A Step Toward NOTES Total Mesorectal Excision for Rectal Cancer

Endoscopic Transanal Proctectomy

Jean-Jacques Tuech, MD, PhD,* Mehdi Karoui, MD, PhD,*† Bernard Lelong, MD,‡ Cécile De Chaisemartin, MD,‡ Valerie Bridoux, MD, PhD,* Gilles Manceau, MD, PhD,† Jean-Robert Delpero, MD,‡ Laurent Hanoun, MD,† and Francis Michot, MD*

Background: Previous publications have suggested that endoscopic transanal proctectomy (ETAP) is a promising technique and may be an alternative to conventional low anterior resection for rectal cancer. The aim of this study was to evaluate the technical feasibility of ETAP, with a particular focus on postoperative and oncological results and on functional outcomes.

Methods: This study was a multicenter prospective study of unselected consecutive patients with low rectal cancer requiring proctectomy and coloanal anastomosis. All patients underwent a standardized procedure. The study endpoints were the safety and adequacy of the oncological resection criteria. All patients were evaluated with the Wexner Fecal Incontinence Questionnaire after stoma closure.

Results: Fifty-six consecutive patients (41 men) underwent ETAP between February 2010 and June 2012. The median age was 65 years (39–83), and the median body mass index was 27 (20-42). No intraoperative complications were encountered. There was no postoperative mortality, and the morbidity rate was 26%. The mesorectum was complete in 47 cases (84%) and nearly complete in 9 cases (16%). The median number of lymph nodes retrieved was 12 (range, 7–29) per patient. The median radial and distal margins were 8 mm (0–20) and 10 mm (3–40), respectively. R0 resection was achieved in 53 patients (94.6%). The median Wexner score was 4 (3–12). Thirteen (28%) patients reported stool fragmentation and difficult evacuation.

Conclusions: ETAP is a feasible alternative surgical option to conventional laparoscopy for rectal resection and may represent a promising step toward rectal natural orifice transluminal endoscopic surgery (NOTES).

Keywords: endoscopy, laparoscopy, proctectomy, rectal cancer, transanal, total mesorectal excision

A recent paradigm shift toward minimally invasive procedures for the majority of surgical specialties has occurred. Natural orifice transluminal endoscopic surgery (NOTES) is a procedure performed through a natural orifice, such as the mouth, the vagina, or the rectum.

From the *Service de chirurgie digestive, Centre Hospitalier Universitaire de Rouen, 1 rue Germont 76031 Rouen Cedex, France; †Assistance Publique Hôpitaux de Paris, Pitié Salpêtrière University Hospital, Department of Digestive and HPB Surgery, Pierre and Marie Curie University Institute of Cancerology (Paris VI), 42-83 Bd de l'hôpital, 75013 Paris, France; and ‡Département de Chirurgie Oncologique, institut Paoli-Calmettes, 232, Boulevard Sainte-Marguerite, 13009 Marseille, France.

The potential advantages of NOTES over laparoscopic techniques include the following: absence of visible scars; faster recovery and shorter hospital stays; elimination of incisional hernia formation and wound complications; and the ability to perform procedures in patients for whom an abdominal incision is not feasible.[1–5] However, despite these potential benefits, most surgeons are reluctant to use this new technique because it requires the opening and closing of a healthy organ and the risk of related complications. This emerging concept has recently been applied to the field of rectal excision. The procedure has been performed in cadaver [6] and porcine models [7] and more recently in humans.[8,9] The main advantage of the transanal route over other access routes for NOTES rectal surgery is that the enterotomy is created at the level of the anus where the coloanal anastomosis will be performed without injuring another healthy organ such as the vagina or stomach. Fajardo et al[6] demonstrated in a multimedia article the feasibility of rectal resection using the transanal endoscopic microsurgery (TEM) system with long articulated instruments. More recently, Telem et al[10] reported NOTES transanal rectal resection with total mesorectal excision (TME) in 32 fresh human cadavers using transanal dissection alone (n = 19), with transgastric endoscopic assistance (n = 5), or with laparoscopic assistance (n = 8). The combined transanal and laparoscopic approach resulted in the lowest rate of complications compared with the transanal approach alone or with transgastric assistance (12.5 vs 26 vs 60%, respectively). On the basis of this extensive experience in human cadavers, abdominal laparoscopic assistance is required for the transition to the clinical application of transanal endoscopic NOTES rectal resection.

The aim of this multicenter prospective study was to report on our experience with endoscopic transanal proctectomy (ETAP) for cancer with a particular focus on postoperative and oncological results and on functional outcomes.

MATERIALS AND METHODS

Patients

All patients with histologically proven rectal adenocarcinoma who were candidates for rectal resection with TME and coloanal anastomosis (CAA) beginning in February 2010 were considered eligible for this study. Proctectomy with CAA was indicated in patients with low rectal cancer (lower edge <6 cm from the anal verge). Pretreatment clinical tumor-node-metastasis stage was defined by digital rectal examination, thoracic and abdominal computed tomographic (CT) scan, endorectal ultrasonography, pelvic magnetic resonance imaging, or a combination of these examinations. Patients with locally advanced tumor (ie, staged cT3, T4, and/or cN-positive disease) and those with very low cT2 cancer (involving the anal canal) were primarily treated with long-course chemoradiotherapy consisting in a total dose of 45 to 50.4 Gy delivered in daily fractions of 1.8 to 2 Gy in a 5- to 6-week period associated with 5-FU.

In patients with very low rectal cancer reaching or involving the anal ring, an intersphincteric resection was performed to obtain a free distal margin. Contraindications for ETAP procedure were the following: cT4 tumors invading the prostate or vagina with no objective response to neoadjuvant CRT and tumors invading the external sphincter and/or the levator ani muscle. These patients underwent abdominoperineal resection and were not included in this study.

Surgery was performed 6 to 8 weeks after the completion of chemoradiotherapy, if needed. All patients received a preoperative mechanical bowel preparation, and peroperative antibiotherapy was given according to local protocols.

Surgical Technique (ETAP)

The procedure has been previously described in a multimedia article by a member of our group.[9] Patients underwent operations led by 4 senior colorectal surgeons trained in laparoscopic TME surgery (M.K., C.C., B.L., and J.J.T.). In an effort to standardize the surgical procedure, one surgeon (J.J.T.) has performed this procedure since February 2010 and trained the 3 other surgeons of the group as a flying surgeon. Throughout the study, regular exchanges (eg, working meetings, phone calls, video exchanges) were organized to maintain the standardization of the procedure.

After general anesthesia, a urinary catheter was inserted, and the patient was placed in the lithotomy position. The operating surgeon sat between the legs of the patient. The Lone Star Retractor (Lone Star Medical Products Inc, Houston, TX) was systematically used to expose the anal canal. The procedure was started by a full-thickness circumferential rectal transection performed above the dentate line, and the perirectal fat was identified. The distal rectum was closed with a purse string suture as soon as possible to prevent cancer cell dissemination in the surgical field and to reduce the risk of septic contamination. The anal canal was then irrigated with a diluted betadine solution. At this step, the correct identification of the lipoma-like surface of the mesorectum was the key point in the procedure allowing the identification of the correct dissection plane. Proximal dissection along the plane of perirectal fat was performed with the rectum mobilized as proximally as possible. The choice between the 3 transanal access systems was left to the surgeon's discretion and included the following: endorec Trocar (Aspide, 42 350 La Talaudière, France), GelPOINT Path Transanal Access Platform (Applied Medical, Rancho Santa Margarita, CA), and SILS port (Covidien, Mansfield, MA).

The single port was inserted transanally, and the pelvic cavity was insufflated with CO_2 to a pressure of 10 mm Hg. We used a 5-mm 30-degree laparoscope, a bipolar grasper and a harmonic scalpel (Ultracision; Ethicon Endosurgery, Cincinnati, OH). The dissection was extended to achieve circumferential rectal mobilization by starting the dissection anteriorly, then posteriorly, and finally laterally. In male patients, the anterior dissection plane (in front of or behind the Denonvilliers' fascia) depended on the tumor's location. For patients with anterior tumor, the Denonvilliers' fascia was sectioned at the inferior border of the prostate and the dissection was then continued in front of the fascia. For those with posterior or lateral lesion, the Denonvilliers' fascia was respected and the dissection performed behind it. On the posterior aspect of the dissection, attention was paid to maintain the plane of the lipoma-like surface of the mesorectum to avoid a dissection too far posterior that would risk presacral vein injuries. On the lateral aspect of the dissection, care was taken to avoid injury to the autonomic nerve. Finally, the peritoneal reflection was identified anteriorly and opened to enter into the peritoneal cavity within the Pouch of Douglass. An abdominal laparoscopic approach was then performed using standard ports (one 10-mm port and three 5-mm ports) or a single multichannel port in

the future ileostomy site. The left colon was fully mobilized, and the inferior mesenteric vessels were divided in the standard fashion. The rectosigmoid was then exteriorized transanally, the sigmoid colon was transacted, and a handsewn coloanal anastomosis was fashioned. At least 1 drain in the pelvic cavity was placed in all cases. A defunctioning ileostomy was routinely performed at the end of the procedure (expect for those who underwent a delayed coloanal anastomosis) and reversal was planned for 2 or 3 months later. The technical procedure for delayed anastomosis with creation of a direct CAA 5 to 7 days after TME excision has been previously reported by Jarry et al.[11] Delayed coloanal anastomosis (DCA) was not routinely performed in our group but reserved for patients in whom a pouch could not be fashioned, that is, obese patients, patients with a narrow pelvis.

ASSESSMENTS

Data were collected prospectively. Operative variables were recorded. The surgeon examined the rectal specimen in the operating room to assess the distal resection margin and the integrity of the mesorectum; the specimen was then sent fresh to the histopathological department. The anterior and posterior surfaces have been photographed to record any perforation and the plane of dissection.[12] The quality of the mesorectum excision was assessed by the surgeon in the operative room and by the pathologist thereafter according to the grading described by Quirke and colleagues.[13] In case of discrepancy between surgeons and pathologists, the worse mesorectal grading was take into account. The assessment by the pathologist was not conducted as a blinded evaluation from the surgeon's assessment. Circumferential resection margin (CRM) involvement was defined as the presence of tumor cells located at 1 mm or less from the radial margin. Morbidity included all complications occurring during the hospital stay or within 30 days after discharge was graded according to the Clavien-Dindo classification.[14] Patients were followed-up according to the French guidelines for rectal cancer.[15] All were reviewed at 1 month and then every 4 months with a physical examination, carcinoembryonic antigen CEA level measurements, and abdominal ultrasonography or thoracoabdominal CT scan. Local recurrence was defined as a radiologically and/or a biopsy-proven tumor within the pelvis. Distant recurrence was defined as radiologic evidence of a tumor in any other area. Fecal incontinence was evaluated in patients followed for at least 1 year after stoma closure using the Cleveland Clinic Florida (Wexner) questionnaire.[16] The bladder function (urinary retention, need of intermittent catheterization) was assessed for all patients during follow-up. The erectile and ejaculatory functions were assessed for male patients during follow-up.

Obesity was defined by body mass index (BMI) and was calculated as follows: weight in kilograms divided by the square of height in meters. The definition of an anastomotic leakage in this study was clinical: pus or fecal discharge from the drain, pelvic abscess, peritonitis or discharge of pus per rectum. All anastomotic leakages were confirmed by water-soluble contrast enema, CT scan, or reoperation. An asymptomatic radiological leak was not considered because the patients did not undergo routine contrast enema after the operation.

Ethical Aspects

A prospectively collected, password-protected electronic database of all ETAP procedures from the 3 institutions was used to identify surgical outcomes in consecutive patients who underwent ETAP for rectal adenocarcinoma. The study was approved by the institutional review board and complied with the Declaration of Helsinki rules and the principles of the Good Clinical Practices guidelines. Informed consent was obtained for every patient.

RESULTS

Population Study

From February 2010 to June 2012, 56 consecutive patients (41 men and 15 women) underwent ETAP with TME. The median age was 65 years (range, 39–83) with a median BMI of 27 (range, 20–42 kg/m^2). Seventeen patients (30.3%) were overweight with a BMI between 25 and 29.9, and 11 (19.6%) were obese with a BMI of 30 or higher.

Using the American Society of Anesthesiology (ASA) classification system, 5 patients (9%) were classified as ASA 1, 40 as ASA 2 (71.4%), and 11 as ASA 3 (19.6%). In all cases, the tumor was located in the lower third of the rectum with a median tumor height of 40 mm (0–50) from the anal verge and of 10 mm (0–30) from the top of the anal ring. Initial tumor staging is detailed in Table 1. Three patients were diagnosed with synchronous liver metastasis, 1 patient underwent a simultaneous liver and rectal resection, and 2 patients underwent rectal and hepatic resection in the staging setting. Forty-seven (84%) patients received preoperative radiotherapy with concomitant chemotherapy.

Operative Data

The ETAP was performed using an endorec Trocar in 42 cases, with a SILS port in 11 cases and with a GelPOINT Path in 3 cases. To obtain negative distal margins, 10 partial intersphincteric resection (ISR) and 1 total ISR were necessary (19.6%). Dissection was performed in front of the Denonvilliers' fascia in 20 males with an anterior tumor. The median time for the transanal rectal dissection was 100 minutes (range: 70–180) and 170 minutes (range: 80–350) for the abdominal transperitoneal dissection, leading to a median length of 270 minutes (range: 150–495) for the total procedure. The abdominal laparoscopic dissection was performed with a single port in 8 cases, by multiport laparoscopy in 41 cases, by laparotomy in 4 cases, and by robotic-assisted laparoscopy in 1 case. In the group of patients operated on by laparoscopy, 3 conversions to laparotomy (3/41, 7.3%) were required due to adhesions from a previous operation in 1 case and because of technical difficulties in an obese male patient (BMI 32) and an obese female patient (BMI 37). No intraoperative complications were encountered. Four elderly patients (80, 81, 83, and 88 years old) underwent an intersphincteric proctectomy, the intestinal continuity was not restored because of altered sphincter function. Forty-six patients underwent transanal coloanal handsewn anastomosis using a colonic pouch in 4 cases, a latero-terminal anastomosis in 29 cases and a straight anas-

tomosis in 13 cases. Six (10.7%) patients underwent a DCA with a median interval of 8 days (range: 8–10) between the first and second stages. Straight anastomosis and DCA were performed in obese patients or patients with a narrow pelvis. In 2 patients, the Pouch of Douglas was opened too early before the completion of the posterior and lateral dissection, leading to a cessation of further transanal dissection due to the loss of the pneumopelvis; the procedure was then completed laparoscopically.

Early Postoperative Outcomes

There was no postoperative mortality. The overall postoperative morbidity rate was 26% (14/56). Three patients developed a clinical anastomotic leakage that did not required reoperation. Three additional patients were diagnosed with pelvic sepsis without evidence of anastomotic leak (2 of them required drainage under CT scan), 5 patients experienced transient urinary disorders, 2 patients required red blood cell transfusion during the postoperative course, and a 79-year-old woman suffered from a cerebral infarction with a favorable outcome. The median hospital stay was 10 days (range: 6–21).

Oncologic Results

Pathological findings are presented in Table 1. The histopathological analysis of the specimen revealed an intact removal of the mesorectum with intact fascia recti (grade 3) in 47 cases (84%) and a nearly complete mesorectum in 9 cases (16%). The median number of lymph node retrieved was 12 (range: 7–29) per patient. The median radial and distal margins were 8 mm (range: 0–20 mm) and 10 mm (range: 3–40 mm), respectively. R0 resection was achieved in 53 patients (94.6%). Among the 3 patients with a CRM of less than 1 mm (R1 resection), all underwent neoadjuvant chemoradiation for a large anterior tumor with a weak predictive margin (<1 mm) on the preoperative magnetic resonance imaging. Among these 3 patients, one developed a local recurrence at 24 months; the rate of local recurrence at the end of follow-up was 1.7% (Fig. 1).

The median follow-up time was 29 months (range: 18–52), and no patient was lost to follow-up. All 4 patients with synchronous liver metastasis underwent hepatic resection; 2 died at 24 and 37 months of metastatic evolution, 1 was alive without recurrence and 1 was living with liver and lung metastases. For the entire series, the overall survival rate was 96.4% (Fig. 2). Among the 52 patients with

TABLE 1. Preoperative Tumor Characteristics and Pathological Findings

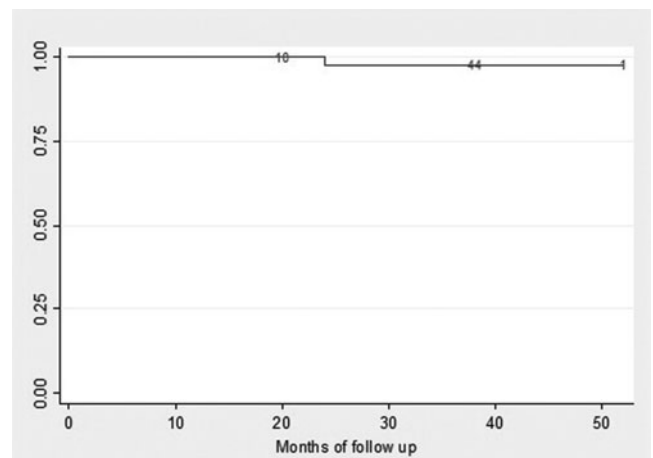| Initial T Staging	n (%)
T1sm3	3 (5.4)
T2	7 (12.5)
T3	44 (78.5)
T4	2 (3.6)
Pathological T stage	
pCR	11 (19.6)
pT1	7 (12.5)
pT2	16 (28.6)
pT3	21 (37.5)
pT4 (resection of seminal vesicle)	1 (1.8)
Pathological nodal status	
pN0	41 (73.3)
pN1	9 (16)
pN2	6 (10.7)

FIGURE 1. Kaplan-Meier curve describes postoperative probability of local recurrence-free survival (censored cases are indicated by numbers shown above the curve).
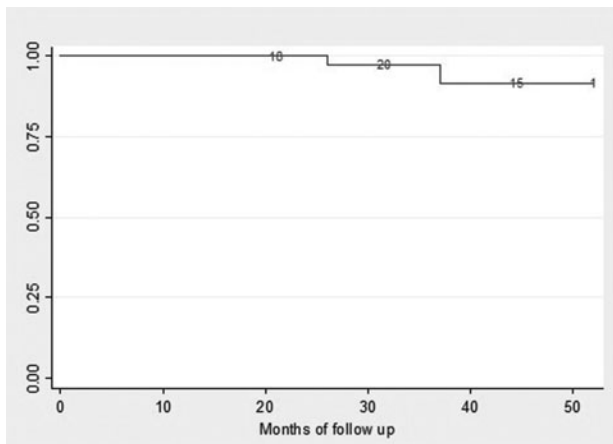
FIGURE 2. Overall survival curve of the entire series, n = 56 (censored cases are indicated by numbers shown above the curve).
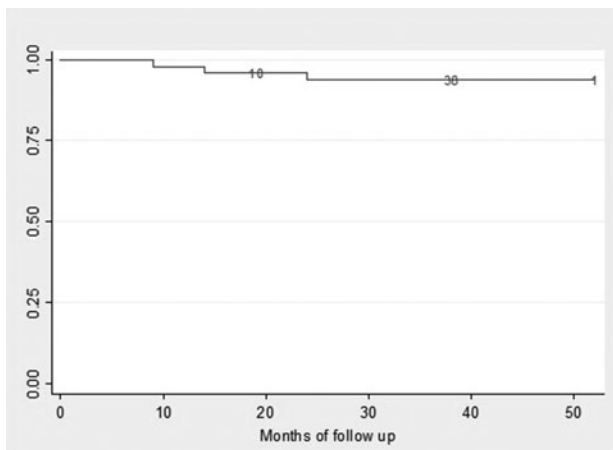

FIGURE 3. Disease-free survival curve for patients without synchronous metastasis (n = 52) (censored cases are indicated by numbers shown above the curve).

nonmetastatic rectal cancer at diagnosis, 2 developed (11, 13 months) unresectable lung metastases and are still alive under chemotherapy.

Among these 52 patients, we observed 2 metastatic and 1 local recurrences; leading to a 5-year estimate disease-free survival rate of 94.2% (Fig. 3).

Functional Outcomes

Intestinal continuity was restored in all but 4 patients with permanent colostomy. Fifty-two patients could be evaluated at least 12 months after surgery (DCA: n = 6) or after stoma closure (n = 46). The median Wexner score was 5 (range: 3–18), 3 patients (5.7%) required a colostomy because of severe fecal incontinence after ISR (Wexner score was: 15, 17, 18). For the remaining 49 patients without stoma, the median Wexner score was 4 (range: 3–12) and 14 (28.5%) had a score of more than 7. Thirteen (28%) patients reported stool fragmentation and difficult evacuation.

Five patients (8.9%) developed postoperative urinary retention, all were treated by temporary urethral catheterization. At 3 months, all patients reported normal urinary function with no incontinence, increase voiding frequency, nor urinary retention.

Fifty-six percent of male patients (23 of 41) reported no sexual activity. Among the remaining 18 male patients, the ejaculation was reported as unchanged in 12 (66.6%), 4 patients (22.2%) reported a decrease in ejaculatory amount, and 2 patients (11.2%) reported a failure to ejaculate. The potency was reported as unchanged in 14 (77.6%), decreased in 2 (11.2%) with an erection quality allowing intercourse. Impotence was reported by 2 patients (11.2%)

DISCUSSION

To our knowledge, this multicentric series is the largest to report specifically on the outcome of ETAP in the treatment of rectal cancer. The study demonstrates that, with abdominal laparoscopic assistance, the ETAP procedure seems to be safe, reproducible and does not negatively impact the oncological dissection or functional outcomes. For patients with low rectal cancer requiring CAA, the ETAP procedure represents an alternative to full abdominal laparoscopic rectal resection. For those with a narrow pelvis (male), visceral obesity or a large tumor diameter, this new approach may be of particular interest.

The feasibility of ETAP combined with abdominal laparoscopic assistance for rectal cancer has been previously demonstrated in porcine and human cadaver models[6,7] leading to worldwide human clinical trials.[17–20] The first clinical reports were published by Sylla et al,[8] who used a multiport laparoscopic instrument, and by Tuech et al,[9] who used abdominal single-port assistance. In this study, we have demonstrated that the use of this new approach led to mortality and morbidity rates of 0% and 26%, respectively. These findings are consistent with the mortality and morbidity rates after rectal resection for cancer reported in the literature. In a meta-analysis of 23 studies comparing laparoscopic and open resection for rectal cancer (4539 patients), Arezo et al[21] reported a mortality rate of 1% in the laparoscopic group and 2.4% in the laparotomy group and an overall complication rate of 31.8% in the laparoscopic group and 35.4% in the laparotomy group.

Since the publication of Heald and Ryall,[22] TME has been accepted worldwide as the gold standard surgical technique for mid and low rectal cancer resection. Despite the standardization of TME surgery and the demonstrated correlation between the quality of the mesorectal excision and the prognosis regardless of the use of neoadjuvant radiotherapy, several studies still report incomplete mesorectum upon pathological examination of rectal specimens in patients undergoing operations for rectal cancer.[23,24] Even in experienced hands, rectal resection with TME for mid or low cancer may be challenging, especially in male patients with a narrow pelvis, in patients with visceral obesity and for large-diameter tumors or tumors treated by neoadjuvant radiotherapy.[25,26] In these circumstances, the dissection of the distal horizontal part of the rectum via the abdomen (by laparotomy or laparoscopy) represents a difficult step during the TME procedure with a risk of excessive traction on the mesorectum, particularly at its distal portion, leading to an increased risk of suboptimal resection. The main difficulty lies in the exposure of the surgical field and the plane of dissection, which is at an angle to the available plane of surgical view. With the transanal route, this horizontal dissection is simplified because the surgeon's view is in the same axis as the low rectum and the plane of dissection. The sharp dissection is hence performed under direct vision in a largely avascular plane following the lipoma-like surface of the mesorectum. The exposure is obtained by gently pushing the distal rectum and mesorectum proximally, which opens the plane of dissection between the mesorectum and the parietal fascia. In our series, we demonstrated that optimal TME quality could be achieved using the ETAP approach, with a complete or nearly complete mesorectum in 84% and 16% of cases, respectively. Another quality marker in rectal cancer surgery is the achievement of negative resection margins. In our series, the rate of

positive circumferential margins was 5.3% (3/56). Our results compared favorably with those reported in the literature, ranging between 8% and 10% of CRM involvement.[27,28] Our study also demonstrated similar lymph node examination after ETAP when compared with the laparoscopic approach.[21] In addition, transanal dissection allows the surgeon to accurately identify the distal resection margin and to dissect it under direct vision. The interest of a transanal access during a proctectomy was emphasized by Marks et al since 1998.[29,30] In this study, a negative distal margin was achieved in all patients. The short oncological outcomes of the current series are in accordance with the results of previously published series.[31–35] From an oncological point of view, ETAP must also be evaluated with long-term results because the dissection route differs from that of the standardized TME technique.

One should emphasize that the ETAP technique is demanding and requires an expertise in both laparoscopic and rectal cancer surgery. However, after a short learning phase, similar results in terms of oncological criteria and morbidity were obtained between the 4 different surgeons involved in this study.

In our study, after the ETAP procedure, the postoperative function was good, with all patients continent to solid and liquid stool. However, it is difficult to draw any further conclusions about the functional outcomes because our group of patients was heterogeneous. The ETAP technique should be reserved for patients requiring a coloanal anastomosis with or without intersphincteric resection. For those who can undergo a colorectal anastomosis, better functional results may be obtained compared with CAA. Prolonged anal dilatation with a 4-cm diameter rectoscope may induce fewer sphincter function problems. Existing manometric analyses of the effects of anal dilatation after TEM indicated a decrease in sphincter tonus ranging from 2.5% to 37% compared with preoperative sphincter pressure, with complete recovery to clinical continence within 6 to 16 weeks postoperatively.[36]

In our study, the effects of nerve damage on functional results and in terms of quality of life have not been evaluated. However, the dissection in contact with the lipoma-like surface of the mesorectum has allowed an anatomical nerve sparing in all cases, as this has been verified during the abdominal time of the procedure. During abdominal dissection of the anterior aspect of the mesorectum, excessive traction of the seminal vesicle from the 10 o'clock and 2 o'clock directions might cause injury of the neurovascular bundle running to the genitalia. During the ETAP procedure, this traction is avoided and may better preserve sexual and voiding function than the usual approach. Further analyses are required to answer to this specific question.

This ETAP approach is a first step toward rectal NOTES surgery, which may represent a progression toward less invasive surgery. Today, we use transanal single-ports, which are routinely used for rectal tumorectomy by TEM and standard laparoscopic instruments. This instrumentation is maladapted and represents the major limiting factor for achieving proximal colon mobilization and splenic flexure transanally. Leroy et al[37,38] described the PROGRESSS technique (perirectal oncologic gateway to retroperitoneal endoscopic single-site surgery) in an acute porcine model and more recently in a 56-year-old woman with a midrectal carcinoma. Leroy referred to the procedure as a "no scar transanal TME." The authors performed a total mesorectal excision using a "bottom-up" approach. The sigmoid colon was mobilized by a posterior retroperitoneal approach, and the colon was divided intraperitoneally. With this report, the door toward the era of pure transanal NOTES for rectal surgery has been opened.

CONCLUSIONS

Our multicenter study demonstrated the feasibility and safety of TME by ETAP with abdominal laparoscopic assistance for rectal cancer. ETAP may represent a promising step toward rectal NOTES. However, before the widespread diffusion of this technique, evaluations of the long-term functional and oncological outcomes are needed.

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