Surg Endosc (2013) 27:3165–3172
DOI 10.1007/s00464-013-2872-0

Transanal natural orifice transluminal endoscopic surgery (NOTES) rectal resection: "down-to-up" total mesorectal excision (TME)—short-term outcomes in the first 20 cases

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Received: 17 November 2012 / Accepted: 5 February 2013 / Published online: 22 March 2013

Abstract
Background The transanal minilaparoscopy-assisted natural orifice transluminal endoscopic surgery (NOTES) approach holds significant promise as a safe and less morbid alternative to conventional low anterior rectal resection. Previous reports have shown satisfactory short-term oncologic results. We evaluated the safety and short-term outcomes in rectal cancer subjects who underwent transanal minilaparoscopy-assisted natural orifice surgery total mesorectal excision (TME) rectal resection.
Methods Twenty selected patients with rectal cancer were enrolled onto a prospective study of minilaparoscopy-assisted natural orifice surgery TME rectal resection. The study endpoints were safety of access (intra- or postoperative morbidity) and adequacy of oncological resection criteria; intact TME; distal and circumferential margins; and number of lymph nodes retrieved.
Results All procedures were successfully completed with the transanal NOTES and minilaparoscopy technique. The mean age was 65 ± 10 years; 55 % of patients were male; the mean body mass index was 25.3 ± 3.8 kg/m^2. Thirty-five percent of tumors were in the distal rectum, 50 % in midrectum, and 15 % in proximal rectum. Coloanal anastomoses were hand sewn in 65 % and stapled in 35 %. Mean operative time was 235 ± 56 min. There were no procedure-related complications. Pathologic analysis demonstrated negative distal and circumferential margins in all patients. An average of 15.9 ± 4.3 lymph nodes were retrieved. The mesorectal fascia was intact in all the specimens.
Conclusions This study demonstrates that transanal NOTES with minilaparoscopic assistance in the hands of a specialized team is safe; meets the oncologic requirements for high-quality rectal cancer surgery; and may offer advantages over pure laparoscopic approaches for visualizing and dissecting out the distal mesorectum. Minilaparoscopic assistance allows one to compensate for the limitations of current NOTES instrumentation to ensure the safety and adequacy of oncologic resection in these difficult cases. Careful patient selection, a specialized team, and long-term outcome evaluation are critical before this procedure can be considered for routine clinical use.

Keywords MANOS · Minimally invasive surgery · NOTES · Rectal cancer · Transanal

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Since the successful transgastric liver biopsy reported by Kalloo et al. [1] and a transgastric appendectomy by Rao in 2004 [2], natural orifice transluminal endoscopic surgery (NOTES) has been touted as the next step in the evolution of minimally invasive surgery. NOTES has been proposed as a surgical innovation allowing surgical procedures via natural orifices. These potential orifices are transoral (gastrotomy), transvaginal, or transanal (colotomy or a

transanal dissection). NOTES reduces the trauma associated with conventional surgery by maintaining the integrity of the abdominal wall. NOTES is still in an experimental phase and is not yet ready for routine clinical practice. Small series of patients have been reported, with only a few multicenter studies available [3]. The safe and responsible introduction of NOTES is an important challenge for the surgical community. However, NOTES does have the potential for complications related to technical limitations [4]. It is apparent that although it is technically possible to perform many types of surgical interventions using pure NOTES, these procedures have not yet been optimized for ease of performance and minimization of risk. Hence, most of the NOTES procedures reported in experimental literature still require refinement before they can be performed in humans and compared with established procedures. Common challenges facing many NOTES procedures include reliable closure of viscerotomies, triangulation of instruments, and stable tissue retraction. These limitations can be overcome with the use of laparoscopic assistance.

In the minilaparoscopy-assisted natural orifice surgery (MANOS) technique, access through the natural orifices can be done from any entry point, not just the vagina, with the advantage of supporting the surgery using minilaparoscopic instruments through tiny abdominal ports. Recently, this surgical approach has been applied to colorectal, splenic and bariatric surgery [5–7].

The feasibility of NOTES transanal surgery has increased its clinical applicability. Transanal NOTES in the field of colorectal surgery is intuitively better suited than other access routes. The enterotomy is created through the diseased organ itself and it is incorporated into the standard colorectal anastomosis. Furthermore, it has a significant advantage in avoiding abdominal extraction incisions in both male and female subjects and therefore represents the natural evolution of minimally invasive colorectal surgery. A pure NOTES colorectal resection, either using transvaginal, transanal, or transcolonic access, has not been reported in clinical practice. Some authors have described complete sigmoidectomy, colon mobilization, high vascular ligation, en bloc lymphadenectomy, and end-to-end anastomosis performed by a single operator using transanal endoscopic microsurgery (TEM) instrumentation in cadavers and swine [8, 9]. After our initial experience using a transanal laparoscopically assisted rectosigmoidectomy in a hybrid manner [10], we have reported the safety and feasibility of this approach in a total colectomy and in a low anterior resection for the treatment of rectal cancer [11, 12]. The aim of this study was to evaluate the safety and feasibility of transanal minilaparoscopy-assisted natural orifice surgery for rectal cancer.

Patients and methods

Patients with biopsy-proven rectal adenocarcinoma or high-grade dysplasia arising from rectal polyps were selected and enrolled onto a single-arm prospective study of minilaparoscopy-assisted natural orifice surgery rectal resection. A total of 20 subjects were enrolled at one center. This study was conducted in Spain at the Hospital Clinic of Barcelona from August 2011 to July 2012. The trial was conducted according to the principles of good clinical practice, and the institutional review board of the Hospital Clinic of Barcelona approved the use of MANOS transanal resection for rectal cancer in humans. Informed consent was obtained from patients after the risks and benefits of the procedure had been explained. Current contraindications to minilaparoscopy-assisted transrectal resection for rectal cancer at our institution include body mass index of >35 kg/m^2, presence of cT4 disease, tumor recurrence, and contraindications to pneumoperitoneum.

All the oncologic principles of open/laparoscopic resection for rectal cancer were strictly fulfilled. Diagnosis and staging was carried out in all cases with colonoscopy and biopsy, endorectal ultrasonography, pelvic and abdominal magnetic resonance imaging, and chest computed tomographic scan.

Neoadjuvant radiotherapy treatment was delivered to the pelvis with a three-field technique in 14 patients (Table 1). The total dose was 45 Gy, with a daily dose of 1.8 Gy administered 5 days each week and chemotherapy with continuous 5-fluorouracil (5-FU) infusion, 225 mg/m^2/day, during 5 days, concomitant with radiotherapy, which they tolerated well. We waited after completion of neoadjuvant therapy between 6 and 8 weeks before surgery. A summary of tumor characteristics and subject demographics is provided in Table 1.

Preoperative and anesthetic preparation

The day before surgery, patients underwent anterograde lavage with Bohn solution (Bohn Laboratories, Madrid, Spain). Prophylactic antibiotics (cefoxitin 2 g) were administered intravenously, and a thoracic epidural catheter was inserted for pain control. The patients were placed in the lithotomy position with stirrups; arms were tucked to the sides. The rectum was irrigated with 1 % diluted iodine solution.

Operative technique

The abdomen was insufflated to a pressure of 12 mm Hg via a Veress needle inserted through the umbilicus. It was then removed, and a 12 mm port was inserted through the same incision for a 30° angle mini scope (3D EndoEye

10 mm videolaparoscope; Olympus KeyMed, Europe). Two ports were inserted in the lower quadrants, a 5 mm port at the planned ileostomy site on the right and a 2 mm port at the drain location on the left. The abdomen and pelvis were inspected by laparoscopy for tumor invasion of the peritoneum and pelvic adhesions that might hamper a proper dissection. After this survey, the transrectal approach was initiated.

Combined transrectal and laparoscopy dissection for all cases, a multiport rectal device (GelPOINT Path Transanal; Applied Medical, USA) was inserted and sealed; CO_2 was insufflated to a pressure of 9 mm Hg. A 3D flexible-tip endoscope (3D EndoEye 5 mm flexible tip videolaparoscope; Olympus KeyMed, Europe) was introduced through the single port device (Fig. 1).

Table 1 Summarized demographic and preoperative characteristics of patients

Characteristic	Value
Age at surgery, years, mean ± SE (range)	65 ± 10.2 (44–77)
Gender	
Male	55 % (11)
Female	45 % (9)
BMI, kg/m^2, mean ± SE (range)	25.3 ± 3.8 (19–33)
ASA classification	
II	75 %
III	25 %
High-grade dysplasia polyps, mean ± SE	15 % (3)
Distance from anal verge, cm, mean ± SE (range)	6.5 ± 3.3 (2–15)
Rectum site	
Low	35 % (7)
Medium	50 % (10)
Upper	15 % (3)
Previous abdominal surgery	25 % (5)
Neoadjuvant CRT	70 % (14)

SE standard error of the mean, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *CRT* chemoradiotherapy

A purse-string suture was placed through the rectal mucosa to tightly occlude the rectum with a 3 to 4 cm margin distal to the tumor. In the case of very low tumors, less than 3 cm of the anal verge, circumferential dissection of the rectum was initiated at the level of the anorectal ring, above the anal sphincter complex, using the Lone Star Retractor System (CooperSurgical, USA). Distal to the purse string, a full-thickness rectal transection was initiated circumferentially. Once within the presacral plane, the mesorectum was mobilized, and the posterior dissection proceeded cephalad in the avascular presacral plane in accordance with total mesorectal excision (TME) principles. This plane of dissection was extended medially and laterally, with a careful maneuvering of the vagina or prostate from the anterior rectal wall to achieve circumferential rectal mobilization. The peritoneal rectal attachments were divided transanally, and the peritoneal cavity was entered (Fig. 2).

Laparoscopic graspers were used to retract and aid the dissection of the rectosigmoid and expose the vascular pedicle. The inferior mesenteric vessels were transected at their base with vascular clips. The remaining mesentery was dissected and sectioned by 5 mm LigaSure device (Covidien, Ireland).

Anastomoses and diverting stoma

After confirming that sufficient length of colon had been freed, the transanal single port was removed, the Lone Star Retractor was positioned and the rectosigmoid was carefully exteriorized transanally. In all cases the specimen was removed transanally.

Proximal colonic resection was performed extracorporeally. Hand-sewn coloanal anastomoses were performed between the proximal sigmoid colon and the distal anorectal cuff in 13 cases. A double purse-string lateral/end-to-end

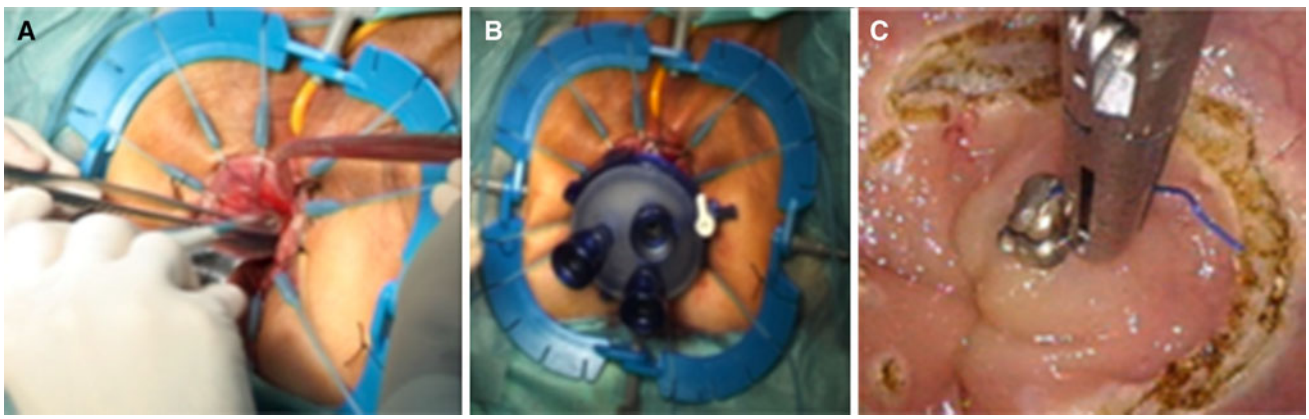

Fig. 1 Transanal dissection. **A** Lone Star Retractor positioned and transanal dissection. **B** View of transanal platform to access the rectal lumen. **B1** GelPOINT path. **C** Full-thickness rectal transection below the purse string

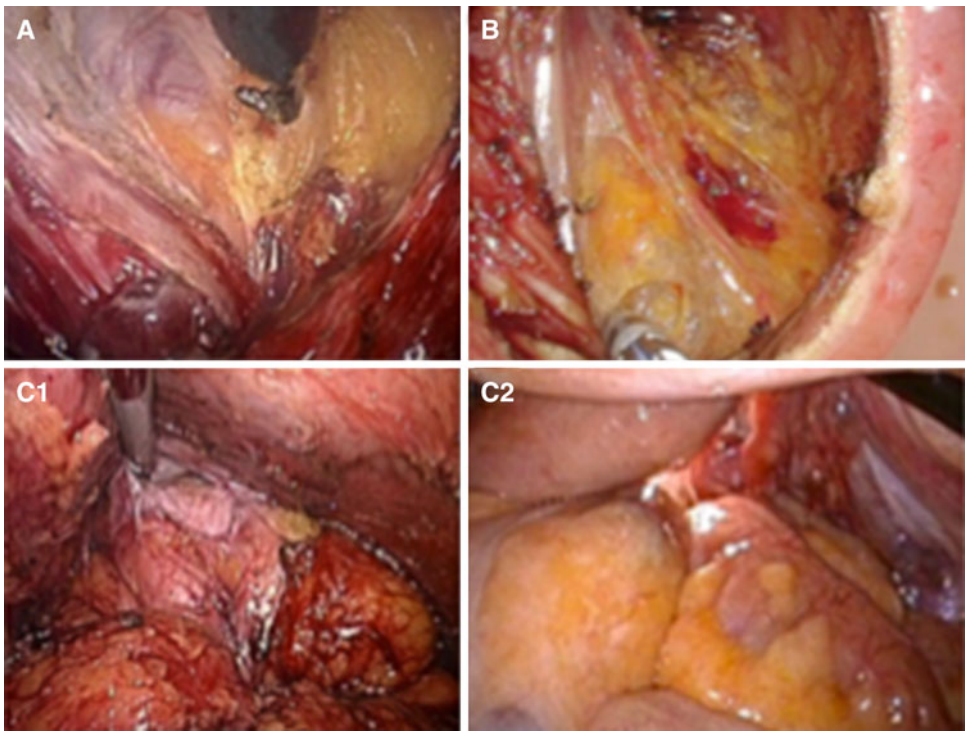

Fig. 2 TME transanal dissection. **A** Anterior dissection. **B** Posterior presacral plane. **C** Division of the peritoneal reflection. **C1** Transanal view. **C2** Laparoscopic control

stapling anastomosis was performed in the other 7 cases [12] (Fig. 3). With the assistance of the laparoscopic graspers, the anastomoses were performed under direct laparoscopic visualization. The anastomoses were tested using the pneumatic air leak test.

In 16 cases, a defunctioning loop ileostomy was exteriorized and matured in a standard Brooke fashion. The right lower quadrant mini port site was used for these. In all patients, a suction drain was placed in the deep pelvis and exteriorized through the left lower quadrant mini port site.

End point parameters and statistics

The end point parameters were to meet the oncological resection criteria (TME, distal and circumferential margins, number of retrieved lymph nodes) and safety of access (as measured by complications). For this purpose, we used the Clavien-Dindo classification [13, 14].

Data of continuous variables are expressed as mean ± standard error of the mean. Binary and categorical variables are reported as counts and percentages. Collected data and analyses were performed by SPSS software, version 16.0 (SPSS, USA).

Results

All procedures were performed in a hybrid manner without laparoscopic/open conversion. The mesorectal plane was dissected entirely transanally up to the level of peritoneal reflection in the superior pelvis. Complete mobilization of the splenic flexure was required in 6 cases; this was performed mainly with laparoscopic assistance.

The main operative and pathological characteristics of patients are listed in Table 2. Pathologic analysis confirmed that distal and circumferential margins were free of tumor. The number of lymph nodes retrieved was greater than 12 in 80 % ($n = 16$) of cases. The quality of the mesorectal plane was reported as satisfactory in all the specimens

The epidural catheter was removed on the second postoperative day, and pain was adequately controlled with oral analgesia. Using the Clavien-Dindo classification, 16 out of 20 (80 %) patients had no complications and 4 (20 %) had at least one complication. The postoperative mortality rate (grade V) was 0 %. The four patients with complications presented the following grades: 2 patients (10 %) had grade I complications, both with urinary retention, and 2 (10 %) had grade II complications, one with postoperative ileus and the other with severe dehydration due to increased ileostomy output. Follow-up visits at 15 and 30 days demonstrated no additional complications or readmissions. Table 3 lists the details in recovery outcomes and postoperative morbidity.

Discussion

Surgical treatment has been in constant evolution in the search for minimizing incisions, regardless of the complexity of the

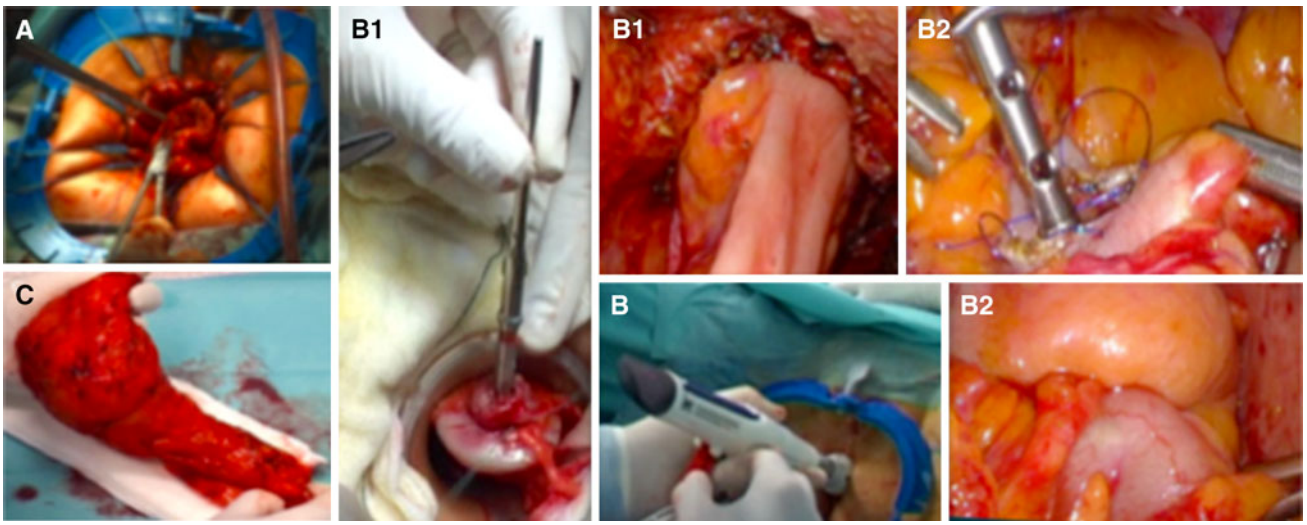

Fig. 3 Anastomosis and specimen. **A** View of the coloanal anastomosis. **B** Double purse-string end-to-end (**B1**)/lateral-to-end (**B2**) stapling anastomoses. **B3** Circular stapler. **C** Specimen with intact mesorectum

Table 2 Operative and pathological case characteristics

Characteristic	Value
Operative time, min, mean ± SE (range)	234.7 ± 56 (150–325)
Laparoscopic ports per patients, mean ± SE (range)	3.2 ± 0.8 (3–4)
Anastomosis	
Hand-sewn coloanal	65 % (13)
Stapling	35 % (7)
Protective ileostomy	80 % (16)
Estimated blood loss, ml, mean ± SE (range)	45 ± 15 (10–110)
Distal margin, cm, mean ± SE (range)	2.6 ± 1.6 (0.7–5)
Circumferential margin, cm, mean ± SE (range)	1.8 ± 0.7 (0.5–3)
No. of retrieved lymph nodes, mean ± SE	15.9 ± 4.3
Pathological stage	
High-grade dysplasia polyps, ypTNM stage	10 % (2)
I	20 % (4)
II	35 % (7)
III	30 % (6)
IV	5 % (1)

SE standard error of the mean, *ypTNM* pathological tumor, node, metastasis classification stage

operation. NOTES represents another step in this ongoing progression toward less invasive procedures. The advantages of such an approach includes reduced incisional pain, decreased wound complications, such as infections and hernias, improved cosmetic results, and potentially faster recovery and return to work [1–4]. Until substantial improvement in NOTES instrumentation is made to optimize this approach, these procedures are likely to require laparoscopic assistance [10–12, 15, 16].

Our first experience in colorectal surgical hybrid NOTES was via the transvaginal approach. Large colorectal specimens can be adequately extracted transvaginally [10, 11]. Consequently, we continued investigating transanal NOTES colorectal surgery because we believed that avoiding abdominal incisions for extraction (in both men and women) represented the natural evolution of minimally invasive colorectal surgery. Prior experimental work by several of us had demonstrated the feasibility and safety of transanal NOTES rectosigmoid resection in swine and cadavers [9, 10]. As a result of this collaboration, the first hybrid transanal rectal resection was performed under institutional review board approval, in a 76-year-old woman with rectal cancer located 8 cm from the anal verge [10].

Transanal NOTES offers the potential to perform major segmental colorectal resections without abdominal incisions aside from assisting instrument puncture sites. In this series, we have developed the technique of hybrid transanal natural orifice surgery assisted by laparoscopy, as described in previous publications [10–12]. With the currently available NOTES platforms, laparoscopic assistance is critical to provide adequate visualization of the inferior mesenteric vessels, dissection of the splenic angle, ureteral protection, and assistance with anastomosis creation. Our experimental studies had taught us that operative time was significantly shortened when laparoscopic assistance was combined with transanal dissection. In this series, we found that this approach was not only feasible, but more importantly, that complete rectal dissection with high-quality TME and a satisfactory number of retrieved lymph nodes could be performed transanally. An important advantage of transanal NOTES for colorectal resections is that rather than creating an opening through healthy viscera to perform the dissection, the enterotomy is created through the diseased organ itself. In addition, placement of a transanal

Table 3 Summarized recovery outcomes and postoperative complications

Characteristic	Value
Days until oral intake, mean ± SE	1.8 ± 0.9
Days until regular diet, mean ± SE	3.8 ± 2.1
Days until discharge, mean ± SE	5.8 ± 2.6
Pain control with oral analgesia, mean ± SE	5.4 ± 2.2
Postoperative morbidity, Clavien-Dindo grade	
I	10 % (2)
II	10 % (2)
III	0 %
IV	0 %
V	0 %
Postoperative hospital stay, days, mean ± SE	6.5 ± 3.1

SE standard error of the mean

purse string below the tumor ensures that an adequate oncologic distal margin will be achieved. In anterior tumors with a high risk of positive circumferential margin, a primary transanal endoscopic approach could facilitate the dissection of the Denonvilliers fascia and minimize injury to the prostate/seminal vesicles and vagina.

Minimally invasive colorectal procedures such as laparoscopy-assisted colectomies have been demonstrated to be safe in the clinical management of malignant disease [17, 18]. Laparoscopic surgery for rectal cancer has been considered technically more demanding compared to that for colon cancer. Microscopic assessment of the specimen is a well-recognized indicator of quality of resection in rectal cancer surgery. Both distal and circumferential resection margins are risk factors of recurrence after rectal excision [19, 20]. In the COST trial [21], rectal cancer was excluded, and in the MRC CLASICC trial [22], a higher incidence of positive circumferential margins after laparoscopic anterior resection for rectal cancer was observed. However, other authors did not observe differences between laparoscopic versus open surgery [23–25]. In our hospital, however, laparoscopic TME has been used without complications for the treatment of rectal cancer even with lateral lymph node metastasis or invasion to the adjacent organs [25]. We observed similar quality of surgery (i.e., R0 resection, satisfactory quality of the TME), with both distal and circumferential resection margins reported negative. The short-term oncologic outcomes of the current series are in accordance with the results of previously published series [26–30] and confirm the preliminary oncologic safety of the transanal approach for rectal cancer. We believe that this approach has the advantage of providing excellent visualization, especially in the narrow male pelvis, and it allows more precise autonomic nerve preservation. However, our study has bias in the selection of patients, and we are cautious about these results.

In this clinical series of hybrid transanal rectosigmoidectomy, we have demonstrated that an adequate oncologic rectal resection can be achieved. Regardless, the long-term oncological outcomes of this technical advance, in terms of local recurrence and survival, need to be further evaluated. Until such results are available, this approach for rectal cancer should be performed under institutional review board protocol by colorectal surgeons with extensive experience in minimally invasive surgery.

We preferred a flexible single-port device. Its pliable design and 40 mm diameter allow for an adjusted fit within the anal canal, with a safe and atraumatic retraction for enhanced exposure and access. This may have a less negative impact on anorectal function compared to TEM (40 mm rigid proctoscope). In some prospective studies, TEM has been associated with short-term anal dysfunction up to 6 weeks after surgery [31, 32]. Other advantages are that the deck on which the ports are anchored is broad and flexible, which allows greater maneuverability and triangulation of the movements and the comfortable use of a flexible 3D camera [33]; ports can be added or exchanged quickly, even an optional 12 mm port; and standard laparoscopic instruments are used to perform the transanal dissection.

To avoid a high leakage rate in patients in whom two or three cartridges are used for rectal division, efforts must to be made to remove the point where two stapler loads intersect [34–39]. The coloanal anastomosis does not have this problem when using the full rectal wall. For stapled anastomoses, we have perfected a technique that consists of a double purse string using a prolapse and hemorrhoid 33 mm circular stapler. This eliminates the need for multiple stapler firings required to transect the proximal end of the rectum. In addition, it allows us to add at least 1–1.5 cm to the distal resection margin. Creation of a diverting stoma seems to effectively reduce the clinical effect of anastomotic leakage and should be constructed in high-risk patients, such as those with very low colorectal anastomosis located 5 cm or less from the anal verge [40], like those presented in this series.

To our knowledge, this study is the largest report of the feasibility and safety of the MANOS transanal approach for rectal cancer, which adds to what was previously reported in smaller case series [12]. However, this study has some limitations. The small sample size limits the statistical power of the study, and because it is a single-arm study, there is no comparative group. Nonetheless, it achieves its goal of evaluating the safety and effectiveness of a correct oncologic resection.

Conclusions

Transanal NOTES/MANOS for rectal resections is still in a developmental stage, and few human studies have been published. The outcomes obtained from the 20 cases included in this prospective clinical series indicate that transanal NOTES can in fact be used to perform rectal cancer resection using laparoscopic assistance to compensate for the limitations in NOTES instrumentation and to ensure the safety and a correct oncologic resection. The improvements of surgical skill and instruments will standardize the NOTES approach, and the safety of the transanal approach for rectal lesions will continue to improve. There is a definite need for further studies to evaluate this approach with the evidence-based clinical practice and oncologic long-term outcomes. Only then may transanal NOTES be seriously considered for rectal resections in a clinical setting.

Disclosures Dr. Antonio M. Lacy is a consultant for Covidien and for Olympus Medical. Dr. Patricia Sylla has received an honorarium from Genzyme for consulting and an honorarium from Applied Medical for teaching. Dr. Rattner is a consultant for Olympus. Drs. Cedric Adelsdorfer, Marta M. Tasende, María Fernández, Salvadora Delgado, and Graciella Martínez-Palli have no conflicts of interest or financial ties to disclose.

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