23.8% of TAE ($p < 0.001$). Local recurrence rate was significantly lower after TEM than after TAE: 6.1 vs. 28.7% TE ($p < 0.001$). A systematic review and meta-analysis of all comparative studies found no differences in terms of postoperative morbidity rates. TEM was associated with significantly lower rates of positive

microscopic resection margins and specimen fragmentation than TAE, with subsequent lower rates of local relapse [2••].

Apart from resection margins positive for residual adenomatous tissue [20, 21], the size of the rectal adenoma represents a risk factor for local recurrence. In a series of 293 TEM procedures for large rectal adenomas treated by TEM, positive margin rate was 21% among patients with adenomas with a diameter of 5 cm or larger and 9% in case of adenomas smaller than 5 cm ($p = 0.007$). A diameter of 5 cm or larger showed a trend towards a higher rate of recurrence even in the multivariate analysis [odds ratio (OR) 3.491, 95% CI 0.941–12.960, $p = 0.062$] (include odds ratio and confidence intervals for this) [20]. Similar findings were observed by McCloud et al. [22] in a series of 75 patients treated with TEM for rectal adenoma: local recurrence rates were significantly lower in patients with an adenoma smaller than 5 cm compared to the patients with an adenoma with a diameter of 5 cm or larger (7.7 vs. 21.7 vs. 33.3%, respectively; $p = 0.035$). Others reported similar results [23]. Based on this evidence, a strict follow-up is highly recommended after a TEM procedure performed for a rectal adenoma larger than 5 cm. When a local recurrence occurs, TEM should be considered a valuable option in those cases where EMR is not technically feasible, with no increased perioperative complication rates and excellent oncologic outcomes [20, 22, 24].

The better outcomes reported after TEM than after TAE are secondary to the better visualization and stability of the operative field that the TEM or TEO afforded by the proctoscope. In addition, transanal endoscopic surgery allows to excise more proximal rectal lesions that cannot be reached by conventional TAE and to precisely close the rectal wall defect. The optimal management of the rectal wall defect is controversial, with some studies suggesting closure, others favoring leaving the defect open and others showing no differences. A recent meta-analysis of the literature by Menahem et al. [25••] including four studies for a total of 489 patients (317 with the defect closed and 182 with the defect left open) failed to find significant differences in overall morbidity (11 vs. 15.4%), postoperative local infection (3.1 vs. 4.9%), postoperative bleeding (5.6 vs. 7.7%), and re-intervention rates (1.9 vs. 1.1%). However, these results were biased by different perioperative management protocols, different surgeon experience, different types of tools used for the tumor dissection, and the distance of the rectal lesion from the anal verge in the studies included in the analysis. Lee et al. [26•] observed similar results in a multi-institutional matched analysis. Of 220 adult patients undergoing local excision from 2004 to 2016 in three institutions in the USA, the analysis suggested that the rectal wall defect should represent a tailored approach. Similar outcomes were found in terms of overall 30-day postoperative complication rate between patients with open or closed rectal wall defect after full-thickness or partial excision (15 vs. 12%, $p = 0.432$ and 7 vs. 5%, $p = 0.552$). Rectal bleeding was the only complication that occurred more frequently in the group of patients with the rectal wall defect left open: 9 vs. 3% ($p < 0.005$). However, the closure of the defect was not independently associated with any postoperative complications. On the contrary, Marques et al. [27•] have observed in a prospective study that the rate of grade 3 complications according to the Clavien–Dindo classification was significantly lower in those patients who had the rectal wall defect sutured by TEM.

Rectal Cancers

The American Society of Colon and Rectal Surgeons [28] and the European Association for Endoscopic Surgery [29••] have stated that transanal endoscopic surgery should be considered appropriate for highly selected T1 rectal cancers with no high-risk features. The current evidence shows that transanal endoscopic surgery with rigid platforms does not jeopardize the long-term survival in patients with "low-risk" T1 cancer according to Hermanek criteria [30–33]. Kidane et al. [34••] published in 2015 the results of a systematic review and meta-analysis of the studies comparing TEM and rectal resection. Early perioperative mortality rate, major complication rate, and the need for a permanent stoma were significantly lower among those patients who were treated with TEM. Regarding oncologic outcomes, 5-year overall survival, 5-year disease-free survival, and 5-year disease-specific survival were similar. Local recurrence rates were significantly higher after TEM than after rectal resection only in patients with high-risk rectal cancers.

While proposing a local excision for rectal cancer, it is important to consider that submucosal tumor invasion is one of the strongest independent risk factors for long-term failure in T1 N0 patients [35, 36], and that the risk of perirectal lymph node metastases rapidly raises with rectal cancer stage, ranging from 0–3% in case of T1 sm1, 15% in T1 sm2-3, to 25% in T2 cancers [37, 38]. Consequently, the rate of local and distant relapse is significantly higher in "high risk" T1 and T2 rectal cancer patients after local excision than after radical rectal resection with TME. Unfortunately, the preoperative workup with both endoscopic ultrasound and magnetic resonance imaging has poor sensibility and specificity for the assessment of the rectal wall invasion and the presence of lymph node metastases [39, 40]. The main reasons for these unsatisfactory results are the high operator dependency, rectal wall fibrosis secondary to previous endoscopic biopsies, endoscopic tumor manipulation, and perilesional inflammation. Therefore, a full-thickness transanal endoscopic surgery should be performed with the concept of macrobiopsy and considered radical if a low-risk pT1 cancer is found at the final pathologic examination. Otherwise, if a more locally advanced rectal cancer is diagnosed, the local excision should be considered the first step in a multidisciplinary setting strategy, including

rectal resection and TME and adjuvant chemoradiotherapy. The use of TEM as macrobiopsy has no adverse impact on oncologic outcomes in patients undergoing further transabdominal rectal resection [33, 41]. However, a TEM procedure makes a further rectal resection more challenging. We compared a total of 17 patients undergoing TEM followed by laparoscopic rectal resection with laparoscopic TME with 34 patients undergoing primary laparoscopic TME [42]. Laparoscopic TME after TEM took significantly longer (206 ± 42 vs. 188.1 ± 12.6 min, $p = 0.025$), and the risk of a permanent stoma was higher (OR 5.25, 95%CI 1.26–21.75, $p = 0.028$). On multivariate analysis, a previous TEM was independently associated with a permanent stoma (OR 4.13, 95% CI 1.09–15.55, $p = 0.046$). The incidence and severity of postoperative complications were similar in both groups.

In order to reduce the risk of complications associated with transabdominal rectal resection and TME, a multimodal organ-preserving approach including neoadjuvant chemoradiation therapy followed by local excision by TEM has been proposed in selected patients with T1-T2 N0 rectal cancer [32, 43–45, 46•]. Even though the preliminary oncologic results of this strategy seemed promising, significant rectal wound-related morbidity [47, 48, 49•] and poor functional outcomes [50•, 51] have been reported in patients submitted to this multimodality strategy, regardless of the schedule of radiotherapy. The high local complication rates, ranging between 25 and 70%, are mainly related to the fact that the suture of the rectal wall involves irradiated tissue. Arezzo et al. [49•] reported a 50% rate of rectal suture dehiscence in 14 patients undergoing short-course radiotherapy followed by TEM: two out of the seven patients eventually developed an enterocutaneous presacral fistula, requiring a colostomy in one case. Postoperative quality of life at 1 month after surgery measured with the European Organization for Research and Treatment of Cancer QLQ-C30 survey score was significantly worse in patients undergoing radiotherapy followed by TEM, while the scores were similar to those obtained in patients undergoing rectal resection and TME.

How About Intraperitoneal Transanal Excision?

First conceived for the local excision of lesions arising from the extraperitoneal rectum, transanal endoscopic surgery is increasingly used also for the treatment of intraperitoneal rectal tumors, with no evidence of added complications or adverse oncologic outcomes. The mean rate of peritoneal opening reported in the literature is 4.8%, ranging between 0 and 32.3% [52]. The treatment modality of a peritoneal opening significantly differs according to the experience and the case load of the operating surgeon, with the need for conversion to abdominal surgery being highest among surgeons at the beginning of their learning curve [53].

We have previously reported our experience of 481 TEM patients. In our analysis, peritoneal opening occurred in 28 (5.8%) cases and there were 23 adenomas and five carcinomas [52]. The peritoneal defect was sutured by TEM in most cases (89.3%), while the procedure was converted to abdominal surgery in three (10.7%) cases at the beginning of our experience. In those cases of peritoneal opening, the TEM procedure takes significantly longer than the uneventful TEM. However, the overall postoperative complication rate and the severity of complications do not significantly differ between the two groups of patients. In particular, the peritoneal entry does not lead to increased rates of pelvic abscesses or other septic complications. Some more caution is required if the peritoneum is opened during a TEM procedure for rectal cancer. To date, a few studies have reported no poorer oncologic outcomes in these patients [52, 54, 55]. However, more data are needed to confirm these preliminary findings.

The Platforms: Is One Better Than the Others?

TEM Versus TEO

There is only one study comparing TEM and TEO for the treatment of rectal tumors. Serra-Aracil et al. [4•] designed a randomized controlled trial enrolling patients affected by rectal adenoma or cancer preoperatively staged T1-2 N0, 2 to 6 cm in diameter, located between 2 and 15 cm from the anal verge. A total of 34 patients were randomized: 17 patients in the TEM group and 17 in the TEO group. Time necessary to assemble the instrumentation, time necessary for excision and rectal wall suturing, and total operative time were not significantly different. No conversion from one platform to the other or to abdominal surgery was necessary. Similar postoperative morbidity rates were observed: 21% after TEM and 18% after TEO. There was no mortality and median hospital stay was 3 days in both groups. The cost analysis that included the fixed costs associated with the equipment and the variable costs (operating theater costs and hospital stay costs) showed that mean costs for TEO were significantly lower than those for TEM (2031 ± 440 € vs. 2603 ± 507 €, $p = 0.003$).

Rigid or Flexible Platform?

TAMIS was first introduced in 2009 as an alternative to TEM, with the aim of overcoming limitations of the rigid platforms, including costs, learning curve, and impaired anorectal function. After the first six cases were published in 2010, we witnessed a wide and rapid adoption of TAMIS, and about 400 TAMIS procedures were done in the following 4 years. Martin-Perez et al. [56••] systematically reviewed 33

retrospective studies (the largest including 50 patients) and case reports and three abstracts published between 2010 and 2013 from 16 countries. The main indication was malignancy (53.5%) and benign polyps (39%). Mean tumor size was 3.1 cm (range, 0.8–4.75); mean distance from the anal verge was 7.6 cm (range, 3–15). Mean operative time was 76 min (range, 25–162) and estimated blood losses were negligible. The overall positive margin rate and specimen fragmentation rates were 4.4 and 4%, respectively, and overall postoperative morbidity rate was 7.4%.

Based on these preliminary results, TAMIS was defined a "giant leap forward" compared to TEM; since setup time is minimal, standard laparoscopic instruments can be used and the cost of each disposable device is relatively low. However, the small number of patients included in most case series, and the short follow-up of only 7 months, limited the interpretation of the results published in 2014. As a result, the authors could not draw definitive conclusions regarding the oncologic efficacy of TAMIS. Furthermore, a full-thickness excision was performed in only 60% of the procedures. During the following few years, several large series of TAMIS procedures with longer follow-up have been published, showing that TAMIS is a viable option for excision of both benign and early rectal tumors, with minimal postoperative morbidity and acceptable recurrence rates [57, 58•, 59••]. However, very few studies have compared TEM and TAMIS [60–62, 63•]. Since TAMIS had a wide adoption without clear evidence of safety and efficacy, we conducted a comparative experimental study using a dedicated trainer box for transanal procedures [60]. Ten surgeons without experience in transanal surgery performed a dissection and suture task by using both TEM and TAMIS platforms in a random order. Accuracy of dissection was similar, while the time needed to dissect and suture was significantly shorter in the TEM group. In addition, the surgeon had to switch from TAMIS to TEM in three cases to complete the suture. Subjective surgeon's appreciation was higher for TEM.

In 2017, Mege et al. [62] conducted a case-matched study that included 74 patients. In this study, 33 patients underwent TAMIS and 41, a TEO. More frequently, adenocarcinoma was the indication in the TEO group (42 vs. 27%; $p? = 0.03$); a full-thickness excision was less frequently performed in the TAMIS group (85 vs. 100%; $p = 0.01?$). Median operative time, major complications and recurrence rate and anorectal function were similar in the two groups. R1 resection rates in the TAMIS groups were twofold those reported in the TEO group (21 vs. 10%); however, the difference did not reach a statistical significance.

Lastly, a retrospective multicenter matched analysis including 247 TEM procedures and 181 TAMIS procedures showed similar postoperative complications, R1 resection rates, fragmentation rates, and cumulative 5-year survival after the two operations [63•].

The results of these studies seem to suggest that TEM and TAMIS are equivalent in achieving high-quality local excision, and the choice of using a rigid or flexible platform should be based on the surgeon preference and equipment availability. Indeed, costs and the steepness of the learning curve should not be considered the reasons to prefer TAMIS over TEM/TEO. To date, there are no comparative cost analyses; however, it has been calculated that the costs of both platforms become equivalent after 18 procedures, considering the cost of each disposable TAMIS device, the costs of specific automated suturing devices used during a TAMIS, and the fact that two surgeons are involved in a TAMIS procedure while TEO is a one-surgeon procedure [60]. Similarly, a cost analysis comparing TEM and open surgery for rectal tumors demonstrated that the high equipment costs of the TEM platform are amortized after only 12 TEM procedures [64].

Supporters of the flexible platforms claim that TAMIS has a shorter learning curve than TEM/TEO. Actually, in the absence of comparative studies, the current evidence does not show significant differences between the two platforms. Helewa et al. [65] have recently demonstrated that 16 TEM procedures are necessary to significantly lower operative time. These results compare favorably with those reported by Lee et al. [66•] in a series of 254 TAMIS, showing that 14 to 24 TAMIS procedures are required to achieve stabilization of the operative time.

Conclusions

Based on the current evidence, TEM and TEO represent the current standard of treatment for large rectal adenomas and selected rectal cancers, with conventional TAE using retractors being indicated only in highly selected distal rectal tumors if the insertion of the platform is not feasible for technical reasons. The role of neoadjuvant treatment in association with TEM/TEO in highly selected patients with clinically staged T2 N0 rectal cancer is still under evaluation. Further large comparative studies are required to assess the use of flexible platforms, considering that the wide adoption of TAMIS might adversely affect the quality of the local excision, mainly if performed by surgeons in low-volume centers, with limited expertise in the treatment of rectal cancer.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have previously published and complied with all applicable ethical standards (including Helsinki declaration and its amendments, institutional/national research committee standards and international/national/institutional guidelines).

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