4 Local Excision: Transanal Endoscopic Microsurgery and Transanal Minimally Invasive Surgery

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Background

TME and Transanal Excision (TAE) for Rectal Cancer

Originally described by Heald and colleagues in 1982, total mesorectal excision (TME) refers to en bloc removal of the rectum and mesorectum along the mesorectal fascia and has been established as the gold standard in the surgical management of rectal cancer [1, 2]. Wide adoption of TME technique, in combination with stage-appropriate neoadjuvant chemoradiation, has dramatically reduced local recurrence rates in resectable rectal cancer. This is true whether TME is performed with sphincter-preserving low anterior resection (LAR) or abdominoperineal resection (APR) [3]. However, these oncologic resections are associated with significant postoperative mortality and morbidity. Across large trials, TME-related mortality ranges from 2 to 4% [4, 5], while morbidity ranges from 35 to 40% and includes infectious, anastomotic, and wound-related complications, as well as urogenital dysfunction and defecatory disturbances [6–9]. Even when TME is performed for stage I rectal cancer, perioperative morbidity remains between 20 and 25%, which does not reflect the surgical and psychological impact of stoma creation [10]. Long-term complications related to ileostomy and colostomy creation include parastomal hernia and stomal prolapse, which are associated with significant morbidity and often require surgical correction [11]. Even when a sphincter-preserving low anterior resection is feasible for low rectal tumors, the functional disturbances associated with the low anterior syndrome and coloanal reconstruction can be debilitating. Cumulatively, the morbidity associated with radical rectal cancer resections is substantial, negatively impacts quality of life measures, and is largely unaffected by the use of minimally invasive laparoscopic or robotic abdominal approaches [12].

Historically, the high morbidity and mortality rates associated with TME have driven the quest for less invasive local surgical approaches. Conventional transanal local excision (Park's operation, or TAE) was developed as a strategy to treat lesions in the distal rectum that could be accessed and removed under direct visualization through the anus. Local excision can also be undertaken via a transsphincteric (e.g., York-Mason) or transcoccygeal (e.g., Kraske) approach. The morbidity of TAE has been shown

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to be substantially lower than that of radical resection, with complication rates ranging from 10 to 17%, mostly consisting of bleeding, transient urinary retention, and fecal incontinence [13, 14]. However, this type of local excision only allows access to lesions within 6–8 cm of the anal verge, with limited exposure and visualization of the surgical field and increased risk of specimen fragmentation and positive resection margins [15].

As local excision techniques gained popularity in the management of early rectal cancer due to their considerable lower-risk profile, concerns arose regarding the oncologic adequacy of local excision relative to radical resection, particularly due to reports of higher local recurrence rates. Mellgren et al. retrospectively evaluated oncologic outcomes of 260 patients with T1 or T2 rectal cancer treated with either TAE or radical resection [16]. Patients with T1 tumors treated with local excision had an 18% rate of local recurrence, as compared to no recurrence in the radical resection group. However, 5-year survival was similar in both groups. Paty et al. retrospectively evaluated 74 patients with T1 rectal cancer treated with local excision and reported a similarly high local recurrence rate of 17%, with a 74% 10-year survival [17]. You et al. used the National Cancer Database to retrospectively compare 765 patients treated with local excision to 1359 patients treated with TME and found that after adjusting for patient and tumor characteristics, the 5-year local recurrence for local excision was 12.5% as compared to 7% for radical resection among T1 tumors [18]. Again, the 5-year survival was comparable for both groups. Confounding most of these earlier retrospective studies is the lack of patient selection, which introduced significant heterogeneity in histopathological features and stage of tumors, as well as in the type of local excision techniques employed.

Transanal Endoscopic Surgery (TES): TEM, TEO, and TAMIS

Transanal endoscopic microsurgery (Richard Wolf Company, Tubingen, Germany) was developed by Gerald Buess in 1982 as an endoscopic approach for local excision of low and mid-rectal lesions [19]. This approach represented a significant technical advancement relative to conventional TAE and endoscopic piecemeal polypectomy, with improved visualization and exposure of lesions, particularly those in the proximal rectum. The original TEM platform, which has been minimally modified over the last 20 years, employs a rigid metal 4-cm wide proctoscope available in two lengths to target the low to middle and middle to upper rectum (Fig. 4.1a). The proctoscope has an external multiport faceplate through which CO_2 is insufflated to achieve distention of the rectum and which accommodates a magnifying stereoscope and adapted dissection instruments. Once positioned transanally, the proctoscope is anchored to the operating table using a locking arm, which achieves a stable operating platform and videoscopic setup. TEM allows for either submucosal or full-thickness rectal dissection with hemostasis achieved with electrocautery, bipolar energy, or clips. Superficial rectal defects can be left open or closed in a fashion similar to full-thickness defects using laparoscopic suturing instruments. The original TEM technique and platform were adapted for the use with conventional laparoscopic equipment and a 2D laparoscopic camera, termed the transanal endoscopic operation (TEO, Karl Storz GmbH, Tuttlingen, Germany, Fig. 4.1b).

Until recently, adoption of transanal endoscopic surgery was confined to a few high volume and centers of expertise. Wider adoption was limited by the prohibitively high costs of the rigid TEM and TEO platforms, scarcity of training centers, and long learning curve required to achieve technical expertise in these procedures. In 2009, at the height of popularity of single-incision laparoscopy, an alternate transanal endoscopic setup using single-incision laparoscopic disposable transanal ports was reported, which was called transanal minimally invasive surgery (TAMIS) [20, 21].

TAMIS has popularized transanal endoscopic approaches through improved access, as disposable equipment is more readily available, less expensive, and compatible with standard laparoscopic equipment [21]. TAMIS platforms are shorter and pliable, thereby increasing the free-

Fig. 4.1 TES (transanal endoscopic surgery) platforms. Rigid platforms include (**a**) TEM (transanal endoscopic microsurgery) (Richard Wolf Medical, Vernon Hills, IL, USA). (**b**) TEO (transanal endoscopic operation) (Karl Storz Endoscopy-America, Inc. El Segundo, CA, USA). TAMIS (transanal minimally invasive) platforms include (**c**) SILS (single incision laparoscopic surgery, Covidien, Mansfield, MA, USA). (**d**) GelPOINT path (Applied Medical, Rancho Santa Margarita, CA, USA)

dom of motion and limiting instrument collision (SILS Port, Covidien, Mansfield, MA, Fig. 4.1c; GelPOINT Path, Applied Medical, Rancho Santa Margarita, CA, Fig. 4.1d). The shorter length, however, limits the extent of proximal rectal wall retraction and exposure, particularly beyond the second or third haustral valves [22]. Rather than using an anchoring arm to stabilize the platform and the stereoscope, a standard laparoscopic camera and scope are used. TAMIS procedures therefore require two operators, a camera holder and an operating surgeon. While a number of case series have been published demonstrating the preliminary feasibility and safety of TAMIS, these studies are relatively small and the data short-term, with no long-term oncologic results of TAMIS yet described.

TES as Compared to TAE and TME

TEM has long been considered an ideal minimally invasive approach to resect large rectal adenomas not amenable to complete endoscopic resection with a colonoscope, incompletely resected adenomas with dysplasia or intramucosal adenocarcinoma, small low-risk carcinoids, and other miscellaneous benign rectal pathologies. Until recently, however, the use of TEM for cancer was most widely accepted for the resection of rectal cancers in patients refusing more oncologically appropriate radical resection, radiation, or abdominoperineal resection and for palliative resection in patients considered medically unfit to undergo radical resection (Fig. 4.2). Routine use of TEM in the curative resection of T1 and T2

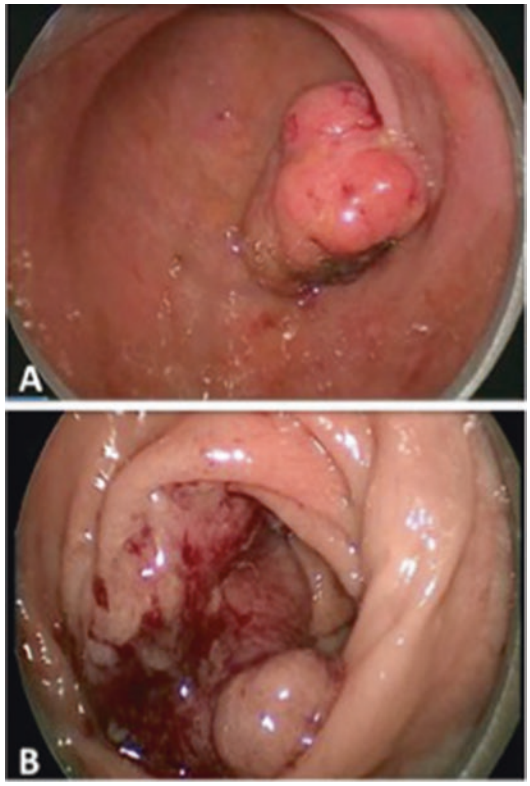

Fig. 4.2 TES resection of malignant rectal lesions: (**a**) Full-thickness curative resection of a 3 cm upper rectal polyp with a small focus of well-differentiated invasive adenocarcinoma (pT1, sm1, LVI). (**b**) Full-thickness for a mid-rectal bleeding T2 rectal cancer in a patient with dementia and major medical comorbidities, not eligible for radical resection of CRT

rectal cancers has been controversial because of unacceptably high rates of local recurrence reported in early series on local excision using TAE and TEM relative to radical resection rates. More contemporary published series, however, have demonstrated that local excision via TEM/TEO may be used with a curative intent in carefully selected cases of T1 rectal cancer with acceptable oncologic outcomes.

Several studies have demonstrated equivalent or superior outcomes of TEM for rectal cancer as compared with other methods of local excision [13, 23]. A recent meta-analysis by Clancy et al. reviewed six studies that compared outcomes from TAE and TEM. Cohorts were highly heterogeneous and included a mix of adenomas and adenocarcinomas as well as tumors of various stages. There were no differences in overall complication rates, but TEM was associated with higher negative margin rates (OR 5.28), reduced specimen fragmentation (OR 0.10), and lower rates of local recurrence (OR 0.25) when compared with conventional transanal excision [15]. However, studies included in this meta-analysis were retrospective, with varying definitions of specimen fragmentation and local recurrence. Although randomized studies comparing local excision techniques are lacking, superior oncologic outcomes with TEM are presumably secondary to the better visualization and more precise dissection that can be accomplished with this approach as compared to TAE. Despite this evidence, TAE is still more commonly used than TEM or TAMIS in many centers because of lack of specific training in TES, low volume of cases, and higher costs related to these procedures [13].

Although originally developed to treat benign disease, indications for TEM have expanded over the last 30 years to include the curative treatment of rectal adenocarcinoma via full-thickness endoscopic excision in select cases. Selection of appropriate tumors for local excision rather than radical resection remains a topic of controversy [24–27]. Unacceptably high local recurrence rates in heterogeneous cohorts treated with TEM alone are still quoted, despite their inherent biases. These earlier retrospective case series reported mixed data from TAE and TEM cohorts and did not use current staging modalities including pelvic MRI. Further, T1 tumors were not sub-analyzed based on histopathologic features that are now known to be of prognostic significance for lymph node metastasis and local recurrence. More contemporary TEM series have demonstrated comparable oncologic outcomes in select cohorts with low-risk T1 tumors relative to radical resection with TME [28]. Authors have adopted standard preoperative staging and detailed pathologic review in order to identify patients with very low risk of occult nodal disease who would in effect likely be overtreated by radical surgery, thus incurring unnecessary morbidity. These carefully selected T1 rectal tumors can usually be safely offered

TEM alone as curative therapy. Moreover, there is mounting evidence to support the potential use of TEM in combination with adjuvant or neoadjuvant chemotherapy for more advanced lesions, when carefully selected [29, 30].

Indications for TES

Benign Disease

TEM was originally developed as an alternative minimally invasive endoscopic approach for rectal adenomas and is currently the preferred approach to resect large or carpeting adenomas that cannot be removed via conventional colonoscopy, particularly in centers that do not use endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) techniques [13, 24, 25]. In such cases, when an underlying malignancy is not suspected, TEM with submucosal dissection can be used in a manner similar to endoscopic submucosal dissection, in order to avoid large full-thickness rectal defects [31, 32]. TEM is also commonly used in the setting of incomplete resection by piecemeal polypectomy or EMR, when a focus of high-grade dysplasia or intramucosal adenocarcinoma with unascertainable or positive deep margins of resection is discovered upon pathology review. In such cases, full-thickness excision of the polypectomy scar by TEM, TEO, or TAMIS is not only diagnostic of any residual tumor or more advanced disease but also therapeutic, as it achieves definitive resection of the lesion [33]. TEM has also been used for a variety of other tumors including early-stage rectal carcinoid, GIST tumors, and presacral tumors, as well as other benign conditions including repair of complex rectourethral and rectovaginal fistulas, stricturoplasty, and repair of colorectal anastomotic complications [34].

T1 Rectal Cancer

Selection of appropriate patients for treatment of rectal cancer with TES alone remains a topic of controversy. Of particular concern are the overall high rates of local recurrence following TEM for unselected T1 tumors, with some early studies reporting rates of local recurrence as high as 26% [35]. Such unacceptably high rates of local recurrence have driven efforts to identify risk factors for lymph node involvement and local recurrence of T1 rectal tumors and better identify T1 tumors that may be suitable for excision by TEM.

Several studies have sought to determine histopathological risk factors for local recurrence. One of the most important risk factors identified has been the degree of submucosal invasion. As described by Kikuchi et al., T1 lesions can be further classified by the level of penetration of tumor into the submucosa, with sm1 representing invasion into the upper third, sm2 into the middle third, and sm3 into the deepest third [36]. The depth of submucosal invasion according to this classification is predictive of local recurrence following TEM, with depth greater than sm1 being highly predictive of local recurrence [37]. In one cohort of 48 patients who underwent TEM for T1 cancer, 10.4% experienced local recurrence at a median follow-up of 54 months. Of these, none of 26 patients with sm1 lesions developed recurrence, while 5 of 22 patients with sm2–sm3 lesions recurred. This suggests that T1 sm2–sm3 lesions may behave more like T2 tumors and are not suitable for treatment with TEM alone. This finding is not surprising given that the degree of submucosal invasion is highly associated with the likelihood of positive lymph nodes, with sm1 lesions having a 0–3% chance of lymph node positivity, whereas T1 sm2–sm3 and T2 lesions have 15–25% lymph node positivity [38].

Additional important histopathologic risk factors for local recurrence following local excision include poor differentiation grade, lymphovascular invasion (LVI), positive resection margins (R1 resection), large tumor size, and the presence of tumor budding [39]. Doornebosch et al. have reported on the importance of tumor size in predicting local recurrence [40]. Out of 62 patients with T1 tumors, the overall 3-year local recurrence following TEM was 31%, with significantly higher local recurrence for tumors larger than 3 cm relative to tumors smaller than 3 cm (39% versus 11%). Local recurrence was lowest

in the subgroup of tumors less than 3 cm with no evidence of sm3 submucosal invasion (7%).

Tumor budding refers to the presence of small discrete clusters of tumor cells (less than five cells) at the invasive tumor edge [41]. Tumor budding has been consistently demonstrated in multivariate analyses to be an independent adverse prognostic factor associated with local recurrence and metastases, as well as significantly worse overall and disease-free survival in colorectal cancer [42]. For submucosally invasive colorectal carcinomas that are candidates for endoscopic resection by EMR or ESD, several large studies have shown tumor budding to be an independent prognostic factor associated with lymph node metastases, local recurrence, and cancer-related death [43]. In a series of 251 submucosally invasive colorectal carcinomas that were ultimately resected using radical resection, high tumor grade, LVI, and tumor budding were the three factors independently associated with lymph node metastases [44]. Compared to patients without any of those risk factors, patients with 1, or 2–3 of those risk factors, had a significantly higher rate of nodal metastases (1% versus 21% versus 36%). This suggests that local excision with polypectomy or TEM with negative resection margins would be sufficient treatment for early T1 colorectal carcinoma with no such risk factors [44, 45]. In the series of 62 T1 rectal cancers resected using TEM by Doornebosch et al., the 3-year local recurrence for tumors less than 3 cm without budding was 10% compared with 38% in tumors greater than 3 cm and with budding [40].

With respect to current consensus and guidelines for the management of early rectal cancer, the 2015 NCCN guidelines currently recommend TEM as an alternative approach for the management of select T1 cancer [46]. According to these guidelines, adenocarcinoma that is to be treated with TEM should have no radiographic evidence of lymph node involvement based on preoperative endorectal ultrasound (ERUS) and/or pelvic MRI, be less than 3 cm in diameter and less than 30% of the rectal circumference, be well to moderately differentiated, and be within 8 cm of the anal verge. These guidelines are based on several recent series that have reported local recurrence rates following TEM of T1 rectal cancers selected using the above selection criteria comparable to those following radical resection. Despite this evidence, there remains considerable controversy with regard to whether TES is a valid alternative to TME for T1 cancer. For example, in a review of 11 national or international guidelines on management of rectal cancer, only eight recommended the use of TES in the treatment of low-risk early rectal cancer [47].

This debate is particularly relevant given the increasing adoption of EMR and ESD for en bloc resection of superficial colorectal cancer (intramucosal adenocarcinoma or T1 sm1 cancers), which has been associated with good short- and long-term oncologic outcomes [25, 48, 49]. In a recent European Association for Endoscopic Surgery (EAES) consensus statement on early rectal cancer, full-thickness excision down to the mesorectum was considered the procedure of choice in order to achieve R0 en bloc resection for T1 tumors determined preoperatively to be well to moderately differentiated, without lymphovascular and perineural invasion, less than 4 cm in diameters and involving <30% of the rectal wall circumference [50]. With regard to ESD, the EAES consensus quoted two recent studies, including one which retrospectively compared 30 ESD and 33 TEM patients for resection of non-polypoid rectal mucosal adenocarcinomas or submucosally invasive adenocarcinomas. No significant differences were noted in en bloc resection rates or R0 resection rates (96.7% versus 97%), procedural or postoperative complications, or need for additional treatment such as radical resection or adjuvant treatment. ESD was associated with shorter operative time and length of hospital stay, and no local recurrence or distant metastases were noted over the study period [48].

T2 Rectal Cancer and Locally Invasive Tumors

While TEM, TEO, and TAMIS are considered acceptable alternatives for curative resection of carefully selected T1 rectal tumors, TES as a

unimodal treatment for T2 or T3 cancer—outside of the palliative setting—is considered oncologically inadequate, due to the higher rates of lymph node metastasis, ranging 12–28% and 36–66% in T2 and T3 disease, respectively [16]. In an early study, Lee et al. retrospectively evaluated 17 patients treated with TEM and 83 patients treated with radical resection for T2 lesions [51]. No patients received adjuvant therapy. Local recurrence was 19.5% in the TEM group as compared to 9.4% in the radical surgery group ($p = 0.035$), although disease-free survival was similar in the two groups. Borschitz et al. reviewed their experience with 40 T2 patients treated with TEM [52]. Of these, 20 patients underwent TEM alone with no further surgery or adjuvant therapy. Over a median follow-up of 59 months, 35% developed local recurrence and 30% systemic metastases. Among patients with high-risk histopathological features such as poorly differentiated tumors or evidence of LVI, the local recurrence rate was as high as 50%. Local recurrence in the case of T3 disease treated with TEM alone is as high as 100% in some case series [53].

The use of neoadjuvant chemoradiation therapy (CRT) prior to full-thickness TEM excision of high-risk T1, T2, and even more advanced rectal cancers, specifically in patients demonstrating clinical downstaging during chemoradiation, has shown particular promise as an alternative treatment strategy to radical rectal cancer resection with TME. Lezoche et al. recently published long-term results from a randomized control trial of patients with preoperatively staged T2 N0 tumors on the basis of ERUS and/or pelvic MRI [30]. A total of 100 patients who underwent neoadjuvant treatment were then randomized to undergo either TEM or laparoscopic TME. At a median follow-up of 9.6 years, the local recurrence rate in the TEM group was comparable to that of the radical surgery group (6% versus 8%, respectively). Moreover, complications and morbidity were lower in the TEM group. Other groups, however, have cautioned early adopters of this strategy about the high incidence of wound-related complications noted in radiated patients undergoing TEM excision of residual tumors or scars. Complications include rectal wound dehiscence which has been associated with severe and refractory pain [54].

Most recently, advocates of organ-preserving strategies have gone one step further and investigated the outcomes of non-operative management of rectal cancers that have demonstrated complete clinical regression following neoadjuvant therapy. This so-called watch-and-wait approach has been evaluated by Dr. Habr-Gama's group in 70 patients with T2 to T4, N0 to N2 rectal cancers without evidence of metastases. Intensive chemoradiation achieved a 68% rate of complete clinical response 10–12 weeks following completion of treatment, as demonstrated by the lack of gross evidence of residual tumor or other mucosal irregularity on endoscopy or imaging following CRT [55]. These patients were subsequently observed and a sustained complete clinical response was observed in 51% of the entire cohort at 3-year posttreatment. The remaining 49% with evidence of recurrent disease underwent immediate or salvage surgery with either TEM or radical surgery. Several European series have corroborated the findings from the Habr-Gama group [29, 56, 57]. With more aggressive CRT regimens, the rates of complete clinical response have surpassed the historical 20% rate, although this has occurred at the expense of increase toxicity and possibly overtreatment early rectal tumors.

While the possibility of multimodal treatment with chemoradiation and local excision for T2 lesions shows promise, current NCCN guidelines recommend that this treatment regimen be used only in the experimental setting [46]. While not currently indicated for curative intent, TEM with or without chemoradiation is still frequently used as compromised or palliative treatment for more advanced lesions in patients who are considered medically unfit to undergo radical resection using either an open or laparoscopic approach. Palliative treatment with TEM is also pursued in those who refuse surgery that could result in permanent colostomy.

Tumor Location and Tumor Size

Prior recommendations considered tumor distance greater than 8–10 cm from the anal verge to be a contraindication to TEM, particularly for anterior tumors of the upper rectum, due to the increased risk of peritoneal entry during full-thickness resection [58]. Inadvertent peritoneal entry during full-thickness TEM excision was previously considered to be a complication requiring immediate conversion to laparotomy with low anterior resection or fecal diversion in order to mitigate the risk of leak and infection [59, 60]. From an oncologic standpoint, peritoneal entry during TEM excision of a rectal tumor was also thought to increase the risk of tumor cell spillage and thus the risk of peritoneal tumor implants [61]. Several contemporary studies from experienced TEM operators have demonstrated that peritoneal entry occurred more commonly during full-thickness resection of lesions located in the upper rectum, anteriorly or laterally along the rectal wall [62–64]. These studies showed that in experienced hands, peritoneal defects could be sutured closed transanally without increase in morbidity. Finally, several studies have demonstrated no adverse short or long-term oncologic outcomes in patients in whom peritoneal entry occurred during TEM excision of rectal tumors [61, 65]. Based on these studies, tumor location 10 cm or more from the anal verge is no longer considered a contraindication to TEM surgery, as long as full-thickness suture closure of rectal defects can be achieved transanally by experienced operators [62, 63, 65–67]. It is important to note that with respect to more complex rectal lesions, the TAMIS published experience with upper rectal lesions is limited, with only three small series reporting on seven cases of peritoneal entry during TAMIS for upper rectal tumors, with conversion to laparoscopy or laparotomy required in six out of seven cases. This has raised the concern that shorter TAMIS platforms may not be adequate to perform full-thickness resection for high-risk rectal tumors [20, 22, 68]. Overall, only lesions within reach of the 15–20 cm rigid proctoscope, and otherwise amenable to resection with TEM, should be considered or full-thickness endoscopic excision.

At the other extreme end of the rectum, TAMIS platforms do not permit access to rectal polyps located within 4 cm of the anal verge [69]. For lesions partially or entirely located within the distal 4 cm of the anorectal canal, the TEM and TEO platforms can often be pulled back maximally to permit exposure without losing excessive pneumorectum. This is in contrast to TAMIS where resection must be combined with a standard TAE approach for the distal-most dissection.

With respect to rectal tumor size, near-obstructing, near-circumferential, and circumferential tumors constitute a contraindication for transanal endoscopic resection with TES. This is in large part because of the difficulty encountered in removing bulky lesions intact with clear margins, suturing large defects with the TEM instrumentation, as well as high risk of rectal stenosis or incomplete closure with this method [26].

Technical Considerations for TES

Preoperative Workup and Staging

Comprehensive preoperative workup is essential in selecting patients who are appropriate candidates for TES as a curative surgical approach. Preoperative assessment consists of complete clinical evaluation including digital rectal examination to assess anal sphincter tone, tumor location with respect to the anal sphincters, and anorectal ring, as well as tumor fixation. Preoperative workup also includes a colonoscopy to evaluate for synchronous lesions and careful pathology review of the biopsied rectal lesion to confirm eligibility for TES. Rigid or flexible proctoscopy is also performed preoperatively by the operating surgeon to accurately determine the distance from the anal verge, tumor size and extent of rectal wall involvement, and orientation along the rectal wall [26, 66]. This assessment is essential in order to assess feasibility of the resection and select the positioning on the operating table.

Standard rectal cancer staging is performed and includes carinoembryonic antigen (CEA) serum levels, CT scans of the chest, abdomen, and pelvis to rule out distant spread, and a pelvic

MRI and/or endorectal ultrasound (ERUS). While the T-stage accuracy of ERUS is largely operator dependent, ERUS is limited in its accuracy in assessing nodal status, with accuracy rates ranging 65–81% [70]. The reported T-stage accuracy of ERUS ranges from 63 to 95% across studies [66]. The accuracy reported in multi-institutional studies is usually lower than that reported in single-institution or single-operator studies, which may relate to variations in equipment as well as the steep learning curve and operator-dependent expertise required to achieve consistency in performance and interpretation of ERUS. Overall, ERUS is relatively less accurate at differentiating between T1 and T2 lesions, with one multi-institutional study reporting only 57% accuracy, as compared with individual studies reporting up to 88% accuracy in identifying T1 lesions with this modality [71, 72]. Despite the accuracy obtained by highly skilled practitioners, a recent study showed that the results of ERUS rarely changed the management plan for patients undergoing TES when used in conjunction with other preoperative staging modalities [73].

Pelvic MRI has supplanted ERUS as the preferred modality for rectal cancer staging. Although standard MRI imaging has comparably low sensitivity (66% versus 67%) and specificity (76% versus 78%) for lymph node assessment, it provides assessment of the circumferential radial margin (CRM), as well as detailed measurements of the tumor relative to sphincters, prostate, vagina, and even the peritoneal reflection [74]. Recent studies have highlighted 3 Tesla MRI imaging as a promising technology to improve nodal staging in rectal cancer. This technology may provide morphologic details beyond nodal size, which is not a reliable predictor of lymph node involvement. When nodal size is combined with other characteristics such as spiculation, indistinct borders, and heterogeneity of internal structure, great accuracy in predicting lymph node involvement may be achieved. In one study that investigated 437 lymph nodes in 42 patients, the sensitivity and specificity for identifying positive nodes were 85% and 97%, respectively, when using 3 Tesla MRI [75]. There is hope that accuracy of preoperative staging will continue to improve with new developments in radiographic technology [66].

Instrumentation

The original transanal microsurgery platform was developed by Gerhard Buess with support from the Richard Wolf Company (Tubingen, Germany). It consists of a rigid beveled proctoscope, 4 cm in diameter, with two lengths (12 and 20 cm) to allow for ease of operation in different parts of the rectum (Fig. 4.1a). The rectal lesion is visualized through a binocular stereoscope that allows for 3D visualization of the rectal lesion with up to sixfold magnification. The proctoscope also accommodates three 5 mm channels for specialized instruments that are angled at their tip. The 20 cm TEM proctoscope is the longest transanal platform commercially available, providing access to the upper rectum and even the rectosigmoid colon. The narrow diameter and rigidity of the metal proctoscope complicates instrument maneuvering through the platform and limits hand movement of the surgeon and instrument separation, resulting in collisions and crossing of instruments. The operating surgeon must rely on rotational movements as opposed to the typical retraction and levering of laparoscopic surgery. For this reason, the specialized laparoscopic tools used in TEM are angled at their tip to facilitate transanal dissection [24].

The system is secured to the operating table with a multi-jointed clamp, creating a stable operating platform. The scope is inserted through a dedicated port built onto the platform, which provides a stable view during dissection. The Wolf TEM setup includes its own combined pump and insufflation system to maintain consistent distention of the rectum, even during smoke evacuation and fluid suctioning [76]. The proctoscope has a detachable faceplate that provides an airtight seal and allows insufflation of the rectum. Pneumorectum is typically accomplished with pressures of 8–16 mmHg, although pressures as high as 20 mmHg are described to maintain adequate visualization in the face of rectal collapse [20].

The transanal endoscopic operation (TEO) platform, from Karl Storz GmbH (Tuttlingen, Germany), has been modified from the original TEM platform to allow for use with a 5 mm laparoscopic camera (Fig. 4.1b) [25]. This system also provides a 4 cm beveled rigid proctoscope that comes in two lengths (7.5 and 15 cm), with a faceplate with three ports in addition to the dedicated camera port (12, 5 and 5 mm), that accommodate conventional laparoscopic instruments. The system also includes an articulated proctoscope holder to secure the system to the operating table. Insufflation is provided with a standard CO_2 insufflator and tubing, and the scope is compatible with the standard laparoscopic camera and laparoscopic tower. The TEO system does not have a built-in system for smoke evacuation, which is achieved by standard laparoscopic suctioning or venting through small valves on the platform itself. This system is lower in cost than the more specialized Wolf TEM system and seeks to decrease the operating room setup time and lessen the learning curve for TEM with the use of more familiar laparoscopic equipment [77]. It should be noted that because of the similarity between TEM and TEO rigid metal platforms, recent studies do not necessarily distinguish between the two rigid platforms and may use the terms TEM and TEO interchangeably, or refer to them as TEM or TES rigid platforms.

In 2009, transanal minimally invasive surgery (TAMIS) was described as an alternative minimally invasive endoscopic setup to resect rectal lesions [20, 21]. The original report is described using a single-incision laparoscopic port, typically used for single-incision laparoscopy, and inserting it transanally in combination with a standard laparoscopic camera, scope, and instruments, to perform submucosal or full-thickness rectal resection. Since this first report, two commercial devices, the GelPOINT Path (Applied Medical, Rancho Santa Margarita, CA) and SILS Port (Covidien, Mansfield, MA), have been FDA-approved for the use in TAMIS (Fig. 4.1c, d). Other single-incision laparoscopic platforms have been used for TAMIS, including several platforms that are not currently commercially available in the United States. One group described using a simpler and cost-effective transanal access device consisting of a surgical glove assembled onto a wound retractor inserted transanally, in combination with laparoscopic trocars and instruments [78]. TAMIS has the advantage of disposable equipment that is more widely available, less expensive, and faster to set up in the operating room than the TEM or TEO platforms. The disposable port will sometimes be sutured to the surrounding perianal tissue to avoid dislodgement [21]. The available devices have three channels that can accommodate standard laparoscopic instruments ranging from 5 to 15 mm, including both rigid and flexible-tipped scopes [22]. The use of extra-long straight laparoscopes, deflectable-tip laparoscopes, and conventional endoscopes can help overcome some of the limitations of maneuvering a rigid scope through TAMIS platforms and reduce instrument collision [79]. High definitions and 3D imaging can also be incorporated to improve image quality and depth of perception. In addition, articulating laparoscopic instruments that were designed for the use in single-incision laparoscopy can be incorporated in TEM, TEO, and TAMIS procedures in an effort to facilitate reaching difficult angles.

Recently, high-flow CO_2 insufflation units (Olympus, Center Valley, PA and Stryker, San Jose, CA) have been used in conjunction with TEM/TEO and TAMIS platforms for active smoke and mist evacuation. These insufflators provide automatic smoke evacuation and high-speed CO_2 insufflation that responds quickly to CO_2 leaks resulting from suctioning and maintaining a stable pneumorectum and stable field of view. The Airseal® insufflation system (SurgiQuest, Inc., Milford, CT, USA) uses a cannula though which a continuous flow circuit occurs, evacuating CO_2 and smoke, recirculating filtered and high-pressure CO_2, and maintaining a stable pneumorectum. The 5–12 mm cannula can only be used through TAMIS platforms and has been described as a useful tool to maintain a stable pneumorectum [80].

Robotic technology has recently been combined with TAMIS, with the first clinical case of robotic transanal endoscopic resection reported in 2012 [81]. A handful of small case series have

since reported preliminary outcomes of robotic transanal endoscopic resection of rectal lesions using a glove port technique, which allows for greater working angles for the robotic arms [82, 83]. Despite a cumbersome perianal setup, and increased costs associated with robotic procedures, the preliminary data demonstrates feasibility of this approach with proposed advantages of ergonomically favorable dissection and suturing.

Preoperative Preparation and Operating Room Setup

Patients typically undergo full mechanical bowel preparation and/or administration of enemas prior to surgery in order to clear the rectum and to allow for adequate visualization. Some surgeons will use enemas or full mechanical bowel preparation selectively, based on anticipation of the possibility of full-thickness excision with peritoneal entry. Most surgeons also use standard perioperative parenteral antibiotic prophylaxis as well as thromboembolic prophylaxis. General anesthesia with complete muscle paralysis is usually recommended for TES in order to avoid abdominal wall contractions during procedures and minimize CO_2 leakage. One recent case report and one case series have demonstrated the safety of performing TAMIS under spinal anesthesia [69, 84].

Regarding patient positioning, patients are either placed in the supine, prone jackknife, or lateral decubitus position (Fig. 4.3). Standard

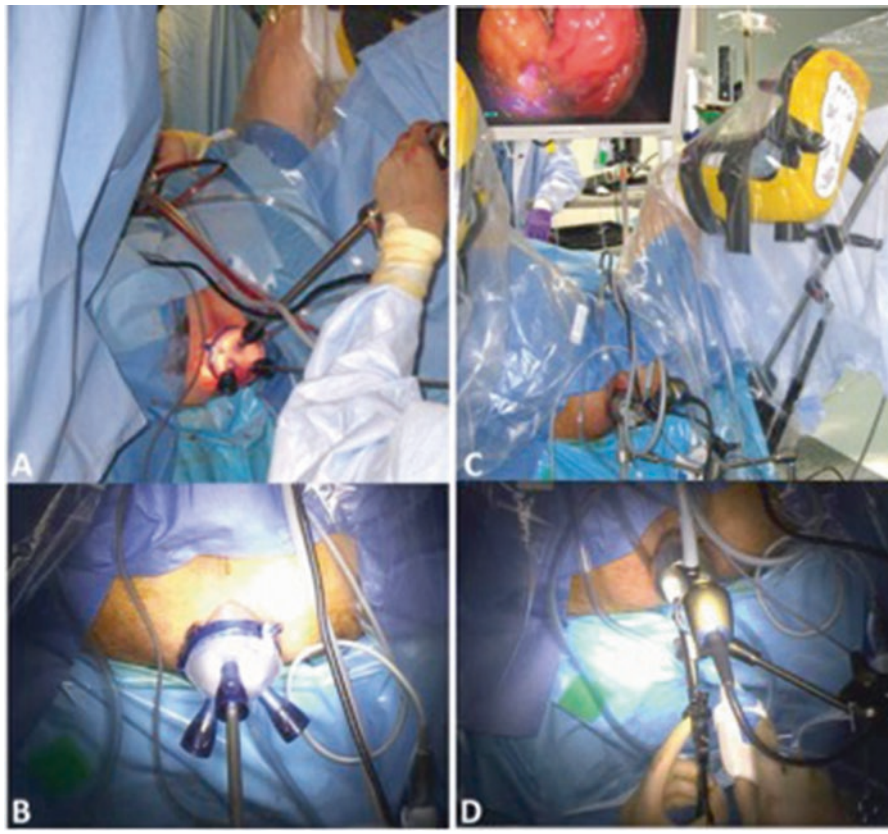

Fig. 4.3 TES setup. The patient is positioned in lithotomy position and the monitor is placed in between the patient's legs for improved ergonomics. The TAMIS platform is inserted transanally and procedures are performed by an operator and an assistant to hold the camera (**a**, **b**). The TEM/TEO rigid platform is inserted transanally, and the platform is secured to the OR table using a U-shaped platform holder. The procedure is performed by a single operator (**c**, **d**)

operating tables are used in combination with leg stirrups or, alternatively, split leg operating tables can be used. The TEM and TEO platforms traditionally require rectal lesion to be in a dependent position for ease of operation. This preference is based on the original design of both platforms, which are beveled at their tip, with the angled camera fixed at the superior aspect of the platform. Thus, for anterior rectal lesions, the patient is typically placed in the prone jackknife position, whereas for posterior lesions, the patient is placed in dorsal lithotomy. For lateral lesions, the traditional teaching is to place patient in the lateral decubitus positioning. Most experienced TEM and TEO surgeons will perform these procedures routinely in dorsal lithotomy regardless of the location of the lesion [76]. TAMIS is usually performed in the dorsal lithotomy position, and the use of a deflectable-tip scope and articulating instruments greatly facilitates exposure and visualization during these procedures [20].

One relative indication for placing patients in prone position includes preoperative anticipation of peritoneal entry during full-thickness excision of high-risk rectal lesions [65]. High-risk lesions for peritoneal entry include anterior and lateral lesions located in the upper rectum or rectosigmoid, as well as circumferential or near-circumferential lesions [61–64]. Peritoneal entry through large rectal wall defects can result in the rapid accumulation of CO_2 into the abdominal cavity and collapse of the rectum. In such cases, closure of the rectal wall defect can be very difficult due to poor exposure. Preemptively positioning the patient in prone position prior these cases limits the amount of CO_2 leakage into the abdominal cavity and helps maintain a stable pneumorectum throughout the case [65].

Dissection

Following patient positioning, transanal platform insertion, and CO_2 distention, the lesion is localized and dissection is initiated (Fig. 4.4). By convention, the lesion is scored circumferentially with electrocautery marks to map out the planned resection margins. In the case of suspected or proven rectal invasive adenocarcinoma, this is followed by full-thickness circumferential dissection through the rectal wall until the mesorectum, or perirectal fat is reached. A 5–10 mm resection margin is usually achieved in order to maximize the likelihood of R0 resection [25, 26, 85]. Submucosal and full-thickness dissection is traditionally accomplished with monopolar cautery, using conventional reusable laparoscopic hooks, spatulas, or articulating disposable instruments based on surgeon's preference and availability. Bipolar energy devices and ultrasonic shears can also be used to improve hemostasis and reduce dissection time. Hemostasis can also be achieved using laparoscopic clips or sutures. Some surgeons routinely excise a portion of the mesorectum attached to the segment of rectum removed in order to increase the chance of including some lymph nodes in their specimen for improved staging. Others have performed rectal sleeve resections for near-circumferential and circumferential rectal tumors. However, more extensive rectal dissection may be associated with higher morbidity, including bleeding, suture line dehiscence and leak, complex perirectal infections, and inadvertent injuries to surrounding organs, as well as postoperative urinary retention [86, 87]. In their series of 196 TEM cases, Guerrieri et al. reported two urethral injuries in male patients which occurred during wide anterior rectal dissection [86]. In addition, wider-than-indicated rectal dissection, including mesorectal dissection, may complicate or compromise the safe performance of salvage TME if warranted based on final pathology results from the TEM procedure. Scarring and inflammation form along the mesorectal plane after prior rectal dissection, which can significantly impact TME procedures.

Following full-thickness dissection, the specimen is oriented with sutures and mounted on a hard surface with pins or sutures for accurate pathologic assessment of resection margins (Fig. 4.5).

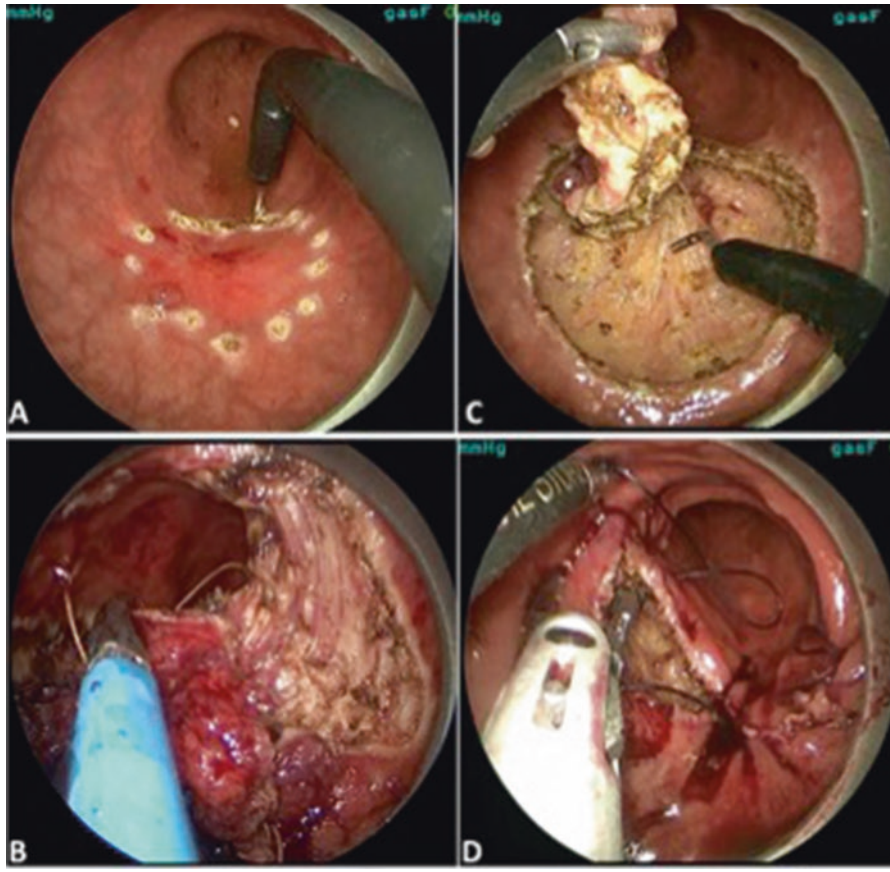

Fig. 4.4 Procedural steps for TES. Following setup and insufflation of the rectum, the lesion is scored with monopolar cautery circumferentially (**a**). The lesion is dissected endoscopically either along the submucosal plane (**b**), or full-thickness, down to the mesorectum or perirectal fat (**c**). Full-thickness rectal defects are closed with sutures (**d**)

Loss of Pneumorectum and Peritoneal Entry

As previously mentioned, peritoneal entry is not an uncommon occurrence during TEM and is no longer considered a complication. Overall, the reported rate of peritoneal entry during TEM ranges from 0 to 32.3% [62, 88] but across large contemporary series with more than 300 patients, that rate is lowered to 5–10.7% [89, 90]. To date, only three TAMIS series of 32–75 patients have reported a 2–9.4% incidence of peritoneal entry [20, 22, 68]. Entry into the peritoneal cavity, with subsequent difficulty maintaining adequate pneumorectum and visualization, presents a considerable technical challenge to the surgeon (Fig. 4.6). For this reason, surgeons will routinely place patients with high anterior lesions, where the risk of accidental peritoneal entry is greatest, in the prone position to mitigate the impact of CO_2 leakage into the peritoneal cavity on successful closure of rectal wall defects [65]. This allows the surgeon to minimize gas losses and maintain a stable pneumorectum. Other strategies to maintain pneumorectum include complete muscle paralysis, minimizing CO_2 leakage, increasing the pressure of CO_2 insufflation, and decompressing the pneumoperitoneum with a Veress needle or trocar [20]. Over time, and in experienced centers as demonstrated in

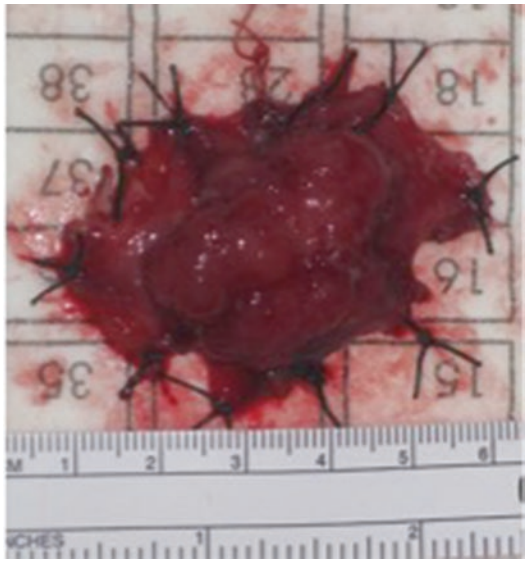

Fig. 4.5 Orientation of the TES specimen. Following exteriorization of the resected specimen, it is oriented with sutures for accurate pathologic assessment of all resection margins

large contemporary TEM series, conversion rates following peritoneal entry have steadily decreased, with conversion rates ranging from 0 to 40% but averaging 10% or less [65]. Interestingly, among the three TAMIS series that reported a total of seven cases of peritoneal entry during TAMIS for upper rectal tumors, six required conversion to laparoscopy or laparotomy from inability to effectively close the rectal wall defect. This may reflect the long learning curve required for managing these complex rectal lesions, and the currently small experience with TAMIS to date. But it may also reflect technical limitations of shorter TAMIS platforms, which do not always permit adequate retraction and exposure of the proximal rectum.

With regard to the morbidity associated with peritoneal entry, several studies have reported no increase in the rate of postoperative complications relative to TEM cases without peritoneal entry [61–65]. Notably, there has been no demonstrated

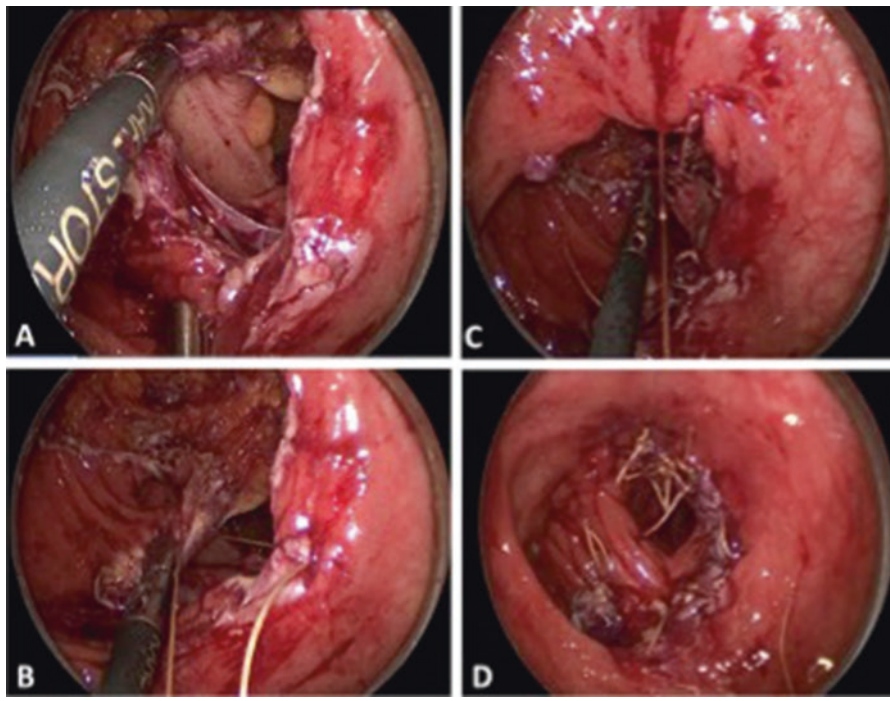

Fig. 4.6 Peritoneal entry during TES. Full-thickness resection of a rectal lesion located anterolaterally in the upper rectum results in peritoneal entry with visualization of the rectosigmoid (**a**). The adverse consequences of CO_2 leakage into the abdominal cavity are mitigated by the prone position (**b**). The rectal defect is closed using interrupted and continuous absorbable sutures without adverse outcomes (**c**, **d**)

increased risk of pelvic sepsis or abscess formation following peritoneal perforation. Fewer studies have evaluated the oncologic impact of peritoneal entry during TEM performed for rectal cancer. Morino et al. followed 13 patients with rectal adenocarcinoma in whom peritoneal perforation occurred during TEM [65]. At a median follow-up of 48 months (range 12–150), no cases of liver or peritoneal metastasis occurred. Two patients with T2 and T3 tumors developed local recurrence and subsequently died of lung metastases.

Rectal Defect Closure Techniques

Many techniques and devices can be employed for closing rectal wall defects during TES. In some select cases, particularly for low or posterior rectal lesions, or in cases of partial-thickness excision, the rectal wall defect can be left open, as there is some evidence that leaving the defect open does not increase complications for such lesions [91]. In a recent study by Hahnloser et al., 35 patients underwent TAMIS for lesions located at a mean of 6.4 ± 2.3 cm from the anal verge, with the rectal defect left open. This group included both full-thickness and partial-thickness defects. No increase in complications was noted between this group and the 38 patients in whom rectal defects were closed [68]. Of note, only 6% of the 35 open rectal wall defects were located anteriorly compared to 28% of 38 closed rectal wall defects. Clearly, for larger, full-thickness lesions, and in particular for high-risk lesions where peritoneal entry has occurred or is suspected, complete and airtight closure is required to decrease the risk of leak and intra-abdominal abscess formation [76, 92]. Prior to closure, particularly in the event of an incomplete bowel preparation and ongoing fecal contamination of the rectal wound, the area can be irrigated with dilute iodopovidone. Most TES surgeons close the defect with running or interrupted absorbable monofilament sutures. A variety of suture materials are described including glycolide and trimethylene carbonate (Maxon), polydioxanone (PDS), and polyglactin (Vicryl) [76]. Intracorporeal suturing devices and techniques can be used, including extracorporeal knot tiers. In order to overcome the technical difficulty of knot tying through a transanal rigid platform, the TEM instruments include an angled needle holder, and sutures can be secured with specialized silver bullets (Richard Wolf, Knittlingen, Germany). Alternatively, a V-loc barbed absorbable suture (Covidien) can be used to avoid having to make a knot. Finally, disposable automated suturing devices can facilitate knot tying including the Endo Stitch™ device (Covidien) and the Cor-Knot device (LSI Solutions, Victor, NY). If peritoneal entry occurs, some authors advocate closing the defect in two layers [76]. In cases where there is concern that the closure is not airtight, further investigation with a gastrografin enema would be recommended in order to rule out a leak.

Postoperative Management and Follow-Up

Following submucosal and low-risk full-thickness TES cases, patients are routinely discharged home on the same day [93]. Patients who have undergone full-thickness excision with peritoneal entry, or patients with extensive medical comorbidities, are typically admitted overnight for observation. Administration of postoperative antibiotics is not routinely recommended, nor is routine imaging, in the absence of clinical indications.

There are no specific guidelines for postoperative surveillance specific to patients who have undergone TES for rectal adenocarcinoma [47]. Current practice follows standard NCCN guidelines for rectal cancer surveillance, including clinical evaluation, CEA, and endoscopic surveillance by flexible sigmoidoscopy every 3–4 months for the first 3 years and every 6 months until year 5 [26, 94]. Other standard testing includes yearly CT scans until year 5 as well as surveillance colonoscopy at 1 year followed by 3 years post-resection. There is no NCCN guideline for surveillance pelvic MRI. However, following TES excision of T1 rectal tumors, particularly T1 tumors with borderline or high-risk features that were or were not treated with TME or adjuvant chemoradiation, most surgeons will recommend bi-annual or annual pelvic MRI for 5 years to rule out locoregional pelvic recurrence.

Outcomes of TES

Operating Time

The average operating time reported in large TEM and TEO case series for rectal neoplasms ranges from 70 to 95 min [28, 53, 86, 95–98]. Some smaller series have reported mean operative times as low as 45 min [35, 99]. Variations in OR time relate to size of the lesion, submucosal versus full-thickness dissection, distance from the anal verge, closure versus non-closure of rectal defects, complexity of the rectal defect closure, and management of intraoperative complications such as bleeding, CO_2 leakage, and peritoneal entry. Additionally, there is a clear learning curve for TEM, with possible improvement in operative time as the surgeon becomes more experienced with the equipment [90].

A small randomized study by Serra-Aracil et al. comparing TEM and TEO in 34 eligible patients with rectal lesions found no differences in lesion characteristics, postoperative morbidity, and final pathology between the platforms used. Although there was a trend toward shorter operative time with TEO, including time to mount the equipment and perform the excision and suture closure, this difference was not statistically significant [98].

Reduced operating time from shorter operative setup and faster procedure completion are commonly cited as one of the main advantages of TAMIS over TEM/TEO as reported by its many adopters. The initial report of TAMIS reported a mean operative time of 86 min which has progressively decreased with a recent series reporting mean operating time of 57 min [21, 100]. Another series reported a median operating time as low as 45 min [69]. To date, no prospective comparative or randomized trial of TEM, TEO, and TAMIS procedures has been published comparing operating time and other perioperative variables.

Mortality and Morbidity

A major advantage of TES is the improved safety profile relative to TME [51, 101–103]. Mortality is well under 1% across most series, even in patients with multiple comorbidities who are deemed unable to tolerate a radical operation [104]. The overall complication rate following TEM is also relatively low relative to standard colorectal resections, with most complications being minor and transient. Published 30-day morbidity rates range from 6 to 23% in the largest TEM/TEO series with cohorts ranging from 262 to 693 patients [25, 53, 88, 89, 100, 101, 105]. Major complications are noted in less than 10% of cases [13, 76, 106]. The most commonly reported surgical complication following TEM is hemorrhage, which is reported in 1–13% of patients, and is usually managed non-operatively [76]. The most common nonsurgical complication is urinary retention, with incidence reported around 5% on average (range, 5–10%) [53, 89]. Other surgical complications include suture line dehiscence, which can range from minor defects usually managed non-operatively with antibiotics and bowel rest, to major defects with leakage and sepsis, requiring return to the operating room for washout and fecal diversion. Additional major TES complications include perirectal and presacral abscess, fistulas, and rectal stenosis. Rare complications include organ injury, with two cases of urethral injury reported following TEM resection of anterior-based lesions [107]. In the largest multicenter series published to date, among 693 combined TEM and TEO cases, conversion to conventional TAE or abdominal procedures was required in 4.3%, and the 30-day morbidity was 11.1%, with hemorrhage and suture dehiscence being the most common surgical complications and urinary tract infections being the most common nonsurgical complication [90].

The relatively low morbidity following TEM procedures is reflected in the short hospital stay and minimal postoperative analgesic requirement. Up to 50% of patients undergoing TEM for rectal cancer are safely discharged on the day of surgery as reported in several recent series [93]. When patients are admitted for observation, average length of hospital stay ranges from 0 to 5 days, with reasons for admission ranging from management of major medical comorbidities to observation following complex cases involving peritoneal entry [24].

In the more limited literature on TAMIS, the published incidence of postoperative complications range from 0 to 25%, with bleeding and urinary retention reported as the most common complications [22]. One review of published TAMIS outcomes between 2010 and 2013 reported a total of 29 complications among 367 patients (7.9%) treated for rectal neoplasms [108]. Bleeding occurred in 2.7% of patients and suture dehiscence in 0.5% of patients. There were no deaths reported following TAMIS, and the average length of hospital stay was only 1.9 days. In the absence of comparative studies evaluating rigid metal versus TAMIS platforms, there is no data on differences in morbidity, mortality, or length of stay between approaches.

Functional Outcomes

By virtue of the prolonged dilation of the anal sphincter by the 4 cm wide rigid and semirigid anal platforms, there is some concern that TEM, TEO, and TAMIS procedures might not only transiently impact anorectal function but might cause permanent deterioration in fecal continence, particularly in patients with compromised anal sphincter tone at baseline. Interestingly, while multiple small TEM studies have documented a transient decrease in sphincter resting pressures on anal manometry that was proportional to the duration of the procedure, resting pressures were noted to return to baseline value 12 months postoperatively [109–111]. Other objective functional measurements, such as mucosal electrosensitivity and rectal compliance, were found not to be generally affected [110]. More importantly, changes in resting anal sphincter pressures did not translate into any detrimental effects on continence. Indeed, a majority of patients reported no change and even some improvement in anorectal function following TEM for rectal lesions. In a study of 41 patients who underwent TEM, Cataldo et al. found no significant changes in the Fecal Incontinence Severity Index (FISI) or the Fecal Incontinence Quality of Life (FIQL) scores reported 6 weeks postoperatively relative to preoperative scores [112]. A recent study that longitudinally assessed anorectal function and quality of life score in 102 TEM patients at 6, 12, 26, and 52 weeks postoperatively relative to baseline values found that the general quality of life scores (EQ-5D) was significantly lower at 6 and 12 weeks but returned toward baseline at 26 weeks. Similar to prior studies, anorectal function as assessed by colorectal functional outcome (COREFO) was worse at 6 weeks postoperatively but returned to baseline at 12 weeks postoperatively [113].

Because of the less rigid design of the transanal ports used in TAMIS, the procedure has been hypothesized to potentially result in less damage to the anal sphincter during transanal surgery. On the other hand, there is also concern that functional outcomes might be worse as compared to traditional rigid platform TES because of more extreme movements and stretch allowed by the flexible platform. Thus far, although published data is limited, short-term functional results following TAMIS have been comparable to historical TEM reports. One small prospective study conducted by Schiphorst et al. assessed functional outcomes in 37 patients following TAMIS using FISI score completed at 3, 6, 9, and 12 months relative to preoperative scores [114]. Interestingly, among 17 patients with decreased preoperative fecal continence at baseline, improved FISI scores were noted in 88%, while among 18 patients with normal continence at baseline, no change in FISI scores were noted in 83%, suggesting preserved long-term anorectal function following TAMIS procedures.

Positive Margins and Specimen Fragmentation

Positive resection margins are an important predictor of local recurrence for both benign and malignant rectal lesions and, along with specimen fragmentation, constitute an important metric of the efficacy of local excision including TAE and TEM. There is a clear association between the risk of local recurrence and the rates of positive resection margins for adenomas. Speake et al. reviewed their series of 80 patients

with adenomas treated with TEM and found that no recurrence occurred in patients with negative margins; however, 10% of patients with positive margins recurred [115]. With respect to rectal cancers resected using TEM, positive margin rates range across series from less than 2% to as high as 8.8% [53, 89, 95, 103, 116, 117].

Clancy et al. recently performed a meta-analysis that included six retrospective studies comparing outcomes of TEM versus TAE for indications ranging from adenomas to adenocarcinomas and other pathologies [15]. Of these studies, five compared rates of negative resection margins and specimen fragmentation in a total of 798 lesions, including 439 TEM and 359 TAE cases. Overall, TEM was associated with a significantly higher rate of R0 resection compared to TAE, with an odds ratio of 5.281 ($p < 0.001$). With respect to rectal cancer specifically, one study included in the meta-analysis by Christoforidis et al. retrospectively compared 42 TEM and 129 TAE procedures performed for pT1 or pT2 rectal cancers [23]. A significantly higher rate of positive margin positivity was demonstrated for TAE, with a 16% incidence of positive margins as compared with 2% with TEM. No tumors removed by TEM demonstrated specimen fragmentation, whereas 9% of TAE specimens were fragmented. However, the authors commented that there was a significant difference in location of the tumors in this study, with tumors resected by TAE primarily located in the lower rectum, whereas tumors resected by TEM were generally more than 5 cm from the anal verge.

Across TAMIS series, which are far fewer in number, rates of positive margins have varied but have generally been less than 6% for larger series including both benign and malignant pathologies [20, 22, 68].

Oncologic Outcomes for T1 Rectal Cancer

Published long-term rates of local recurrence for T1 tumors treated with TEM range from 0 to 26% (Tables 4.1 and 4.2) [121]. This is in comparison with local recurrence of 6% or less for T1 tumors treated with radical TME [125]. As previously detailed, wide variations in published oncologic outcomes following TEM reflect heterogeneous selection criteria including histopathological tumor analysis (grade, submucosal extent, size, lymphovascular invasion, tumor budding), staging methods (ERUS, pelvic MRI), surgical techniques used (TAE versus TEM), the use of adjuvant or neoadjuvant CRT, and outcome measures reported (positive resection margins, fragmentation versus en bloc resection,

Table 4.1 Summary of local recurrence rates for series of T1 tumors treated with TEM. Included series reported on at least 40 patients treated with TEM alone

Study	Location	Year	Criteria for TEM	Number of patients	Mean follow-up time (months)	Local recurrence (%)
Mentges [118]	Germany	1997	Primarily G1/2	64	29	4
Floyd [119]	United States	2006	None specified	53	34	8
Borschitz [120]	Germany	2006	G1/2, no LVI, R0 resection	66	74	6
Baatrup [121]	Denmark	2009	None specified	72	Not stated	13
Tsai [53]	United States	2010	Prior excision, metastatic disease	51	54	10
Doornebosch [116]	Netherlands	2010	None Specified	81	Not stated	21
Morino [122]	Italy	2011	None specified	48	54	10
Ramirez [95]	Spain	2011	G1/2, no LVI	54	71	7
Amann [123]	Germany	2012	G1/2, no LVI, R0 resection	41	34	10
Stipa [117]	Italy	2012	R0 resection	86	85	12
Guerrieri [28]	Italy	2014	<3 cm, G1–3, <8 cm from anal verge	110	82	0

Table 4.2 Summary of studies comparing TEM to radical resection for T1 rectal cancer

Author	Year	Study type	Criteria	Number of patients		Follow-up (months)		Local recurrence		5-year overall survival	
				TEM	RR	TEM	RR	TEM	RR	TEM	RR
Winde [124]	1996	Randomized control	Excluded patients >pT1 on final histology, poorly differentiated tumors	24	26	41	46	4.2	0	96	96
Heintz [102]	1998	Retrospective	Tumors were well or moderately differentiated, without lymphovascular invasion	46	34	52		4.4	2.9	79	81
Langer [14]	2002	Retrospective	Excluded poorly differentiated tumors, no limitations on diameter of tumor	20	18	22	34	10	0	100[a]	96.3[a]
Lee [51]	2003	Retrospective	Excluded poorly differentiated tumors, positive margins (R1)	52	17	31	35	4.1	0	100	93
Palma [103]	2009	Retrospective	Excluded poorly differentiated tumors, any evidence of lymphovascular invasion	34	17	87	93	5.9	0	88	82
de Graaf [101]	2009	Prospective	Any pT1 tumor, no limitations on diameter or tumor grade stated	80	75	42	84	24	0	75	77

[a]2-year overall survival

local recurrence, overall survival, etc.). Variance in surgeon experience may also account for differences in outcomes. As previously detailed, in series where T1 tumors were carefully selected based on well-defined histopathological features, local recurrence rates have been shown to approach those of radical surgery with TME. Heintz et al. conducted a retrospective study of all TEM cases performed between 1985 and 1996 and classified T1 tumors as low risk versus high risk, where low-risk features included good to moderate differentiation and the absence of LVI [102]. Using these strict criteria, they were the first to demonstrate a 4.4% local recurrence rate with TEM relative to 2.9% following radical surgery. On the other hand, in the same study, TEM for high-risk tumors was associated with a 33% risk of recurrence following TEM, relative to 18.2% following radical resection. Several similar studies have demonstrated local recurrence rates ranging from 0 to 10% when strict selection criteria for TEM excision of T1 tumors were used [28, 95, 118, 120, 123]. In a prospective series of 66 T1 rectal cancer cases, Borschitz et al. reported similar differences in local recurrence rates when T1 tumors were stratified according to histopathological features following TEM [120]. Local recurrence rates were 6% versus 39% in low- versus high-risk tumors. Another prospective cohort of 110 patients with T1 rectal cancers selected for TEM on the basis of good to moderate differentiation, size less than 3 cm, and distance of 8 cm or less from the anal verge demonstrated no local recurrence at a median follow-up of up to 82 months (range 48–144) [28, 96, 107].

Few TAMIS series have reported on short-term oncologic outcomes given the comparatively recent and limited experience with this approach in rectal cancer (Table 4.3). In a series of 50 TAMIS cases, 1 patient out of 16 patients (6.3%) with pT1 rectal cancer developed a local recurrence over a median follow-up of 20 months [20]. In the largest series of 75 TAMIS cases, 13 T1 rectal cancers were resected with no recurrence at a median follow-up of 385 days [68].

Table 4.3 Summary of data for TAMIS surgery

Study	Year	Number of patients	Port type	Final pathology	Operative time (min)	LOS (days)	Positive margins (%)	Morbidity (%)
Atallah [21]	2010	6	SILS	adenoma (3) pTis (1) pT1 (1) carcinoid (1)	86	1	17	0
Van den Boezen [126]	2011	12 (two converted to TAE)	SILS	adenoma (9) pT1 (1) pT2 (2)	55	1	0	8.3
Barendse [100]	2012	15	SSL	adenoma (7) pT1 (1) pT2(3) carcinoid (1) fibrosis (1)	57	1.5	13	7.7
Lim [127]	2012	16	SILS	pT1 (3) pT2–3 (8) mucocele (1) carcinoid (4)	86	3.0	0	0
Ragupathi [128]	2012	20	SILS	adenoma (14) unspecified malignant (6)	79.8	1.1	5	5
Albert [20]	2013	50	SILS/ GelPOINT	adenoma (25) hyperplastic (2) pTis (1) pT1 (16) pT2 (3) pT3 (3)	74.9	0.6	6	6
Seva-Periera [129]	2013	5 (one converted to LAR)	SSL	pTis (2) pT2 1) fibrosis (1)	52	1	0	25
Bridoux [130]	2014	14	Endorec	adenoma (10) pT1 (3) pT2 (1)	60	4.0	7.1	21
Lee [69]	2014	25	SILS	adenoma (6) pT1 (9) carcinoid (9) GIST (1)	45	3	0	0
Schiphorst [114]	2014	37 (one converted to LAR)	SILS	adenoma (23) pTis (7) pT1 (4) pT2–3 (2)	64	1	16	8
McLemore [22]	2014	32	GelPOINT/ SILS	adenoma (10) pTis (1) pT1 (6) pT2 (4) carcinoid (2) fibrosis (9)	132	2.5	3	25
Gorgun [131]	2014	12	GelPOINT	adenoma (10) pT2 (1) carcinoid (1)	79	1	0	25
Hompes [83]	2014	16 (one conversion)	Transanal glove port, da Vinci robot	adenoma (6) pT1 (2) pT2 (1) pT3 (1) fibrosis (5)	108 (36 min docking)	1.3	13	13
Hahnloser [68]	2015	75	SILS	adenoma (35) pTis (11) pT1 (13) pT2(9) pT3 (1) carcinoid (1) hamartoma (1)	77	3.4	4	19

Table 4.4 Summary of local recurrence rates for series of T2 tumors treated with TEM with or without adjuvant therapy

Study	Location	Year	Treatment Strategy	Number of patients	Follow up	Local recurrence
Lezoche [134]	Italy	1998	TEM + adjuvant RT	20	35	10
Maslekar [104]	United Kingdom	2008	TEM ± adjuvant or neoadjuvant CRT	22	32	18
Baatrup [121]	Denmark	2009	–	47	–	26
Ramirez [95]	Spain	2011	TEM + adjuvant CRT	22	71	9
Allaix [135]	Italy	2012	TEM ± neoadjuvant or adjuvant RT	42	70	22
Stipa [117]	Italy	2012	TEM ± neoadjuvant or adjuvant RT or CRT	38	85	37
Guerrieri [28]	Italy	2014	Neoadjuvant RT or CRT + TEM	185	53	13[a]

Included studies reported on at least 20 patients
[a]This represents both local recurrence and distant metastases

Across 15 TAMIS series including a total of 348 patients, margin positivity rates for lesions ranging from benign rectal lesions to T3 rectal tumors range from 0 to 17%, which is comparable with historical R1 resection rates following TEM, supporting the preliminary conclusion that TAMIS is a likely a safe alternative to TEM for carefully selected T1 lesions [20, 68, 69, 100, 108, 126, 128, 130, 132]. However, large series with longer oncologic outcomes are lacking.

Oncologic Outcomes for T2 Rectal Cancer

With the exception in palliative cases, TES excision of T2 rectal cancer without the use of adjuvant chemoradiation is considered unacceptable, given reports of local recurrence rates as high as 43% in small TEM series [133]. A review of oncologic outcomes following TEM excision of T2 tumors in larger series (Table 4.4) demonstrates local recurrence rates ranging from 5 to 40%, reflecting variations in the use of neoadjuvant or adjuvant CRT and specific regimen used. Overall, the use of adjuvant and/or neoadjuvant treatment in conjunction with local excision of T2 rectal cancers using TEM is associated with a trend toward improved local control. Guerrieri et al. reported outcomes in 88 patients with preoperatively staged T2N0 tumors on the basis of ERUS with or without pelvic MRI [86]. Patients were treated with neoadjuvant therapy followed by full-thickness TEM excision, with nearly 50% tumor downstaging to pT1 or pT0 lesions on final pathology. Over a median follow-up of 81 months, 6% of patients developed local recurrence, 3% developed distant metastases, and overall disease-free survival was 90%. Of note, no recurrent disease occurred in patients who were downstaged or who showed significant downsizing of the tumor on final pathology. Lezoche et al. reported long-term outcomes of the same cohort, and at a median follow-up of 97 months, the local recurrence rate was 5%, and the rate of distant metastases was 2%, with a 93% disease-free survival [96]. In a randomized trial of 70 T2 rectal tumors treated with neoadjuvant CRT followed by either full-thickness TEM or radical surgery, at a median follow-up of 84 months, Lezoche et al. reported no significant differences in local recurrence rates (5.7% versus 2.8% in the TEM and radical resection groups, respectively). There was no difference in overall survival, which was 94% in both groups [30, 136]. These results, as well as those from a number of case series, suggest that neoadjuvant treatment followed by TEM excision may be considered in preoperatively staged and selected T2N0 low rectal tumors. Using this strategy, local recurrence rates range 0–10% [52, 137–141]. However, it is important to consider that chemoradiation is associated with substantial morbidity and may also complicate

completion of TEM and result in increased wound-related complications, as suggested by several reports describing an increased incidence of suture line dehiscence, delayed TEM wound closure, and rectal pain [54, 107]. The ACOSOG Z6041 prospective phase II trial is assessing oncologic outcomes of preoperatively staged T2N0 rectal cancer treated with neoadjuvant CRT followed by local excision [29]. A total of 72 patients completed protocol treatment with 64% of tumors downstaged with CRT and 44% with evidence of a complete pathologic response. However, complications from CRT were substantial, with 39% of patients developing grade 3 or greater adverse events during the course of neoadjuvant treatment. At a median follow-up of 56 months, the 3-year disease-free survival was 86.9% in the per protocol group [142]. These high rates of adverse events led to revision of the protocol with dose reductions for both chemotherapy and radiation. Overall, in the absence of long-term oncologic data from ACOSOG Z6041 and other similar trials, this approach should be considered only in the setting of clinical trials.

Multiple authors have evaluated the combination of local excision of rectal cancer, including TAE and TEM, and adjuvant chemoradiation. Borschitz et al. reviewed the cumulative results from 267 patients with T2 rectal cancer from 13 case studies treated with TEM followed by adjuvant radiation (RT) or CRT [52]. Among a total of 64 patients treated with local excision and RT alone, 18% experienced local recurrence, whereas among 107 patients treated with both chemotherapy and radiation, this figured dropped to 11%.

Radical Resection Following TES

In patients with locally advanced rectal cancer, multiple studies have shown no difference in oncologic outcomes when TEM is followed by immediate salvage radical resection compared to initial radical resection. In many instances, accurate staging of suspected rectal cancers can be difficult based on location low in the rectum, difficulties with tumor sampling for an accurate diagnosis, and the current limitations of imaging modalities. This has led to the increasing use of TES to provide an excisional biopsy for suspected and early rectal cancers in order to guide further therapy. In a case-matched study, 25 patients who underwent TEM followed by immediate radical surgery based on unsuspected adverse pathological findings were compared to 25 patients who underwent TME as primary therapy [143]. No differences in operative time or intraoperative complications were noted between the groups, suggesting that prior TEM does not greatly increase the technical difficulty of future TME. More importantly, no differences in local and distant recurrence rates were noted between the groups.

However, when radical resection is undertaken later as salvage therapy for local recurrence following TEM, outcomes are generally poor [144, 145]. Baron et al. evaluated 21 patients who underwent immediate APR following TEM because of adverse histopathological features and compared this group to 21 patients who underwent salvage APR for local recurrence [146]. The disease-free survival for the immediate reoperation group was 94%, but in the salvage group, it was only 56%.

Obstacles and Limitations of TES

Training

A major obstacle to widespread adoption of TES has been the relative technical complexity of the operation and long learning curve given the relatively low volume of eligible patients with early rectal tumors suitable for TES, even at larger institutions. Although similar to single-incision transabdominal laparoscopy, transanal minimally invasive surgery is more challenging from an ergonomic standpoint as a result of the very narrow and shallow working space within the rectum. The transanal surgeon must overcome a steep learning curve, learning how to mazimize the working space for precise dissection and stable visulation and master their suture skills in this environment. The impact of the learning curve

for TEM has been investigated. Koebrugge et al. reviewed 105 TEM cases performed between 2002 and 2007 and demonstrated a significant decrease in the operative time, incidence of postoperative complications, and length of stay between patients treated during the later years of experience as compared to patients treated earlier in their experience with TEM [147]. Barendse et al. reviewed the cumulative experience of four colorectal surgeons who performed a total of 693 TEM resections of rectal lesions and demonstrated that conversion rate, operative time, and complication rates all decreased with increasing surgeon experience [90]. There is speculation that the adoption of TAMIS, with its use of ports and equipment that are familiar to surgeons skilled in laparoscopic surgery, may shorten the learning curve; however, this hypothesis has yet to be investigated.

Cost of TES

Multiple studies have attempted to address the cost of TEM, particularly in relation to the cost of radical resection. Of note, these studies include all indications for TEM, including resection of adenomas. In comparison to radical resection, the cost of TEM per procedure performed is certainly cheaper than radical resection. Cocilivo et al. performed an analysis of the cost of TEM and found that the cost per patient of TEM was $7775 USD as compared to $34,018 for low anterior resection [148]. This analysis did not include the cost of the TEM device, which is significant and certainly mitigates the cost savings associated with TEM, particularly if the procedure is not frequently performed. Maslekar et al. performed a case-control study to consider cost of TEM at a single institution [149]. A total of 124 TEM procedures were performed over 5 years and compared to 124 radical resections performed during the same time period where patients were matched on the basis of tumor and patient characteristics. The cost saving associated with TEM was found to be more than ten times the initial cost of TEM equipment during this time period.

Some studies have also attempted to address the cost of TEM in comparison to TEO or TAMIS. TAMIS, in particular, uses a disposable transanal platform which is less expensive relative to the capital investment costs of the specialized TEM and TEO platforms. This is particularly important when considering the relatively limited oncologic indications for TEM and the small proportion of patients who are appropriate for this approach. In a high-volume institution where TEM is performed frequently, the initial cost of the reusable metal platform and equipment may be offset by the number of cases performed, which may ultimately be cost-effective. Serra-Aracil et al. estimated the cost per procedure with 50 TEM procedures performed per year, taking into account fixed costs (non-reusable equipment) and variable costs (operating time, length of stay, and disposable equipment). Under these assumptions, the cost of TEM was 2310 euros, compared to 2220 euros for TAMIS and 1920 euros for TEO [26]. However, 50 procedures may overestimate the typical number of TEM procedures performed per year, even at those institutions with the largest experience.

Conclusion and Future Directions

Transanal endoscopic surgery is a minimally invasive approach to the rectum that has expanded in indications since its introduction over 30 years ago. The recent introduction of disposable transanal platforms and equipment may reduce operating time and cost of these procedures and facilitate widespread adoption of this approach by surgeons familiar with laparoscopic techniques in other settings. TES can be used in the curative treatment of rectal adenomas and select T1 rectal adenocarcinoma with oncologic results that are equivalent to TME. Moreover, TES results in much lower mortality and morbidity than TME, as well as improved functional outcomes. Currently, the use of TES for more advanced rectal cancer is limited to the experimental and palliative settings, but there is increasing evidence that in combination with neoadjuvant and/or adjuvant chemoradiation, TES may facili-

tate organ preservation and serve as an acceptable alternative to radical surgery for T2 or even T3 tumors in the future.

Furthermore, TEM and TAMIS represents an exciting new medium for the advancement of natural orifice transluminal endoscopic surgery (NOTES). A transanal endoscopic approach offers the possibility of "incisionless" transanal colorectal resection, whereby rectal and/or colon dissection followed by specimen extraction is performed primarily through the anus. The first case of transanal NOTES rectosigmoid resection with TME for a locally invasive rectal cancer was reported in 2009 with laparoscopic assistance [150]. Since then, a growing number of series on hybrid and pure transanal TME (taTME) cases have been published, demonstrating the feasibility and procedural and preliminary oncologic safety of taTME in carefully selected patients, with promising oncologic results [151, 152]. Future advances in surgical optics, multiport transanal platforms, and endoscopic instrumentation will help further the extent and scope of procedures that can be performed through a primarily transanal endoscopic route.

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