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REVIEW

New trends in colorectal surgery: Single port and natural orifice techniques

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Abstract

Single-incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopic surgery (NOTES) have rapidly gained pace worldwide, potentially replacing conventional laparoscopic surgery (CLS) as the preferred colorectal surgery technique. Currently available data mainly consist of retrospective series analyzed in four meta-analyses. Despite conflicting results and lack of an objective comparison, SILS appears to offer cosmetic advantages over CLS. However, due to conflicting results and marked heterogeneity, present data fail to show significant differences in terms of operative time, postoperative morbidity profiles, port-site complications rates, oncological appropriateness, duration of hospitalization or cost when comparing SILS with conventional laparoscopy for colorectal procedures. The application of "pure" NOTES in humans remains limited to case reports because of unresolved issues concerning the ideal access site, distant organ reach, spatial orientation and viscera closure. Alternatively, minilaparoscopy-assisted natural orifice surgery techniques are being developed. The transanal "down-to-up" total mesorectum excision has been derived for transanal endoscopic microsurgery (TEM) and represents the most encouraging NOTES-derived technique. Preliminary experiences demonstrate good oncological and functional short-term outcomes. Large-scale randomized controlled trials are now mandatory to confirm the long-term SILS results and validate transanal TEM for the application of NOTES in humans.

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Key words: Surgery; Colon; Rectum; Cancer; Laparoscopy; Single-port; Natural orifice transluminal endoscopic surgery

Core tip: Despite lack of irrevocable proofs and unresolved technical issues, single-incision laparoscopic surgery (SILS) and natural orifice transluminal endoscopic surgery (NOTES) became inevitable options in today's colorectal surgery armamentarium. In comparison to conventional laparoscopic surgery, colorectal SILS offers a cosmetic advantage with no compromise of surgical morbidity, oncological appropriateness or increased cost. The "down-to-up" total mesorectum excision appears as the most encouraging NOTES-related technique for clinical application in humans. It further offers potential benefits in functional and oncological outcomes. Well-designed randomised studies are now essential to validate the long-term results of these novel techniques.

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INTRODUCTION

Laparoscopic colorectal surgery (LCS) has been confirmed as a safe and equivalent alternative to open surgery in the management of benign and malignant colonic diseases. Compared with open surgery, LCS reduces postoperative pain and duration of ileus, improves respiratory function, accelerates postoperative recovery, shortens hospital stay and enhances cosmesis[1-5]. Moreover, prospective randomized trials have demonstrated similar oncologic outcomes for LCS compared with open surgery in colon cancer patients[6-11]. In recent studies, laparoscopic resection for rectal cancer resulted in fewer postoperative complications[12-14] without compromising the oncological outcome[13,15].

LCS requires the usage of multiple ports, with each one representing a potential risk of hemorrhage, intraperitoneal organ injury, postoperative pain and herniation[16,17]. When laparoscopic surgery is intended for organ resection, as in colorectal surgery, a larger incision is required for specimen retrieval; this constitutes the major cause of morbidity in terms of pain, surgical site infection and herniation[18]. In a prospective study, the Pfannenstiel's incision used for specimen retrieval led to unsatisfactory cosmetic results in 40% of patients[19]. Dedicated questionnaires have recently demonstrated increasing patient interest in cosmesis, emphasizing their preference for more minimally invasive options compared with standard laparoscopy[20,21].

In this overwhelming tendency towards minimally invasive surgery, the ultimate goal would be to perform "scarless surgery" with similar safety profiles, efficacy and long-term outcomes as the standard laparoscopic surgery. Natural orifice transluminal endoscopic surgery (NOTES) is the ideal illustration of possible achievement of this objective, providing a scar-free surgery with the abolishment of incision-related complications, postoperative pain and adhesions[22]. Since its first description in 2004[23], NOTES has continuously gained interest, as illustrated by the increasing number of publications[24]. With less than 10% of total surgeries using NOTES[24], colorectal procedures remain in the early stages of development and are mainly performed in cadaver and animal studies[25]. Applications of this surgery in humans remain limited. Difficulties related to the access site are still under evaluation and remain unresolved[26-29]. Other limitations include available instruments, working angles and specimen extraction[30-32]. Currently, in the field of colorectal surgery, NOTES is mostly performed under laparoscopy assistance, designated as "hydrid" NOTES[33]. However, the transanal endoscopic microsurgery (TEM) initially described by Buess *et al*[34] more than twenty years ago has inspired a novel approach to rectal cancer surgery based on a transanal, down-to-up approach to the mesorectum. This undoubtedly represents the most encouraging NOTES-related technique[35-39].

On the other hand, primarily driven by the increasing experience in LCS, progression towards single incision laparoscopic surgery (SILS) was natural, logical and feasible[40,41,51]. In SILS, all incisions are concentrated within a single location, typically at the umbilicus, a natural embryologic scar or occasionally at the planned site of a stoma. SILS advantages have been claimed to extend beyond cosmesis. Compared with LCS, further reduction of parietal incisions and surgical stress are hypothesized to correlate with lower postoperative pain, fewer port site complications, a better morbidity profile, shorter hospital stay and reduced cost while also providing a better cosmetic result[42,43]. Thus, short-term outcomes are supposed to improve while the safety and satisfaction criteria of the patients are met[20,44]. With relatively minor changes to existing laparoscopic techniques, all colorectal procedures have been successfully performed with the SILS technique[45,46]. The worldwide popularity of this attractive technique has rapidly grown, as proven by the drastic increase in the number of publications over the past 3 years[47]. Lately, numerous studies have aimed to demonstrate the real benefits of SILS over conventional laparoscopic surgery (CLS) regarding short-term outcomes and appropriateness for oncological resections. However, conclusive advantages and long-term results need to be confirmed by large-scale, randomized controlled trials (RCTs).

In this study, we reviewed the current world literature regarding these novel colorectal techniques. After a short summary of the historical background, we will focus on the principal results of their applications in humans, paying special attention to comparison with CLS. Technical challenges and fields of future development will also be discussed.

LITERATURE RESEARCH

A systematic review of the published literature on colorectal SILS and NOTES was undertaken. The search was performed in October 2013 using PubMed, MEDLINE and the Cochrane Central Register of Controlled Trials. RCTs were recorded from the official web site www.clinicaltrial.gov. The following search terms were used: colorectal, colon, colectomy, rectum, proctectomy, total mesorectum excision, NOTES, NOSE, SILS, minimally invasive surgery and single port/trocar. Articles written in English or French were included irrespective of study type or publication status. A manual search of the reference lists of relevant papers was also performed to identify additional trials. Full-text reprints of all potentially appropriate articles were reviewed. The two reviewers separately classified the available articles into SILS, NOTES, comparative studies and future development. Hybrid techniques and non-human studies were included as appropriate for further discussion. Duplicate publications and those not written in English were excluded. The following information was extracted from each study concerning SILS: authors, year of publication, study population characteristics, study design, inclusion and exclusion criteria, number

of benign and malignant cases, performed procedures, oncological results, long-term follow-up, postoperative morbidity, postoperative length of hospital stay and cost. NOTES-related articles were scrupulously reviewed for organ-access site, performed procedures, used techniques, surgical outcome and oncological appropriateness.

HISTORICAL REVIEW

SILS was first reported in 1992 by Pelosi *et al*[48] as a transumbilical approach for appendectomy in a pediatric series and supracervical hysterectomy with bilateral salpingo-oophorectomy[18]. In 1997, Navarra *et al*[49] realized the first single-incision transumbilical cholecystectomy. This procedure was followed by the first single-port appendicectomy in 1998[50]. The first reports on colorectal resections through a transumbilical single-port access site were published in 2008[40,51] as a radical right hemicolectomy for polyp with extracorporeal ileocolic anastomosis. After initial experimental modeling[52], Bucher *et al*[41] realized the first transumbilical SILS sigmoidectomy for benign disease in humans. Progressively, more complex colorectal procedures have been successfully performed, such as anterior rectal resection, conventional proctocolectomy and total proctocolectomy with ileal pouch anal anastomosis[42,53-55]. Recently, in a large prospective series, Vestweber *et al*[45] demonstrated that SILS was suitable for all colorectal surgeries for benign and malignant diseases.

NOTES was first reported by Kalloo *et al*[23] in 2004 as a transgastric diagnostic peritoneoscopy. Within a year, the first human transgastric appendicectomy was presented at the Annual Conference of the Society of Gastrointestinal Endoscopy of India[56]. Aiming to encourage NOTES research and outline the areas of human application, the collaborative Natural Orifice Surgery Consortium For Assessment And Research (NOSCAR) was created from the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and the American Society for Gastrointestinal Endoscopy (ASGE)[57]. Following the creation of this consortium, many experiments on porcine models were performed, such as endoscopic gastrojejunal anastomoses[58], transgastric splenectomy[59], transgastric cholecystectomy[60], transgastric abdominal exploration and pelvic organ resection[61]. In 2007, the first successful NOTES in humans was described: cholecystectomy through transgastric[62] and transvaginal routes[63].

CLINICAL EXPERIENCE IN COLORECTAL SILS

The currently available data are mainly comprised of non-randomized, retrospective case series and fail to show formal superiority of SILS over CLS. Constant calls for RCTs[46,64-79] outline the urge for consistent data comparing these two techniques. However, since the earliest descriptive series, colorectal procedures were found to be safely performed under SILS[42,65,71,80]. It is surprising that the feasibility of the procedure has been the sole unchallenged conclusion[53,68,69,73-75,81,82], as if SILS was an intuitive, natural progression of CLS. Presently, SILS stands as an irrefutable alternative to colorectal CLS and merits scrupulous attention.

Heterogeneous reports indicate increased, equal or even decreased[75,83] operative time in SILS compared with CLS. However, most retrospective studies did not report any differences between SILS and CLS[68,69,74,78,82,84-92]. Conversely, four additional reports revealed a significant increase in operating times[77,93-95]. With prospectively collected data, Kim *et al*[77] clarified that operative time in SILS was significantly increased compared with CLS irrespective of the performed procedures (*i.e.*, right or left colectomy, rectal resection). Nevertheless, operative time decreases with accumulating experience[67,93,96], and the fiftieth case is considered the time-point when SILS becomes fully efficient[77]. The gap between accumulated experiences in CLS and early performances of SILS may explain the operative time differences observed in the initial series[65]. In fact, three recent meta-analyses failed to show a significant difference in operative times between CLS and colorectal SILS[66,70,79].

Despite contradictory results[97,98], the hypothesized reduction of postoperative pain in SILS has been extrapolated from studies on cholecystectomy[99]. Compared with LCS, the reported results on postoperative pain after colorectal SILS are equivocal. Some studies favor SILS[77,86], whereas others favor CLS[68,74,82]; no significant differences are in reported in the remaining studies[69,89,100]. This disparity might be attributed to different scoring methods [*i.e.*, number of doses[68], frequency of administration[74,77,91], visual analogue scale (VAS)[89,91,100,101], maximal pain score[74]] or types of analgesia (*i.e.*, epidural[68,78,89,102,103], Demerol equivalents[69]). Kim *et al*[77] identified a significant reduction in narcotic frequency administration, whereas three comparative studies demonstrated a significant decrease in postoperative pain on the first[86,91,101] and second postoperative day[86,91]. Additionally, Vasilakis *et al*[91] concluded the advantage of SILS in reducing immediate postoperative pain when patients were evaluated in the recovery room. The mean VAS score, doses of painkillers and time spent before transfer were significantly reduced in the SILS group patients compared with those of the CLS group patients. This finding could be related to the reduction in wall trauma by the SILS techniques. Conversely, Lu *et al*[82] stated that VAS scores were significantly increased in SILS colectomy patients compared with LCS patients (3.07 *vs* 2.41, respectively, $P < 0.001$). Despite the fact that the reduction of postoperative pain was one of the main arguments for the application of SILS in colorectal surgery, only one RCT has examined this topic[104]. This study reported a lower median pain score in SILS patients compared with the CLS group but no difference in total morphine usage, albeit on a small number of patients. The only meta-

analysis addressing this issue failed to find any significant differences between colorectal SILS and CLS[70]. Authors insisted on the inadequacy of existing data for homogeneous comparison and valid conclusions with respect to the inherent biases of retrospective studies and a lack of standardization in surgical techniques, analgesia protocols and pain assessment.

Overall, early postoperative complications after colorectal SILS occur in 9% to 31.5% of patients[45,47,64,74-77,79,84,105]. Severe complications (Clavien grade Ⅲ and Ⅳ[106]) occur in 3.2% to 9.6% of cases[64,77,78], mainly including deep vein thrombosis, bleeding (1.2% to 1.7%)[64,105] and leakage (0% to 6.7%)[47,64,77,86,101]. Occurring in 1.6% to 4% of cases, ileus remains the most frequent minor complication[47,64,76,96,105]. In a series of consecutive unselected patients, Osborne *et al*[75] reported significantly increased rates of anastomotic bleeding and urinary retention when high anterior resection is performed using SILS techniques compared with CLS. Bleeding and transfusion requirements after colorectal resection are typically comparable between SILS and CLS[68,77,82,84,86,89,91-93]. Ramos-Valadez *et al*[90] observed an increase in bleeding with CLS; however, the difference was not clinically significant given that transfusion was not required for any patient. Globally, all available comparative studies precluded any significant difference in complication or morbidity rates between these techniques[68,69,74,77,82,84,86-90,93,94,100]. Three meta-analyses[66,70,79] confirmed that the safety profile was comparable despite significant heterogeneity and inherent selection bias in the study design.

Intraperitoneal organ lesions under SILS techniques are reported in less than 1% of the cases[72,77,85,101,105]. It is worth noting that available data clarify whether the blind angles encountered in SILS techniques increase the risk of organ injury when compared with CLS. To demonstrate a significant difference for such a low rate, the comparison would require a large-scale study, comparable to what was needed for the assessment of bile duct injury after open *vs* laparoscopic cholecystectomy[107]. The reduction of peritoneal adhesions and subsequent bowel obstruction was among the claimed advantages of SILS, but there are no long-term studies so far that confirm this hypothesis.

Although rare, port site complications after laparoscopy include infection, bleeding and delayed hernia. Because complications are related to the increased number of ports[108], SILS was hypothesized to decrease these risks[16,66]. After a follow-up of 15 mo, umbilical incisional hernias have been reported in 4% of colorectal SILS patients[96]. However, this rate averages 0% to 1% in most studies[45,101]. Colorectal SILS are frequently performed through an umbilical incision, which is further enlarged for specimen retrieval. These facts have been specifically associated with an increased risk of trocar site hernia in large retrospective[109] and prospective[18] studies. However, no difference was found in trocar site hernia rates (0.6%) when comparing conventional gastrectomy with single-port laparoscopic sleeve gastrectomy[110], which is comparable to colorectal SILS for parietal incision placement and enlargement. We consider that parietal incisions in SILS are easier to close than those made in conventional laparoscopy. When closing the incision, the surgeon should better conceive SILS as a minilaparotomy than an enlarged laparoscopy and apply a careful running suture instead of an approximate wide stitch. Early infection is reported in 2.5% to 10% of cases[45,47,64,78,84-86,96,100,101], and SILS does not appear to alter this risk compared with CLS[46,86,91,100,101]. Wound bleeding and hematoma rates are seldom reported in the literature; when reported, these rates vary from 1.2% to 5.0%[45,64,90]. In a cohort study including 1142 SILS procedures, Weiss *et al*[111] reported comparable parietal complication rates with the exception of infection, which appears to be more frequent in colorectal procedures (2.5% *vs* 1.05%). Despite the fact that reduced port-site complications was one of the most defended arguments in favor of SILS, it is surprising that no consistent data confirm this hypothesis to date.

To assess the oncological appropriateness of SILS for colorectal cancer, numerous studies compared surgical margins with those found in CLS. No significant differences were detected between the two groups[68,69,74,77,82,84,90,92,93]. This finding was supported by the meta-analysis conducted by Zhou *et al*[66], stating that SILS was equivalent to CLS for R0 resection and specimen length. The number of retrieved lymph nodes was also equivalent between the two techniques in most studies[68,69,74,77,78,84-86,90,92,93] with the exception of the study that favored SILS over CLS. This finding may be explained by more rigorous lymph node harvesting to fulfill the oncologic criteria of minimal retrieval. In one recent meta-analysis[70], the number of nodes harvested was significantly increased in SILS compared with CLS (P = 0.035) with no evidence of statistical heterogeneity or bias. Conversely, another meta-analysis reported that the two techniques were equivalent for lymph node retrieval[66]. Nevertheless, the oncological appropriateness and quality of resection do not appear to be compromised with SILS techniques in colorectal cancer patients. In a case-matched comparative study with a mean follow-up of 13 mo, Papaconstantinou *et al*[92] reported a similar disease-free survival rate of 92% in the SILS and CLS groups. Moreover, the authors did not observe any port-site recurrence in either group; these findings are similar to those reported by Huscher *et al*[78] in a RCT after a follow-up of 22 mo. Finally, long-term outcomes of colorectal SILS for malignant diseases can not presently be assessed given the lack of long-term follow-up in the available data[64].

Cosmetic benefits were naturally expected from the early descriptions of SILS procedures given that a reduced incision length logically equals improved cosmesis[41,81]. Although refuted by some authors[69,74,86,90,91,93,94], many studies favored SILS given its significantly shorter incision[68,82,87,89]. This finding was confirmed by three meta-analyses[66,70,79]. However, Leblanc *et al*[81] suggested

that cosmetic evaluation should only be undertaken after the healing process is complete. Moreover, most authors rely on subjective criteria, such as their own impression or collected feedback by nurses and medical team members[68,71,74,77,82]. Only a single study reported higher cosmetic score in SILS than in CLS but failed to show a difference in body image scores[87]. An objective cosmetic score that considers a patient's perception of his/her body image needs to be developed as it may help provide a more accurate assessment of the cosmetic advantage of SILS over CLS[47,66,76,105]. On the other hand, it is natural to accept the cosmetic advantage of SILS when performed in a planned stoma site, such as abdominoperineal resection, total colectomy or restorative proctocolectomy for familial adenomatous polyposis or ulcerative colitis[46,53,55,73,77,112]. In patients with previous colectomy, the second-stage restorative procedure can be accomplished by placing the SILS port in the right iliac fossa after mobilization of the terminal ileostomy[54]. In these particular settings, the cosmetic benefit combines with the reduction of parietal trauma because the single access point is used for organ dissection, specimen extraction and stoma formation, thus moving closer to the aspired result of a virtually scar-free procedure.

Overall conversion rates vary from 0% to 16.7%[47,64,69,71,72,74-76,78,84,85,90,94,96,100,101] and from 0% to 16.6%[45,47,64,69,72-78,90,93,96,113,114] for LCS and open surgery, respectively. However, two recent collective reviews[79,105] estimated that conversion rates ranged from 3.7% to 8.0% and 1.6% to 2% for CLS and open surgery, respectively. These results appear to be more adequate to actual applications because high conversion rates were commonly stated during the learning period in early series[72,85]. Nonetheless, SILS does not increase the conversion rates in most comparative studies[69,74,77,84,86,88-92,94,100]. This observation was confirmed in three meta-analyses on colorectal procedures that demonstrated comparable rates between the two techniques[66,70,79]. The most reported causes of conversions are bleeding and technical difficulties, such as adhesions, large tumors, poor visibility from thick omentum and perforated diverticulitis[45,47,72,74,76]. Additionally, significantly increased conversion rates have been reported in rectal surgery (up to 25%) compared with colonic resections (as low as 3%)[79]. In our opinion, a novel approach must primarily provide safety to gain widespread acceptance. At any time, every new technique should allow a fallback solution should the patient's safety be compromised or if the expected result is suboptimal. This is our vision of the new era of laparoscopy, wherein an initial SILS technique possesses the potential to add additional trocar(s) in difficult cases, just as CLS permits conversion to laparotomy whenever deemed necessary by the surgeon. Conversion should not be perceived as a failure of the approach but rather a technical solution to provide a better outcome. With increasing experience, surgeons should naturally be able to perform the procedure exclusively with SILS more frequently.

The median duration of hospitalization is a particularly variable parameter driven by clinical factors (such as patient characteristics, type of performed surgery and occurrence of postoperative complications) and differences in hospital discharge practices (based on economic considerations and social support)[66]. Nevertheless, different comparative studies have questioned this issue, and most of these studies failed to demonstrate significant reduction of the length of stay with SILS[68,69,74,75,82,84,85,87-90,93,94,100]. Others claimed that patients operated on with SILS were discharged significantly earlier than patients with CLS[77,83,86,91,92,95]. All results of the three meta-analyses converged to suggest the advantage of SILS in terms of duration of hospitalization[66,70,79]. Because reduced postoperative pain is questionable and the complications profile is comparable (see above), faster postoperative recovery after SILS may be attributed to earlier bowel movement and faster tolerance to normal diet, as demonstrated in a couple of studies[75,77] and confirmed in a single meta-analysis[66]. Since 1997, when Kehlet *et al*[115] introduced the concept of enhanced recovery after surgery, different measures and strategies were implemented to reduce surgical stress and improve the postoperative course. Among these strategies, laparoscopy has been proven to play a crucial role in patients undergoing colorectal resection[116-119]. Apart from the controversial benefits of new minimally invasive techniques *per se*, we consider SILS and NOTES perfectly integrate the trend of reducing the surgical burden. Thus, these techniques may not fully reveal their presumed advantages unless integrated in a global fast-track strategy.

When initially compared with conventional laparoscopy, SILS was considerably more expensive than CLS due to newly released sophisticated trocars and the common use of dedicated instruments[81]. With increasing interest in SILS and subsequent competition between industrials, recent studies claimed that the cost of the SILS port is only a little more than four conventional ports[65,84]. Surprisingly, in a comparative study, Fujii *et al*[68] demonstrated that the cost of access instruments in SILS was significantly cheaper than CLS. The initially reported cost excess may be outweighed by accumulating experience that leads to a reduction in operative time and routine usage of conventional instruments. However, only a demonstration of reduced morbidity, faster postoperative recovery and reduced length of stay will ultimately render SILS cost-effective[70,105].

Since the initial reports on SILS, early postoperative mortality has been anecdotally reported. This observation is confirmed by recent collective reviews that estimate mortality rates to be less than 1% after colorectal SILS[76,105]. A unique case of intraoperative death is reported in the current literature[47]. The event was secondary to the avulsion of the middle colic vein during colon exteriorization, leading to massive blood loss and subsequent multi-organ failure. Adair *et al*[85] declared a case of early postoperative death from pulmonary embolism. Two cases of postoperative death were

described; one secondary to cardiopulmonary failure on the following day after SILS sigmoidectomy[112] and the other as a complication from metastatic disease after palliative SILS right colectomy[95]. Given that mortality rates are low among both SILS and CLS, comparison requires a large randomized study with precise clustering of patients based on their operative risks.

CLINICAL EXPERIENCE IN COLORECTAL NOTES

The human "pure" colorectal NOTES experience started with Bernhardt *et al*[120] and Palanivelu *et al*[121], who described the transvaginal appendicectomy in 2008. A single-canal standard gastroscope was used as the sole instrument, and the procedure was successfully performed as an "atypical" endoscopic intervention. Rapidly, the limits of conventional endoscopic instruments were expected if more complex colorectal NOTES procedures were to be performed. In fact, colorectal surgery comprises wide organ dissection and commonly necessitates the restoration of continuity (*i.e.*, confection of an anastomosis). The latter represents the most crucial limiting step for NOTES. Meanwhile, as bridges for "pure" NOTES, alternative techniques, such as "hybrid" NOTES and transanal TEM, have extended the application of these novel techniques in humans.

After the first report of transanal sigmoid resection in cadavers by Whiteford *et al*[30] and the demonstration of its feasibility and safety in swine[122,123], Sylla *et al*[124] described the first successful total mesorectum excision (TME) using transanal endoscopic microsurgery with laparoscopic assistance in a human. Later, Zorron *et al*[33] reported two successful clinical cases of laparoscopy-assisted transanal TME: one with the use of a standard colonoscope and the other with a transanal single port device. To date, a couple of small, effective series promoted the feasibility of transanal TME with minimal laparoscopic assistance for rectal cancer[35-38]. In addition to proof of feasibility, acceptable complication rates and appropriateness of oncological resection, efforts are still needed for technique optimization and routine clinical application. Recently, Leroy *et al*[125] described the first case of "pure" NOTES transanal TME with intraperitoneal division of the colon and a side-to-end hand-sewn coloanal anastomosis in a woman. However, considerable work is still required for standardization of these techniques before clinical application can be routinely advocated. Clinical postoperative advantages and long-term oncological outcomes are further issues to be assessed if we aim to precisely identify the real place for these emerging techniques among conventional approved procedures. In our experience (in press), "pure" NOTES TME for rectal cancer was achieved in 10 of the 16 selected patients. These patients had hand-sewn coloanal anastomosis without diverting stoma. Lymph node dissection, vessels ligation and splenic flexure mobilization were performed through the unique transanal approach with conventional laparoscopic instruments. We demonstrated a favorable morbidity profile with appropriate oncological parameters even after neoadjuvant chemoradiotherapy. The "down-to-up" TME allows for a magnified view, shorter focal length between the operator's eye and the most critical part of the mesorectum (*i.e.*, its distal half), better definition of the pelvic nerves, less disruption of the distal mesorectal cone and better sphincter conservation for very low rectal tumors. In addition, preservation of the abdominal wall is achieved, and the cosmetic goal is reached. In the other six patients who needed laparoscopic abdominal assistance, we consider the umbilical SILS (except for abdominoperineal amputation) to be the ideal access site, combining direct vision for "up-to-down" mesorectum dissection, ease of splenic flexure dissection, a diverting stoma site and an improved cosmetic result (*i.e.*, after stoma closure).

The minilaparoscopy-assisted transvaginal approach for colorectal procedures was initiated by Lacy *et al*[126] and Burghardt *et al*[127], who achieved the first radical sigmoidectomy and right colectomy, respectively. Since then, minimally invasive surgeons have integrated natural orifice access to their repertoire. Minilaparoscopy-assisted natural orifice surgery (MA-NOS) refers to a surgery initially using NOTES with the addition of a laparoscopic tool. The largest port is then hidden in the natural orifice, which serves as both a working channel and an extraction site. Lacy *et al*[128] described the first laparoscopically assisted transrectal MA-NOS for total colectomy in a man. They stated that until longer, more flexible, better-adapted instruments were available to address the specific needs of NOTES, laparoscopic assistance should be provided, at least to assist with visualization, retraction and full-thickness closure of viscerotomy. Recently, Fuchs *et al*[129] reported their prospectively collected data on minilaparoscopy-assisted transanal colon resection for benign diseases in women. All tasks requiring a port diameter > 5 mm were transanally performed *via* a specially designed transanal endoscopic applicator. The authors showed that a transcolonic route was feasible and safe in humans, representing a major encouraging argument in favor of "pure" NOTES application.

On the other hand, natural orifice specimen extraction (NOSE) aims to reduce the abdominal wall trauma induced by specimen retrieval in laparoscopy[130-132]. A recent prospective report confirmed that the colon specimen could be extracted through the anus or vagina with acceptable morbidity rates[133]. Transanal NOSE is deemed feasible and safe for rectal cancer according to the collected results in a 2-year follow-up study[134]. Further improvement consisted of the NOSE-SILS combination, including when the laparoscopic port is hidden within the umbilicus or an existing or planned stoma site, allowing for the performance of a virtually scarless surgery[131,135]. Leroy *et al*[136] described the first

transumbilical SILS sigmoidectomy with transrectal specimen extraction. Based on the success of the procedure, the authors insisted on the need for a prospective study to assess feasibility, infectious risks, safety in oncologic cases and functional outcomes for the short- and long-term.

TECHNICAL CHALLENGES IN COLORECTAL SILS

With growing experience in colorectal resections, it became obvious that SILS generates new challenges and magnifies difficulties compared with LCS[65,71,81]. Even experienced surgeons are facing a new learning curve because the skills required for SILS are different from those acquired in LCS[137]. The handling of straight instruments in parallel with the laparoscope through a small single incision decreases the range of movement for the surgeon and complicates the holding of the camera by the assistant[95]. Given the inline axis of the camera and the instruments, the movement of one of the instruments may result in inadvertent displacement of the others. This explains the difficulty encountered when performing even relatively simple tasks[138]. Furthermore, the lack of instrument triangulation increases the complexity of organ exposure and dissection[73,81,95]. This is particularly evident in SILS for colorectal procedures given that the exposure of different abdominal quadrants is often required; this feature is in contrast with cholecystectomy or appendicectomy, which both involve only one abdominal quadrant[139].

To regain triangulation and improve exposure, initial reports found it judicious to use specially designed, curved, S-shaped and reticulating instruments in colorectal SILS[41,81]. To date, only a few teams still recommend the adoption of these dedicated tools[71,87,89,112,136]. Conversely, most authors consider the use of these tools to add complexity[90,139]. As experience accumulates, difficulties are overcome, and most authors confirm that all colorectal SILS procedures can be performed using conventional straight instruments[42,45,47,53,65,67,69,74,77,78,84,91,100]. The use of tools of various lengths or an extra-long laparoscope, preferably with a right-angle light-cord, can be of value in reducing external clashing[88,90]. In several cases, a semi-rigid endoscope camera with a flexible tip (EndoEye; Olympus America, Center Valley, PA, United States) expands visualization possibilities and brings additional safety during dissection[139].

In a desire to overcome these difficulties and because SILS might serve as a step toward NOTES, we wondered whether we could adhere to the fundamentals of endoscopy. For a gastroenterologist performing operative endoscopy, the operator handles both the visualization task and the effector instrument, so that eyes and hands depend of the same brain. As a result, inefficacious time-outs during the procedures are shortened and the execution of orders is accelerated. Thus, we advise holding the camera in one hand and the operative instrument in the other. According to this scheme, the role of the assistant is to retract the organs and tissues, providing a "neo-triangulation". Giving this static task to another person significantly reduces the conflict of instruments in the reduced space available. We consider that this setting considerably shortens and facilitates the learning curve in early experiences.

SILS application in inflammatory bowel disease harbors further specific difficulties. In the case of total colectomy, most authors advocate a clockwise dissection because the right hemicolon represents the most difficult part of the procedure and is associated with the highest rate of conversion[140-142]. In restorative proctocolectomy, the SILS port is ideally inserted at the planned site of ileostomy in the right iliac fossa[54]. However, to facilitate exposure for initial cases, alternative placement of the SILS port in the umbilicus has been described[143]. The stoma site in the right iliac fossa is then used for an additional 5-12 mm port, resulting in a hybrid SILS procedure.

Because SILS is technically challenging, efforts have been delivered to identify clinical parameters associated with increased difficulty. Some authors consider emergent conditions, T4 tumors and a history of abdominal surgery to be contraindications for the procedure[45,47,69,78,84]. A poor ASA score[45,77,90] and a large bulky mass[45,73,77,90] have also been reported as contraindications. Visceral obesity stands as a major clinical parameter that increases the dissection difficulty[43], lengthens the operative time[43] and predisposes to conversion[69]. Early reports[65,72,78,85] focused on careful selection of patients for initial SILS procedures. In early experiences, it was prudent to consider patients with no history of inflammatory disease (*i.e.*, diverticulitis) or prior abdominopelvic surgery as well as BMI < 30 kg/m^2[45] as surgical candidates.

Various adjunct procedures have been proposed to overcome the difficulty of SILS. Leroy *et al*[144] reported the usefulness of locking the anvil of the circular stapler in the proximal colon by a transparietal magnet to facilitate mesenteric dissection. The authors suggest that this technique harbors several additional advantages, such as the performance of a "fully laparoscopic" procedure with intraperitoneal anastomosis, solving the issue of fascia incision enlargement. This feature is particularly useful in left-sided safe and carries no increased risk for infectious complication[145]. Another comparable trick utilizing a magnetized intracorporeal vascular clip to retract the organ *via* an extracorporeal magnet was described by Uematsu *et al*[103]. Finally, Fujii *et al*[68] described the colon-lift technique as an easy, efficient and economical trick that does not require special instruments and may be applied to radical resections.

Because both SILS and NOTES present the same conformational challenges of inline vision, absence of triangulation and difficult surgical exposure, it could be argued that application of colorectal SILS is a step towards colorectal NOTES with a potential transfer of skills[65]. However, no consistent data are currently

available to support this argument.

TECHNICAL CHALLENGES IN COLORECTAL NOTES

As initially identified by the NOSCAR[57] and further outlined by the regular meetings of the SAGES/ASGE and EAES/ESGE societies[146-149], NOTES still exposes technical issues that need to be resolved before standard human application can occur. These issues include ideal access to the peritoneal cavity, prevention of infections, viscerotomy closure, suturing/anastomotic devices, spatial orientation and the development of an adequate multitasking operating platform. NOTES techniques also require near-perfect endoscopic skill[30] and raise an ethical problem regarding the injury of healthy access organs[150]. In a recent evaluation of ergonomics, NOTES was found to uniquely limit visualization, complicate tissue manipulation and reduce the ability to autonomously perform tasks. NOTES requires close collaboration among the entire team to safely complete the procedure[151]. In this review, special attention is directed toward the specific difficulties of NOTES application in colorectal surgery.

In early NOTES experiences for end-organ resection, such as cholecystectomy, transgastric and transvaginal accesses were favored over transanal and transcolonic approaches[62,63,152,153]. This preference was driven by major unresolved issues regarding the risks of infection, bacteria spillage in the peritoneal cavity and secondary leakage after closure[26]. However, theoretical microscopic fecal contamination is not a specific risk to NOTES and may also apply to laparoscopic, open and TEM resections[128]. To fully elucidate this concern, a prospective study comparing peritoneal contamination in NOSE/NODES and non-NOSE/NODES colorectal procedures should be performed[136]. The transgastric approach exposes the blood vessels and surrounding organs to the risk of injury. Moreover, it does not provide adequate access to the pelvis and the lower part of the abdomen. To date, colorectal resection has not yet been achieved through the transgastric route[149]. Vaginal access can be realized *via* direct vision through a speculum or direct laparoscopic visualization. The vaginotomy is usually executed at the posterior fornix or at the apex in patients with a previous hysterectomy[154]. To improve access, the uterus can be anteriorly fixed using a transparietal suture. For increased reach, laparoscopic bariatric instruments can be used when working through the vagina. In such a limited access site, a flexible tip laparoscope can significantly reduce the intersection of the instruments[154]. The transvaginal approach offers the advantage of direct access to the pelvic organs, but the technique is only applicable in 50% of the population. The procedure also exposes patients to the potential risks of dyspareunia and infertility; however, the actual occurrence of these risks has not yet been specified in clinical studies[147]. However, when precise precautions and contraindications are respected, the complication rate of the transvaginal approach is reported to be less than 5% according to the latest Euro-NOTES status paper[149]. In a prospective cohort study of 106 sexually active women, Linke *et al*[155] confirmed that the transvaginal access technique is safe, with a risk of sexual dysfunction in less than 5% at one year. The transanal/transrectal approach offers several valuable advantages for colorectal surgery. First, the entry point and secure closure can be achieved under direct view in all patients[124,156]. Second, this approach provides direct access to the operative field and upper abdominal quadrants through a short anal canal. Third, it allows passage of larger diameter instrumentation and retrieval of larger specimens[33]. However, removal of organs through the anus is clearly limited by the extent to which the anal canal can be safely dilated. Despite the lack of objective limits, specimens with large tumors or bulky mesenteries are not ideal candidates for this technique. The potential effect of prolonged anal dilation on short- and long-term anal sphincter function requires objective evaluation[32].

On the other hand, efforts are constantly delivered to assure safe and sterile colonic access. Ultrasound guidance after decontaminating the hydroperitoneum for ideal entry point definition[27,28], curved over tube[157] and dedicated closure technique[27-29,158] are promising experimental practices that may encourage the first human application[158]. Even if obviously present, the risk of contamination remains subject to further discussions. Fifteen years ago, in a prospective, double-blind, randomized controlled study, Schardey *et al*[159] showed that perioperative oral decontamination significantly reduces esophagojejunal anastomotic leakage after total gastrectomy. The use of non-absorbable antibiotics, such as polymyxin, tobramycin, vancomycin and amphotericin B, may lower the bacterial load and prevent infection, even if total sterility is not achieved. It is possible that a similar practice with antibiotic enemas can resolve the issue of postoperative infection and leakage after transcolonic/transrectal NOTES. This hypothesis deserves to be evaluated in a well-designed study before clinical application. Moreover, acquired experience during war surgery changed the paradigm in the treatment of colorectal wounds (*i.e.*, systematic stoma or exclusion)[160,161]. In certain circumstances, especially after simple perforation with acceptable vascularity, ideal closure can be performed with outcomes comparable to conventional treatment. NOTES through the colon or rectum is a perfect illustration of these ideal situations because access is achieved through an otherwise healthy organ. The 2010 summary report of the Euro-NOTES[148] recommends local disinfection and perioperative antibiotics for the transvaginal and transgastric approaches, but antibiotic lavage does appear to be necessary. At this stage, the transanal/transcolonic approach was not widely used and specific recommendations have not been updated so far.

One of the most attractive features of transanal

NOTES is the availability of TEM as a stable platform. In this setting, the transanal route is no longer conceived as a port for remote organ access through an otherwise healthy viscera (like the transgastric or the transvaginal routes). Instead, the colotomy/proctotomy is created through the diseased organ itself and secondarily closed in the form of an anastomosis[124]. This technique resolves the issues of viscerotomy closure and adequate endoluminal purse string, which remain major difficulties in NOTES[50,162]. However, the TEM platform was conceived twenty years ago initially for the resection of endoluminal rectal lesions[34]. The extension of the TEM technique towards "pure" NOTES must be accompanied by the development of improved, more convenient devices for greater intra-abdominal access[154]. In an experimental study of radical sigmoidectomy using TEM, Whiteford *et al*[30] outlined the specific technical and instrumental limitations encountered in this technique. The acute angle of the sacral promontory considerably limits the instrument's reach and generates difficulty for colon mobilization beyond the descending part. In a comparative study in cadavers, Rieder *et al*[31] showed that conventional TEM instrumentation does not allow adequate colon mobilization when compared with standard laparoscopy. To perform proper left colectomy, a combined technique using transgastric flexible access has been described in experimental models[122,163,164]. However, these promising experiments have not reached clinical application to date. The arrival of new, dedicated platforms is a promising step for the development of NOTES. Zorron *et al*[33,156] claim that the perirectal NOTES access is easier to learn and allows the freedom for more creative dissection than the TEM platform. Likewise, the Transanal Endoscopic Operations (TEO®) (Karl Storz, Tuttlingen, Germany) facilitates circular, full-thickness rectal resection for both intra- and extra-peritoneal application[165]. In preparation for transitioning to human application, Telem *et al*[166] reported a series of transanal NOTES rectosigmoid resections in 32 fresh human cadavers using TEO® transanally. The procedure was successfully performed using transanal dissection alone in 19 cadavers, necessitating transgastric endoscopic assistance in 5 cadavers and laparoscopic assistance in 8 cadavers. The mesorectum was intact in all cases, but the specimen length was increased in cases where assistance was employed. However, enteric perforation occurred in 8 cases (25%), all of which were cadavers undergoing "pure" NOTES. This highlights the limits of the transanal approach for clinical application unless combined with a laparoscopic approach. Recently, Leroy *et al*[167] described the perirectal oncologic gateway for retroperitoneal endoscopic single-site surgery using the IsisScope (Karl Storz, Tüttlingen, Germany) passed through the TEO for the accomplishment of "pure" NOTES total mesorectum excision in pigs. To our knowledge, no clinical series has validated the added value of these instruments in terms of safety, morbidity or oncological outcomes.

CONCLUSION

The irrevocable benefits of CLS in colorectal surgery without compromise of functional or oncological outcomes have encouraged surgeons to further reduce invasiveness[1-15]. The fundamental hypotheses driving SILS promotion are reduced postoperative complications and pain, shorter hospital stays, earlier returns to normal activity, fewer port-site complications and improved cosmetic results. With approximately equivocal results, SILS has not yet been proven to substantially improve outcomes when compared with CLS. However, actual data, including all available meta-analyses, are excluded from retrospective series, resulting in inevitable heterogeneity and bias in conclusions[66,70,79].

From another point of view, the present literature failed to demonstrate that the postoperative course or the patient's safety was degraded when SILS was used instead of CLS. To date, data have not consistently proven that SILS increases postoperative pain, augments complication/morbidity rates, induces proper port site complications, prolongs the duration of hospitalization or affects the mortality rate. Moreover, recent studies demonstrate that appropriate resection of colorectal neoplasms can be achieved with SILS and provide short-term results comparable with CLS[68,69,74,77,78,82,84-86,90,92,93]. Based on these findings, it is undeniable that SILS represents a potential alternative to CLS. In addition, if the intuitive cosmetic advantage of SILS over CLS[41,51,68,74,77,82] is confirmed by the means of objective scores, one may consider SILS as the preferred approach in this new era of laparoscopy.

Despite fundamental differences (such as dissection in a single abdominal quadrant, resection of an end-organ with no need for anastomosis and absence of oncologic requirements), the comparison of SILS with conventional laparoscopic techniques in well-standardized procedures, such as laparoscopic cholecystectomy, can aid in the evaluation of its advantages, safety and limitations. In a systematic review and meta-analysis performed by Arezzo *et al*[168] encompassing approximately 1000 patients, SILS offered similar overall morbidity and parietal complications compared with conventional laparoscopy. The claimed advantages of enhanced cosmesis and reduced postoperative pain were confirmed despite longer operative times. Based on these encouraging results, the authors organized a multicenter randomized trial (NCT01104727) to provide a strong evidence-based evaluation of the benefits and risks of SILS[169]. This trial may allow for a better assessment of the real place of SILS among conventional laparoscopic techniques.

It is surprising that SILS emerged as a novel technique in colorectal surgery before some of its fundamental advantages could be validated in well-designed studies. The most illustrative example is the absence of evidence for surgical stress reduction in SILS when compared with CLS. To date, a single study is available that addresses this issue[89]. Based on C-reactive protein levels as the sole

marker of inflammation, this study failed to demonstrate any significant difference between the two groups in a small number of patients. In the current era of evidence-based medicine, it is obvious that SILS did not yet acquire solid statistical confirmation. However, large concordant clinical experiences bring sufficient empirical proof for feasibility and safety in benign and malignant colorectal diseases. We believe that unless well-designed studies demonstrate irrevocable disadvantages of SILS, this promising technique henceforward will occupy a privileged place in the armamentarium of today's colorectal surgeon.

Presently, four RCTs (NCT01320267, NCT01656746, NCT01319890 and NCT01480128, www.clinicaltrial.gov) are underway comparing SILS with CLS in colorectal surgery. Answers are particularly awaited regarding the potential benefits on the postoperative course (*i.e.*, reduced surgical stress, post operative complications and pain, improved patient satisfaction and safety), the long-term surgical outcome (*i.e.*, bowel function and late wound hernia) and the oncological appropriateness of the short-term (*i.e.*, margins, lymph node retrieval) and long-term results (*i.e.*, global, disease-free and disease-specific survival rates)[66]. Consequently, the cost-effectiveness of SILS can be thoroughly evaluated given that only solid proof of postoperative course improvement, reduced hospital stay and/or lower complication rate can outweigh the induced cost increase[64].

Rectal SILS procedures are typically integrated in large colorectal series. As mentioned by Maggiori *et al*[79], a study dedicated to rectal SILS that includes more than 20 patients is not available. To the best of our knowledge, the results of SILS proctectomy have never been assessed nor compared with those of CLS. In a recent meta-analysis, Fung *et al*[64] indicated that the role of SILS in rectal surgery requires a separate study. In this respect, data from a RCT (NCT01579721, www.clinicaltrial.gov) have been collected for the assessment of SILS in rectal cancer. The results are eagerly awaited and are expected to provide valuable, unheralded knowledge on rectal surgery and the real benefits of SILS for proctectomy.

In today's enthusiastic vision of surgery, NOTES represents the "ideal scar-free surgery" with the claimed advantages of reduced postoperative pain, quicker recovery, less postoperative morbidity and optimal cosmesis. However, since the first definition of the NOTES concept in 2006[57], major difficulties have inhibited the clinical breakthrough of NOTES. Efforts are regularly delivered by the SAGES/ASGE and EAES/ESGE societies to promote research and safely bring this concept into clinical practice[146-149,170]. In this respect, the NOSCAR and the EURO-NOTES Clinical Registries were developed to compile safety data and authorize human trials. In the 2-year activity report of Euro-NOTES[147], a total of 533 patients were entered. Cholecystectomy remains the most frequently performed procedure in 435 patients (81.6%) and was performed through the transvaginal approach in 423 patients (97.2%). Transanal/transrectal colorectal resections are noticeably gaining interest as potentially attested by the rapidly increasing number of procedures performed in humans. In almost one year, this number approximately tripled from 32 patients to greater than 100 patients in the Euro-NOTES activity report[147] and the latest summary of the 2012 Euro-NOTES meeting[170]. It is worth noting that, with the exception of peroral myotomy, transabdominal trocar has commonly been used for dissection and/or safe access, transforming the procedure into "hybrid" NOTES. This technical adjunct provides the required safety for the application of NOTES in humans during the initial experiences[147]. Case reports of "pure" colorectal NOTES have recently been described, but this approach has not yet achieved wide acceptance[170].

Among the topics at different committees, the risk of infection has been the most frequently discussed[149]. Statements concerning this issue have changed considerably since 2006-2007 when infectious problems were particularly feared, especially in the transcolonic/transanal approaches. This attitude has changed with repetitive successful descriptions of transanal/transrectal/trancolonic NOTES procedures[170]. Initial recommendations of the Euro-NOTES regarding infection were published in 2011[148]. This authority recently stated that "infection is no longer a major concern, and the frequency of infectious NOTES complications is rather low… The danger of infection was overestimated in the beginning of NOTES research". Under validated conditions of sterility and disinfection, the incidence of infections for all transluminal procedures ranges from 0.5% to 11%[149]. However, this paper also confirms the necessity of comparative prospective trials to validate these data and support the clinical application of NOTES.

Platforms and new technologies occupy a major portion of the discussions in the NOTES communities meetings[146,148,149,170]. Initial reports focused on the importance of close collaboration between surgeons, endoscopists, engineers and commercial providers to make NOTES a routine, daily practice. The principles features of the optimal multitasking platform have been described in the Euro-NOTES meeting summary from 2010[148]. However, such a flexible platform delivering all requirements for NOTES is not readily available for clinical practice[146,147,149,170]. Alternatively, during the past few years, new conceptual ideas and applications of available tools have at least partially compensated for this lack of innovative instruments. The "down-to-up" transanal TME represents the most illustrative example of this shift. This novel technique represents a practical application of the fundamentals of NOTES (*i.e.*, natural orifice access and parallel working instruments) with the use of familiar tools (TEM platform and single-port devices)[146]. However, flexible NOTES platforms are still believed to further enlarge dissection possibilities and advance NOTES promises into practice[146,170]. These possibilities are almost entirely dependent on engineering

innovations and commercial commitment in this field[146].

The guarantee of a safe endoluminal closure remains one of the fundamental problems limiting the application of NOTES in humans[146,148]. Several closure devices are currently available that promise appropriate endoluminal closure. However, laparoscopic control of adequate closure remains necessary until large-scale studies confirm the low failure rate[146]. From this point of view, transanal/transrectal colorectal resections represent a remarkable conceptual improvement toward "pure" NOTES possibilities by taking advantage of anastomosis to achieve a full-thickness site closure[149]. This finding is in complete accordance with the SAGES/ASGE assessment that controlled incision in the viscera is no longer perceived as an iatrogenic perforation and intraperitoneal contamination, as long as the viscerotomy closure is secure[146]. However, transcolonic/transrectal NOTES should be restricted to interventions where the access site is incorporated in the anastomosis and resected with the specimen[170]. Along with the presumed advantages of NOTES surgery, we insist that the "down-to-up" approach of the rectum brings considerable advantages regarding the preservation of pelvic nerves, distal mesorectal cone integrity and easier sphincter conservation. Larger clinical experiences are needed to fully standardize this technique and validate its presumed advantages in well-designed studies. The ongoing prospective clinical trial initiated by Sylla *et al*[124] (NCT01340755) will hopefully provide valuable knowledge on transanal TME for rectal cancer.

Since the initial reports, working groups focused on interdisciplinary approaches and outlined the need for close collaboration between surgeons and gastroenterologists[148]. It is now evident that NOTES requires high qualifications in both interventional endoscopy and advanced laparoscopy[146]. A critical step before the application of NOTES to patients consists of long experimental training phases as well as extensive clinical and technical experience[149]. Accreditation by scientific societies through certified experts in the field may also contribute to success[147].

In contrast to the first reports in which the transgastric route was favored (mostly by gastroenterologists), the present data indicate that NOTES can be performed for multiple procedures through different organs with acceptable morbidity and failure rates[149]. NOTES techniques are increasingly being performed in dedicated centers worldwide[146,149]. Continuing assessment of results is crucial for the standardization of future procedures and validation of indications[147]. Today, feasibility is no longer a concern, but the full potential of NOTES must be revealed[146]. Limited experience in the clinical application of colorectal NOTES procedures hinders clinical outcome analysis at the moment[162]. NOTES remains a constantly progressing concept with considerable technological and practical hurdles that must be overcome[156]. Safety remains a prerequisite before confrontation in clinical trials and confirmation of the presumed advantages of this "ideal" approach.

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