

Review

Mini-invasive surgery for colorectal cancer

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Abstract

Laparoscopic techniques have been extensively used for the surgical management of colorectal cancer during the last two decades. Accumulating data have demonstrated that laparoscopic colectomy is associated with better short-term outcomes and equivalent oncologic outcomes when compared with open surgery. However, some controversies regarding the oncologic quality of mini-invasive surgery for rectal cancer exist. Meanwhile, some progresses in colorectal surgery, such as robotic technology, single-incision laparoscopic surgery, natural orifice specimen extraction, and natural orifice transluminal endoscopic surgery, have been made in recent years. In this article, we review the published data and mainly focus on the current status and latest advances of mini-invasive surgery for colorectal cancer.

Key words Laparoscopy, colorectal cancer, robotic technology, single-incision laparoscopic surgery, natural orifice specimen extraction, natural orifice transluminal endoscopic surgery

Since Jacobs *et al.*^[1] reported the first laparoscopic colectomy in 1991, the enthusiasm for mini-invasive surgery for colon cancer has been increasing every year^[2]. A series of randomized, prospective clinical trials have confirmed that the oncologic outcomes of laparoscopic colectomy are equivalent to those of open surgery (Table 1)^[3-6]. Meanwhile, laparoscopic colectomy significantly improves the short-term outcomes of patients, such as lower pain scores, less estimated blood loss, and shorter length of hospital stay^[7-10]. However, mini-invasive surgery for rectal cancer remains controversial because total mesorectal excision (TME) is limited by the confines of the bony pelvis and the goal of preserving the autonomic nerves. The main concern is that oncologic outcomes may be compromised by laparoscopic rectal cancer surgery. Substantial evidence is lacking, but some multicenter, prospective, randomized clinical trials are undergoing (Table 1)^[10-14].

As mini-invasive surgery for colorectal cancer gains popularity around the globe, several technologic innovations have been made (Table 2). Robotic surgery is an emerging technology that provides 3-dimensional imaging, tremor filtration, and motion scaling^[15,16]. With these advantages, robotic rectal cancer resection may overcome the limitations of conventional laparoscopic surgery. With the development of laparoscopic techniques and the invention of new surgical equipments, scarless surgery is becoming increasingly

popular. In single-incision laparoscopic surgery (SILS), also termed single-port laparoscopic surgery, the surgeon operates through a single entry point with a single incision of only 25–30 mm. Several studies have found that colorectal SILS is feasible and safe and requires a significantly shorter total skin incision^[17-20]. Another innovation is natural orifice specimen extraction (NOSE). For this procedure, the specimen is extracted from a natural orifice such as the vagina or anus; therefore, an additional incision in the abdominal wall is not needed. Several studies confirm that NOSE is a safe and effective approach with acceptable complication rates^[21-25]. The final innovation is natural orifice transluminal endoscopic surgery (NOTES). NOTES is the only type of surgery that lacks scarring of the abdominal wall, thus, NOTES may represent the next step in the evolution of mini-invasive surgery^[26,27].

In this article, we review the published data and highlight the current status and latest advances of mini-invasive surgery for colorectal cancer.

Mini-invasive Surgery for Colon Cancer

The benefits of mini-invasive surgery have been well established for some surgical procedures, such as laparoscopic cholecystectomy^[28,29]. Thus, there has been great enthusiasm for laparoscopic colectomy since Jacobs *et al.*^[1] reported the first laparoscopic colectomy in 1991. Early studies demonstrated the feasibility of laparoscopic colectomy^[1,30,31]. However, several reports showed that laparoscopic colectomy was associated with a high rate of trocar site and wound recurrences^[32-34]. Berends *et al.*^[32] reported that 21.4% of patients developed abdominal wall metastases after laparoscopic colectomy. Moreover, some reports documented that patients who converted from laparoscopic to open surgery had a significantly shorter cancer-specific survival than patients who did

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Table 1. Characteristics of multicenter, randomized, controlled trials of laparoscopic colorectal surgery compared with open surgery for colorectal cancer

Trial	Type of cancer	Reference(s)	Surgery pattern	Cases (n)	Conversion rate (%)	Follow-up (months)	DFS	OS
COST	Colon	[6,7]	LR	435	21	84	69.2% (5-year)	76.4% (5-year)
			OR	428			68.4% (5-year)	74.6% (5-year)
COLOR	Colon	[5,9]	LR	534	19	53	74.2% (3-year)	81.8% (3-year)
			OR	542			76.2% (3-year)	84.2% (3-year)
Barcelona	Colon	[3,8]	LR	111	11	95	NA	62% (7-year)
			OR	108			NA	50% (7-year)
CLASICC	Colorectal	[4,10,38]	LR	526	29	62.9	89.5 months (median)	82.7 months (median)
			OR	268			77.0 months (median)	78.3 months (median)
COREAN	Rectal	[11]	LR	170	1.2	UN	NA	NA
			OR	170		UN	NA	NA
COLOR II	Rectal	[12]	LR	699	17	UN	NA	NA
			OR	345		UN	NA	NA

COST, the Clinical Outcomes of Surgical Therapies trial; COLOR, the COlon cancer Laparoscopic or Open Resection trial; CLASICC, the Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer trial; COREAN, the Comparison of Open versus laparoscopic surgery for mid and low REctal cancer After Neoadjuvant chemoradiotherapy trial; COLOR II, the COlorectal cancer Laparoscopic or Open Resection II trial; LR, laparoscopic resection; OR, open resection; Conversion rate, the percent of patient in the laparoscopic group converted to open procedure; DFS, disease-free survival; OS, overall survival; UN, unknown; NA, not available.

Table 2. Advantages and disadvantages of different mini-invasive surgical techniques for colorectal cancer

Surgery pattern	Advantages	Disadvantages
Conventional laparoscopic surgery	Relatively cheaper, a mature technology, shorter operation time ^[47-52]	Steep learning curve, requires an abdominal wall incision, tremor, 2-dimensional vision, poor ergonomics, requires a skilled assistant, and limited degrees of freedom of the instruments ^[47-52]
Robot-assisted laparoscopic surgery	Three-dimensional vision, 7 degrees of freedom of the instruments, enhanced ergonomics, tremor filtration, superior dexterity, less steep learning curve ^[15,16,47-60]	Lack of tactile sensation and tensile feedback, expensive, limited intracorporeal range of motion, long operation time ^[15,16,47-60]
SILS	Smaller abdominal wall incision, better short-term outcomes ^[17-20,63-65]	High cost, requires specific articulated instruments, steep learning curve ^[17-20,63-65]
NOSE	No need of an abdominal wall incision or specific devices, better short-term outcomes ^[21-25]	Not suitable for every patient, risk of intraabdominal contamination and extraction site tumor implantation, highly variable in operative steps and devices ^[21-25]
NOTES	No scar on the abdominal wall, avoidance of incision-related complications, less impairment of the peritoneal immune system ^[26,27,66-70]	Risk of abdominal infection, hernia, and extraction site tumor implantation, difficulty in achieving a stable operating field, unavailability of adequate instrumentation ^[26,27,67-70]

SILS, single-incision laparoscopic surgery; NOSE, natural orifice specimen extraction; NOTES, natural orifice transluminal endoscopic surgery

not convert to open surgery^[35-37], and Chan *et al.*^[35] demonstrated that patients in the conversion group had a 7% higher risk of local recurrence (9.8% vs. 2.8%). Moloo *et al.*^[36] found a significantly lower 2-year survival rate after converted procedures compared to laparoscopic surgery (75.7% vs. 87.2%).

To determine whether laparoscopic colectomy has worse oncologic outcomes than open surgery, a series of multicenter, prospective, randomized trials have been performed, including the Clinical Outcomes of Surgical Therapies (COST) trial^[6,7], the Barcelona trial^[3,8], the COlon cancer Laparoscopic or Open Resection

(COLOR) trial^[5,9], and the Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer (CLASICC) trial^[4,10,38]. The CLASICC trial is the only trial that includes patients with either colon or rectal cancer^[4,10,38]. To date, the results of long-term follow-up have been published, and all of the trials found similar short- and long-term oncologic outcomes^[3-10,38]. The lymph node yield, circumferential resection margin-positive rate, postoperative morbidity, and mortality were not significantly different between open surgery and laparoscopic colectomy^[3-6]. After a median follow-up of 62.9 months, the CLASICC trial found that overall survival (OS) and disease-free survival (DFS) were similar between the open and laparoscopic groups^[4]. The COST trial also confirmed that the OS, DFS, and overall recurrence rates were not significantly different between two groups after a median follow-up of 7 years^[6]. The results of the Barcelona trial even suggested a tendency of higher cancer-related survival and OS rate for the laparoscopic group after a median follow-up of 95 months^[3]. Moreover, the results of these trials uniformly demonstrated that mini-invasive surgery showed several advantages over conventional open surgery, including lower pain scores, less use of narcotics and analgesics, shorter length of hospital stay, and a faster return of bowel function^[7-10].

Since the publication of these results, an increasing percentage of surgeons and patients have begun to support laparoscopic colectomy. Rea *et al.*^[39] found that patients were 4.5 times more likely to undergo a laparoscopic approach for colon cancer after the results of the COST trial were published. Based on these results, the Society of American Gastrointestinal and Endoscopic Surgeons and the American Society of Colon and Rectal Surgeons recommend laparoscopic colectomy as an alternative treatment for curable colon cancer^[40]. In conclusion, laparoscopic colectomy is a feasible and safe surgical treatment for selected colon cancer patients.

Mini-invasive Surgery for Rectal Cancer

Mini-invasive surgery for colon cancer has been well established as an alternative to open surgery, but laparoscopic rectal cancer surgery remains controversial. Because of the anatomic complexity of the pelvis and the demand for more technical expertise for TME and to preserve the autonomic nerves than is required for colectomy, the main concern is that oncologic outcomes may be compromised by laparoscopic rectal cancer surgery. Several randomized trials have shown that laparoscopic rectal cancer surgery is as effective and safe as open surgery^[41-44], but substantial evidence is still lacking. Several randomized, multicenter, prospective clinical trials are underway, including the Comparison of Open versus laparoscopic surgery for mid and low REctal cancer After Neoadjuvant chemoradiotherapy (COREAN) trial^[11], the European COLOR II trial^[12], the Japanese Clinical Oncology Group (JCOG) 0404 study^[13], and the American College Of Surgeons Oncology Group (ACOSOG) Z6051 trial^[14].

The CLASICC trial is the first randomized, multicenter trial to compare open surgery with laparoscopic surgery for colon and rectal cancers^[4,10,38]. A total of 374 rectal cancer patients were included in the CLASICC trial: 132 underwent open surgery, 160 underwent laparoscopic TME, and 82 converted from laparoscopic to open

surgery with a conversion rate of 34% (82/242). The rates of positive circumferential and longitudinal margins were not significantly different between the two groups. The long-term follow-up (median, 62.9 months) results of the CLASICC trial were published in 2013. No significant differences between the open and laparoscopic groups in OS and DFS were observed, and conversion did not significantly affect the median OS and DFS of rectal cancer patients^[4]. The CLASICC trial demonstrated that mini-invasive surgery was as safe as open surgery for rectal cancer, although the conversion rate was high. The COREAN trial is the first randomized, multicenter trial to compare open surgery with laparoscopic surgery for middle and low rectal cancer after neoadjuvant chemoradiotherapy in Korean patients^[11]. A total of 340 patients were randomized into the open surgery ($n = 170$) or laparoscopic surgery groups ($n = 170$), and only 2 (1.2%) converted to open surgery. The circumferential resection margin, number of harvested lymph nodes, and perioperative morbidity were not significantly different between the two groups. The following short-term outcomes favored laparoscopic surgery: less estimated blood loss, earlier recovery of bowel function, and less use of analgesic drugs. The COREAN trial showed that laparoscopic surgery was feasible and safe for middle and low rectal cancer after preoperative chemoradiotherapy. However, long-term follow-up data that includes OS and DFS results are needed. The COLOR II trial is being undertaken at 30 centers and hospitals in 8 countries, where 1,103 rectal cancer patients were randomized into open surgery ($n = 364$) and laparoscopic groups ($n = 739$). The short-term results of the COLOR II trial were published in 2013^[12]. The completeness of the resection, positive circumferential resection margin rate, and perioperative morbidity and mortality were not different between the groups. Similar to the other two trials, laparoscopic surgery was associated with less use of analgesics, less blood loss, earlier recovery of bowel function, and a reduced hospital stay. To date, the COLOR II trial is the largest multicenter, randomized trial to compare laparoscopic surgery with open surgery in patients with rectal cancer, and the short-term results of the COLOR II trial confirmed results from previous studies that indicated that laparoscopic surgery was feasible for rectal cancer and improved in-hospital recovery. However, long-term oncologic outcomes are essential to determine the definitive role of laparoscopic surgery for rectal cancer. Recently, Ohtani *et al.*^[45] conducted a meta-analysis that included 2,095 rectal cancer patients (1,096 in the laparoscopic surgery group, and 999 in the open surgery group) from 12 randomized trials. Laparoscopic surgery was associated with less blood loss, more rapid return of oral intake, and shorter hospital stay, but had similar 5-year OS and DFS rates, local recurrence, wound site recurrence, distant metastasis, urinary dysfunction, and sexual dysfunction as conventional open surgery.

Mini-invasive surgery for rectal cancer has not been definitely determined. The current data suggest that laparoscopic TME provides short-term benefits similar to those associated with laparoscopic colectomy, and the short-term and long-term oncologic outcomes are similar to those of open surgery. We believe that the long-term results of the ongoing randomized trials will confirm that laparoscopic surgery is not inferior to open surgery.

Robot-assisted Laparoscopic Surgery

Although laparoscopic surgery for colorectal cancer has been extensively studied, mini-invasive surgery for colorectal cancer is still underused^[46]. An important reason for this is the steep learning curve of this technique^[47-49]. In addition, some other limitations that hinder the development of laparoscopic surgery include tremor, 2-dimensional vision, poor ergonomics, the need of a skilled assistant, and the limited degrees of freedom of the instruments^[50-52]. Robotic surgery is thought to be able to overcome these limitations by providing 3-dimensional vision, 7 degrees of freedom of the instruments, enhanced ergonomics, tremor filtration, and superior dexterity^[15,16,53,54]. These advantages of robotic surgery make it extremely suitable for pelvic dissection, especially for patients with a narrow pelvis and/or local advanced disease. However, the limited intracorporeal range of motion hinders its use in colon cancer^[55]. Moreover, when compared with laparoscopic colectomy, robotic surgery shows no significant benefits and is associated with higher cost and longer operation time^[55,56]. Robotic systems might be used for complex procedures, such as the dissection of lymph nodes around major vessels because of its tremor filtration and superior dexterity^[16].

Baik *et al.*^[57] conducted a randomized, prospective trial that compared the short-term results between robot-assisted low anterior resection ($n = 56$) and standard laparoscopic low anterior resection ($n = 57$). The results indicated that the operation time was not significantly different between the two groups, but the conversion rate was 0 for the robotic group versus 10.5% for the laparoscopic group. Moreover, the macroscopic completeness of the resected specimen was better for the robotic group, and robotic surgery was associated with quicker return of oral intake, shorter length of stay, and a lower serious complication rate (5.4% vs. 19.3%). Scarpinata *et al.*^[52] recently conducted a meta-analysis that suggested that robotic rectal surgery could potentially offer better short-term outcomes, especially for patients who were obese, male, received neoadjuvant radiotherapy, and had middle or low rectal cancers. These results demonstrate the safety and feasibility of robot-assisted low anterior resection with better short-term outcomes. Moreover, the robotic system is likely to improve local disease control and eventually improve OS^[58,59]. Another advantage of the robotic system is its less steep learning curve. Bokhari *et al.*^[60] found that the learning curve of robot-assisted laparoscopic rectal surgery was passed after 15 to 25 operations.

Robotic surgery has many advantages over laparoscopic surgery, but some limitations in the current robotic technology still exist. When compared to conventional laparoscopic surgery, robotic surgery is associated with longer operation time, higher cost, and lacks tactile sensation and tensile feedback for the surgeon^[15,16,52,57]. Meanwhile, the majority of the current studies are retrospective and from a single clinical center. Multicenter, randomized, prospective trials are needed to compare the short-term and long-term outcomes of robotic surgery with those of conventional laparoscopic surgery. The United Kingdom Medical Research Council trial of RObotic versus LAparoscopic Resection for Rectal Cancer (UK MRC ROLARR) trial

is undergoing^[61]. The ROLARR trial is a multicenter, randomized, prospective trial that compares robot-assisted surgery with laparoscopic surgery in the treatment of rectal cancer. The results of the ROLARR trial will give us definite answers.

Single-incision Laparoscopic Surgery

Single-incision laparoscopy (SIL) is a recently developed technique in laparoscopic surgery in which the surgeon operates through a single incision of only 25–30 mm. SILS is thought to reduce the length of incision and port-related complications compared with the conventional multiport laparoscopic approach. SILS has been applied to procedures such as appendectomy, splenectomy, cholecystectomy, and bariatric surgery^[62]. To date, only a few small studies on the application of SILS to colorectal surgery have been published^[17-19]. Bucher *et al.*^[17] first reported their successful experience of SILS right colectomy. Champagne *et al.*^[18] reported a multicenter, case-control study that compared single-incision laparoscopic colectomy (SILC, $n = 165$) to multiport laparoscopic colectomy (MLC, $n = 165$). Eleven percent of patients undergoing SILS were converted to MLC; the operation time and length of hospital stay were similar between the two groups; and SILC was associated with a significantly shorter length of incision and lower pain scores. A recent meta-analysis of 1,075 procedures (494 single-incision and 581 multiport laparoscopies) found that colorectal SILS was associated with significantly shorter skin incision and length of hospital stay compared with multiport laparoscopic approach^[20].

Although initial studies demonstrate the feasibility and safety of SILS, the following are some disadvantages of SILS: it requires costly, specific articulated instruments^[63,64]; the surgeon must be experienced in laparoscopic surgery^[65]; and there is an additional learning curve for this technique^[65]. The benefits of SILS have not been determined; large, randomized clinical trials are needed to evaluate the short-term and long-term results of SILS.

Natural Orifice Specimen Extraction

In conventional laparoscopic surgery, a short-length incision is needed to remove the surgical specimen and perform the anastomosis, which may cause some additional complications compared to a fully laparoscopic procedure^[25]. To avoid an incision in the abdominal wall, one solution is to extract the specimen through a natural orifice, such as the vagina or anus. This approach is termed NOSE (**Figure 1**) and is thought to be a bridge to NOTES. Transanal extraction is suitable for left-sided colectomy and rectal surgery, whereas transvaginal extraction is suitable for all colorectal procedures, especially for right-sided colectomy and large specimens. Several studies found that NOSE was safe and feasible for selected patients^[21-25]. Park *et al.*^[21] conducted a case-control study that compared the clinical outcomes of transvaginal specimen extraction with those of conventional laparoscopic colectomy for the surgical treatment of colon cancer. The surgical morbidity was lower in the NOSE group compared with the conventional group although the difference was not significant (4/34 vs. 9/34, $P = 0.119$). Both the

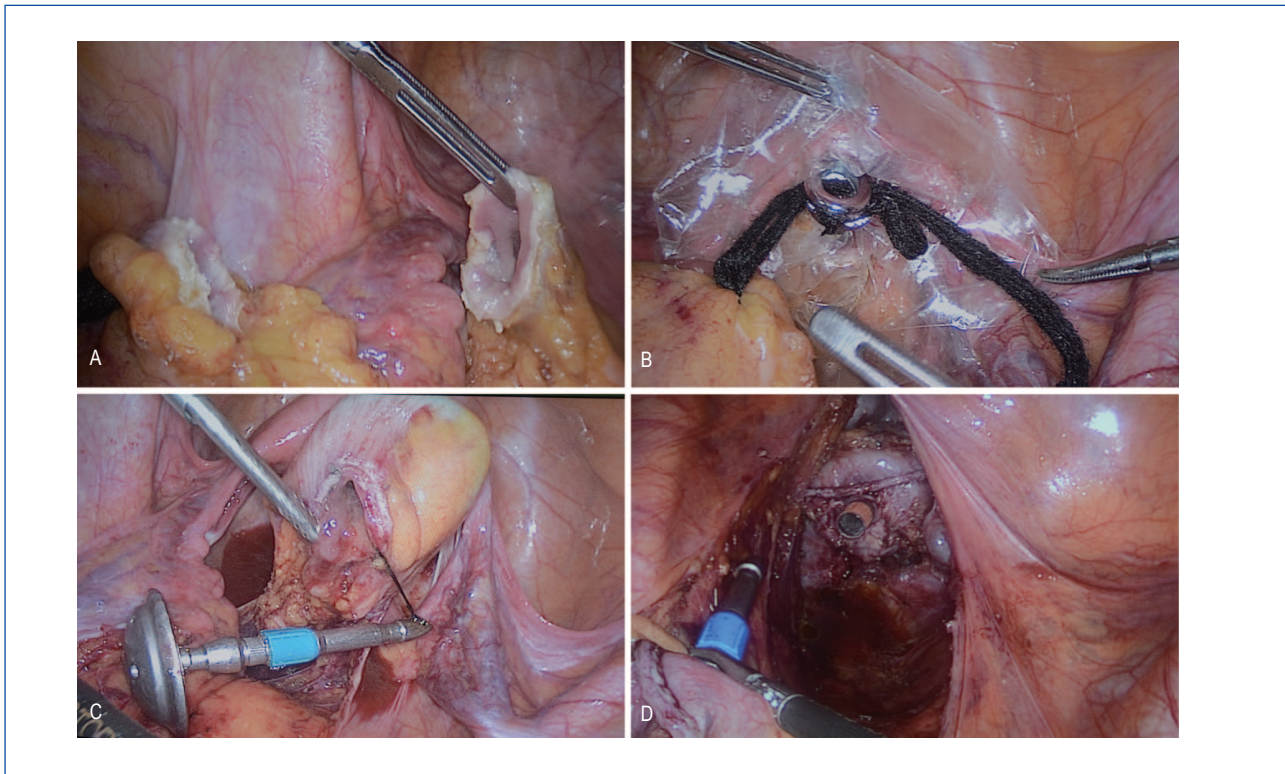


Figure 1. A validated technique for the performance of transanal specimen extraction. A, after the tumor is resected, the distal intestine is opened. B, the specimen is then extracted through the anus, and a specimen retrieval bag is used to prevent contamination of the tract. C, the anvil of the stapler is placed into the peritoneal cavity through the anus. D, a standard mechanical anastomosis is constructed intracorporeally.

transvaginal access site recurrence rate and posterior colpotomy-related complication rate were 0% (0/34) after a median follow-up of 23 months. Moreover, NOSE was associated with a lower pain score, shorter hospital stay, and better cosmetic results. Franklin *et al.*^[22] reported the results of 303 patients who underwent laparoscopic colorectal procedures with NOSE (277 transanal and 26 transvaginal) for specimen extraction. The results showed that NOSE was a safe and feasible technique for selected patients, and the rate of postoperative complications was as low as 3.6%.

Initial data suggest that NOSE has some advantages over conventional laparoscopic technique, but many problems must be solved. Currently, NOSE has not been standardized, and highly variable operative steps and devices exist^[21-25]. Moreover, some patients may not be suitable for NOSE, e.g., patients with a high body mass index, anal stenosis, a small caliber rectum, large tumors, and a bulky mesocolon. Compared to conventional laparoscopic techniques, NOSE may cause some special complications, including peritoneal bacterial infection, anal sphincter dysfunction, and sexual dysfunction. In addition, NOSE may lead to extraction site tumor implantation although no study has reported extraction site metastasis. Further randomized, multicenter trials are in great need to evaluate the short-term and long-term results of NOSE.

Natural Orifice Transluminal Endoscopic Surgery

The final goal of mini-invasive surgery is the so-called “scarless” surgery. NOTES, which creates a visceral incision instead of skin incision to gain access into the peritoneal cavity, meets the criteria of scarless surgery^[26,27]. The potential advantages of NOTES include improved cosmesis, faster recovery time, reduced pain, and avoidance of incision-related complications. Because of these advantages, NOTES is thought to be the next step in the evolution of mini-invasive surgery^[26,27].

Currently, most NOTES procedures in colorectal cancer patients are experimental and use hybrid techniques that combine NOTES with conventional laparoscopy. Moreover, most of the studies are from single institutions with small sample sizes. To date, no prospective, randomized clinical trials of NOTES for colorectal cancer have been published. Whiteford *et al.*^[66] first reported transanal NOTES sigmoidectomy in human cadavers in 2007. Since then, several studies have demonstrated the feasibility and safety of NOTES colectomy or TME using hybrid techniques in human patients^[67-69]. Lacy *et al.*^[67] reported their successful transvaginal minilaparoscopy-assisted NOTES radical sigmoidectomy in a 78-year-old woman with a sigmoid adenocarcinoma. de Lacy *et al.*^[68] reported 20 patients with

rectal cancer who successfully underwent transanal minilaparoscopy-assisted NOTES TME with excellent short-term outcomes. Recently, Leroy *et al.*^[70] were the first to report a pure transanal NOTES TME in a 56-year-old woman with a midrectal neoplasia.

Although initial small studies found that NOTES was feasible and safe when used for colorectal diseases, the technique of NOTES is currently experimental, and the benefits of NOTES over conventional laparoscopic surgery have not been established. In addition, some factors may hamper the wide use of NOTES^[26,27]. The first is oncologic concerns and safety concerns, especially regarding viscerotomy closure because viscerotomy closure may cause abdominal infection and hernia. The second is the need of novel instruments to improve NOTES. Current laparoscopic instruments are not completely suitable for NOTES in terms of a stable platform and anastomosis. The third is the high cost and additional learning curve of NOTES. To overcome these limitations, new instruments and techniques are needed. The benefits of NOTES over traditional laparoscopic techniques have not been determined, and level I evidence is needed.

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Conclusions

Mini-invasive surgery has been demonstrated to be safe and feasible for colon cancer and resulted in improved short-term outcomes and equivalent oncologic outcomes when compared with open surgery. Mini-invasive surgery for rectal cancer has not been definitively determined, but the results of ongoing, multicenter, randomized, controlled trials will give us conclusive answers. As laparoscopic surgery gains popularity, some innovations that will overcome the current laparoscopic surgery limitations or further decrease abdominal wall trauma are underway. Although these innovations are currently experimental, they hold great promise and represent the evolution of mini-invasive surgery.

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