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Review

REVIEW

Re-appraisal and consideration of minimally invasive surgery in colorectal cancer

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Abstract

Throughout history, surgeons have been on a quest to refine the surgical treatment options for their patients and to minimize operative trauma. During the last three decades, there have been tremendous advances in the field of minimally invasive colorectal surgery, with an explosion of different technologies and approaches offered to treat well-known diseases. Laparoscopic surgery has been shown to be equal or superior to open surgery. The boundaries of laparoscopy have been pushed further, in the form of single-incision laparoscopy, natural-orifice transluminal endoscopic surgery and robotics. This paper critically reviews the pathway of development of minimally invasive surgery, and appraises the different minimally invasive colorectal surgical approaches available to date.

Key words: colon cancer; rectal cancer; minimally invasive surgery; laparoscopy; robotic surgery; transanal total mesorectal excision; natural-orifice specimen extraction

Introduction

Laparoscopy has revolutionized surgery during the last three decades; however, the roots of minimally invasive surgery can be traced back much earlier, to ancient times. The first description of endoscopic procedures came from Hippocrates, who inserted different instruments into various body orifices, in order to observe anatomy and pathological processes [1]. The first 'celioscopies' were described in the early 20th century by the German surgeon Kelling, who used a cystoscope inserted through an abdominal wall incision in dogs to insufflate the abdomen with filtered air [2]. Bernheim described his experience with 'organoscopies' in his series of 17 live human subjects in 1911 [3].

The major breakthroughs in the field of laparoscopic surgery followed the technological advancements in the field of video-laparoscopy, led by the introduction of solid state cameras in 1982 and development of better laparoscopic equipment [4]. The first laparoscopic appendectomy was described by Semm in 1982, while the first laparoscopic cholecystectomies were first performed by Muehe in 1985 and, subsequently, Mouret in 1987 [5]. These milestone events have revolutionized the surgical treatment of acute appendicitis and symptomatic biliary disease, fully transforming the operative and post-operative courses for these patients. This process has led to the rapid, widespread adoption of the laparoscopic approach as the 'gold standard' for cholecytectomy and appendectomy.

The advantages of laparoscopy have been well delineated and include reduced post-operative pain, reduced suppression of pulmonary function, fewer wound complications, expedited ileus resolution, fewer adhesions, shortened hospital stay, earlier recovery, improved cosmesis, and reduced costs than with laparotomy [6–9]. These advantages cleared the way for surgeons to adopt this approach for other abdominal diseases. Jacobs *et al.* published the first series of 20 laparoscopy-assisted colectomy for both benign and malignant indications, concluding that the laparoscopic approach was feasible and safe [10].

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Despite this enthusiasm, colorectal surgeons were very slow to adopt the laparoscopic approach. This hesitation may have been attributed to several causes: increased complexity of colorectal surgeries, compared with other abdominal operations, due to multi-quadrant surgery, including vascular control, large-size specimen removal, and construction of an anastomosis. These features required complex tools, increased operating times and longer learning curves. In addition, there were numerous concerns regarding the oncological outcomes of laparoscopic resection for colon and rectal cancer, namely the ability to perform adequate lymphadenectomy and rate of port site metastasis.

Early reports of exceedingly high rates of port site metastasis—up to 21%—questioned the oncological safety of laparoscopy for colorectal cancer and hindered its adoption [11, 12]; subsequent investigations eliminated this concern, suggesting that the excessive rates were probably a reflection of the learning curve and flawed surgical technique. A port site metastasis rate of approximately 1% was found in a review of 1737 patients undergoing laparoscopic colectomy for cancer: similar to the rate reported for the open approach [13, 14].

Laparoscopic *vs* open colectomy

Several sentinel trials have been designed in order to address the oncological safety of the laparoscopic approach. The Clinical Outcomes of Surgical Therapy (COST) trial was a randomized, controlled trial (RCT), which compared laparoscopic colectomy to laparotomy. Laparoscopy was associated with significant short-term advantages over laparotomy, including a shorter median hospital stay and less parenteral and oral narcotic use. More importantly, the COST trial clearly demonstrated the oncological safety of the laparoscopic approach, with similar overall and disease-free survival rates between the open and laparoscopic groups [14, 15].

The COlon cancer Laparoscopic or Open Resection (COLOR) trial presented similar results. Patients who underwent laparoscopic resection had better short-term results than the open group, including less blood loss, earlier recovery of bowel function, reduced analgesic use, and a shorter hospital stay. In addition, the number of harvested lymph nodes was similar in both groups and long-term oncological results were also comparable, with similar recurrence rates, disease-free survival, and overall survival rates [16, 17].

Parallel results were noted in the Conventional versus Laparoscopic Assisted Surgery In Colorectal Cancer (CLASICC) study [18–20]. The CLASICC trial included a subset of patients with rectal cancer, in whom a higher circumferential radial margin involvement was noted in the laparoscopic approach group; however, the long-term oncological results of local and distant recurrence rates were similar in both groups.

Several large, multicenter, prospective, randomized trials have been designed in order to compare the laparoscopic approach with laparotomy for rectal cancer and assess short-term- as well as long-term oncological safety. The European COlorectal cancer Laparoscopic or Open Resection II (COLOR II) trial is an international, randomized, prospective, multicenter study comparing the outcomes of laparoscopic and conventional resection of rectal carcinoma with curative intent. The primary endpoint is loco-regional recurrence rate three years post-operatively. Secondary endpoints assess quality of life, overall and disease-free survival, post-operative morbidity and health economy analysis [21]. The laparoscopic approach group experienced less blood loss, quicker return of bowel function and shorter hospital stay, but longer operation times than the open approach group. The immediate oncological concerns of the resection—including resection margins and completeness of resection—were similar in both groups. At 3-year follow-up, both groups had similar loco-regional recurrence rates, disease-free survivals and overall survival rates [22].

The Comparison of Open versus laparoscopic surgery for mid and low REctal cancer After Neoadjuvant chemoradiotherapy (COREAN) trial also found less blood loss in the laparoscopic group, earlier recovery of bowel function and less use of narcotic medication than in the open approach group—again, despite longer operation times. The quality of the oncological resection was equivalent between the two groups, including circumferential resection margin involvement rates, macroscopic quality of the total mesorectal excision (TME) specimen, and the number of harvested lymph nodes [23]. The 3-year disease-free survival rates were similar in both groups [24].

The superiority of the laparoscopic approach for rectal cancer was recently challenged in two randomized, controlled studies (AlaCaRT and ACOSOG Z6051). The laparoscopic approach failed to meet the criteria for non-inferiority, defined by a non-statistically validated composite endpoint [25, 26].

Adoption rates for the laparoscopic approach

In spite of the encouraging results of the above trials, especially in treating colon cancer, the adoption rates for the laparoscopic approach in colorectal surgery initially remained relatively low. One contributing factor may have been the low perceived cost–benefit ratio of the laparoscopic approach in colorectal surgery, when compared with laparoscopic cholecystectomy. The laparoscopic approach dramatically revolutionized the post-operative course of patients undergoing cholecystectomy, quickly causing adoption rates exceeding 90%. Conversely, the improvements that laparoscopy conferred on colorectal patients have been less profound. Furthermore, differences were even less significant when enhanced recovery pathways were employed for patients undergoing open colorectal surgery. When combined with the steep learning curve and the host of new skills required to perform the surgery, as well as the lack of structured, safe and effective training for practicing surgeons, the initially low rate of 36–55% of colectomies being performed laparoscopically in the United States is understandable [27–29].

A recently published article by Moghadamyeghaneh *et al.* reviewed the Nationwide Inpatient Sample database for patients who underwent elective colectomy for colon cancer or diverticular disease from 2009 to 2012. The laparoscopic approach was attempted in only 55.4% of the 309 816 patients who underwent elective colectomy, with a 12.4% conversion rate. In 2009, only 45% of patients with colon cancer underwent an attempted laparoscopic colectomy, increasing to 53.5% by 2012 [29]. This figure is even lower when considering that laparoscopy is employed only in up to 10% of rectal cancer surgeries in the United States [30]. A significant disparity was also identified in the adoption rates of laparoscopy, between urban and rural areas and in high-volume- compared with low-volume centers. A recent study evaluated this subject in the state of Nebraska in the years 2008–11. Only 28% of colectomies for cancer were laparoscopically performed, while rural colon cancer patients were 40% less likely to receive laparoscopic colectomy than urban patients [31]. Yeo *et al.* evaluated trends and outcomes in patients undergoing elective open, laparoscopic, and robotic colectomy from 2009 to 2012, using the National Inpatient Sample. They identified 509 029 colectomies, of which 266 263 (52.3%) were open, 235 080 (46.2%) were laparoscopic, and 7686 (1.5%) were robotic. The majority of minimally invasive colectomies were still being performed at high-volume, rather than low-volume centers (37.5% *vs* 28.0% and 44.0% *vs* 23.0%; $P < 0.001$). A total of 36% of colectomies were performed for cancer [32].

The laparoscopic approach to rectal cancer necessitates unique and advanced technical expertise in order to perform a complete mesorectal excision. The ACOSOG Z6051 trial had one of the highest rates of complete or nearly complete TME for the laparoscopic approach (92%), with a relatively low rate of conversion (11%); however due to the non-statistically validated composite end point, it has failed to demonstrate non-inferiority of laparoscopy compared with the open approach [25]. Moreover, the authors have proven superior oncological outcomes using laparoscopy [33].

Notwithstanding the aforementioned difficulties, there seems to be a clear advantage in the laparoscopic approach for treatment of colorectal cancer. Those advantages are of huge significance to the healthcare system, as national health expenditure in the United States has reached $3 trillion and is expected to reach $5 trillion by 2023 [34]; thus, it is imperative to reduce the cost of colorectal surgery by increasing efficiency, shortening the post-operative length of stay, and reducing the post-operative complication rate. The laparoscopic approach fulfils these goals, while allowing similar oncological outcomes.

Hand-assisted laparoscopic surgery

Hand-assisted laparoscopic surgery (HALS) has been endorsed as a bridge to increased adoption rates and reduction of the learning curve for laparoscopic colectomy [35–37]. The mini-laparotomy—made through either a mid-line or Pfannenstiel incision, with subsequent placement of a hand port to allow for insertion of the surgeon's hand into the peritoneal cavity—allows for the return of tactile sensation that is lost in the totally laparoscopic approach. It was assumed that the hand port allows easier dissection and retraction, which may reduce operation time and allow for performing more technically complex cases via HALS than with straight laparoscopy. The HALS method is akin to training wheels on a bicycle.

A recent review of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database compared patients undergoing open colectomy with those undergoing HALS colectomy, with 1740 matched patients in each group. After adjusting for difference in baseline comorbidities, the open group displayed significantly higher overall morbidity, superficial, deep, and organ-space surgical site infection, urinary tract infection, ileus, re-operation, re-admission, and hospital stay. The authors suggested that the HALS technique might be a bridge to straight laparoscopy or a tool during difficult cases, where it can positively influence the short-term outcomes after colectomy, as compared with the open technique [38].

However, when comparing HALS to straight laparoscopy, in two recent papers reviewing the American College of Surgeons NSQIP database, one review of 7843 patients who underwent either straight laparoscopy or HALS showed that operation time was marginally shorter in the HALS group, while overall morbidity, superficial surgical site infection and ileus rates remained slightly higher in the HALS group [39]. In a review of the same database during the years 2012–13, 13 949 propensity-matched patients undergoing either elective HALS (43.6%) or straight laparoscopy were compared. Patients undergoing HALS colectomy had significantly higher rates of post-operative ileus, wound complications, and 30-day re-admission, without any differences in operation time [40]. In a recent study by Midura *et al.*, laparoscopic sigmoid colectomy was yet again associated with substantially shorter post-operative stay and earlier return of bowel function than with HALS [41]. Cobb *et al.* reported a 10.6% incisional hernia risk at one year following HALS colectomy [42].

HALS techniques facilitate the dissection, rectal transection, and construction of the anastomosis in patients with rectal cancer. Utilization of the HALS technique may encourage blind- and blunt dissection of the rectum, which contradicts the fundamental principles of TME, which specifically involves precise, sharp dissection in the areolar tissue plane under direct visualization, emphasizing the avoidance of violation of the mesorectal fascia and preservation of the autonomic nerves. Any deviation from those sound oncological principles may potentially threaten the completeness of the TME and increase the risk of local recurrence, while affecting the functional results after the proctectomy.

Although HALS is still advocated by some surgeons—especially for technically demanding cases—it has been shown to be clearly inferior to straight laparoscopy and its use in routine colectomy should thus be limited to an educational tool. Once the surgeon gains sufficient laparoscopic skills, the hand can be left outside the abdominal cavity and the benefits of laparoscopy can be conferred upon the patient.

Robotic surgery for colorectal cancer

Conventional laparoscopy is known to have several limitations, which lengthen the learning curve and may have contributed to the slow adoption rates. These limitations are particularly relevant in highly demanding colorectal procedures, especially in the highly technically challenging pelvic dissection for mid- and low rectal cancers.

The daVinci® robotic system (Intuitive Surgical, Inc.) has been specifically developed to overcome many of the shortcomings of laparoscopic surgery, especially allowing for stable, highly magnified 3D viewing of the operating field, offering precisely controlled EndoWrist (Intuitive Surgical, Inc.) instruments with seven degrees of freedom and filtering of physiological tremor, overcoming the fulcrum effect of laparoscopy, and preserving the natural eye–hand–instrument alignment hand-in-hand with better overall ergonomics. These advantages have led to high adoption rates of the robotic platforms in other specialties such as in urology, changing the surgical management of prostate cancer. The rate of robot-assisted radical prostatectomy has risen sharply, from 8% in 2004 to more than 90% currently, due to the clear advantages of the robotic approach.

While the first robotic colectomies were reported in 2002 by Weber *et al.* for benign disease, and by Hashizume *et al.* for malignant disease, and the first proctectomy was reported by Giulianotti *et al.* in 2003 [43–45], the adoption rates remained low in colorectal surgery as no advantages over conventional laparoscopy have been proven.

Robotic colon surgery

There has been an abundance of conflicting data regarding whether robotic colectomy offers advantages over the laparoscopic approach; however, most studies do agree on the fact that the robotic approach harbors significant disadvantages compared with laparoscopy, in the form of significantly increased cost and longer operation times [46–51].

Petrucciani *et al.*, in a meta-analysis of six studies, compared 168 patients who underwent robotic right colectomy with 348 patients who had undergone conventional laparoscopic right colectomy. Both approaches were equivalent with regard to estimated blood loss, conversion rates to open surgery, lymph nodes retrieval, rate of anastomotic leakage, re-operation rate, overall morbidity and mortality, and length of hospital stay; however, the robotic approach resulted in significantly longer operation times [52]. Park *et al.* had similar results in a randomized, clinical trial, which also showed that the robotic approach exhibited markedly longer operation time (195 *vs* 130 minutes; $P < 0.001$) and overall hospital costs ($12 235 *vs* $10 320; $P = 0.013$) [53].

A study by Ezekian *et al.* used the NSQIP database in the years 2012–13 to identify 15 976 patients who underwent minimally invasive colectomy. Results showed that 96.9% of the colectomies were performed using the conventional laparoscopic approach, while 3.1% (498 cases) were performed with robotic assistance. In this study, there were no differences in the rates of conversion to open surgery or in 30-day overall morbidity or mortality. After matching, there were no differences in perioperative outcomes between the two groups. However, as always, operation times were significantly longer in the robotic group [54]. Benlice *et al.* examined the 2013 NSQIP database, matching and comparing three groups, each consisting of 387 patients undergoing colectomy via an open, laparoscopic, or robotic approach. In this study, the robotic approach initially seemed to result in shorter hospital stay and longer operation times, with lower morbidity rates (fewer instances of superficial surgical site infection, bleeding requiring transfusion, ileus and ventilator dependency) than with laparoscopic and open surgery; but when adjusting for confounders, outcomes among the three groups were comparable except for hospital stay, which was shorter in the robotic group [55]. Yeo *et al.* found that the rate of iatrogenic complications was higher for robotic surgery ($OR = 1.73$) and, at the same time, the median cost of robotic surgery was higher than for laparoscopic colectomy ($15 649 *vs* $12 071) [32].

There is a plethora of data suggesting the feasibility and safety of the robotic approach for colectomy; however, the robotic approach has failed to offer any advantages over conventional laparoscopic colectomy. Unfortunately, the significant disadvantages of higher cost and longer operation times have been repeatedly demonstrated. Based on these data, the robotic approach is not justifiable.

Robotic rectal surgery

Laparoscopic TME for rectal cancer has been shown to be feasible, although fairly complex, especially in obese patients and/or in patients with a narrow pelvis. The robotic platform is therefore alleged to be potentially beneficial during pelvic dissection in patients with rectal cancer; however, a multitude of scientific papers have compared robotic TME to laparoscopic TME, without proof of concept. Thus, although theory-based claims in favor of robotics continue unabated, the results have, in reality, failed to supply proof.

A meta-analysis by Scarpinata *et al.*, comparing the robotic approach against the laparoscopic for rectal surgery, concluded that the robotic approach was associated with increased cost and operating time, but with lower conversion rates, regardless of the surgeon's experience [56]. Another meta-analysis of eight trials compared 344 patients who underwent robotic TME with 510 patients undergoing laparoscopic TME; while the conversion rate to open surgery was significantly lower in the robotic group, there were no significant differences in the oncological outcomes, the number of lymph nodes retrieved, or the circumferential resection margin (CRM) positivity rates [57]. While this meta-analysis did not reveal the usual, significantly longer operating time for the robotic approach, a longer operating time has been repeatedly proven as an expensive disadvantage [56–62]. The robotic approach has not demonstrated any advantages in terms of the number of lymph nodes harvested, CRM positivity or DRM involvement [57–63], nor local recurrence, disease-free survival, or overall survival [64–66].

As previously mentioned, several studies have detailed the significantly higher cost of the robotic approach over conventional laparoscopy [32, 67–70]. The added expense is attributable to several factors including the high costs of purchase and maintenance of the robotic platform and of disposable instruments, while additional costs are also related to the increased operating time in comparison with laparoscopy. A study by Moghadamyeghaneh *et al.* used the nationwide in-patient sample database to examine the clinical data of patients with rectal cancer who underwent elective abdomino-perineal resection between 2009 and 2012 in the United States. While conversion rates to open surgery were lower in the robotic group than with laparoscopy (5.7% *vs* 13.4%), there were no significant differences in the morbidity rates of the laparoscopic and robotic approaches; in addition, the robotic approach incurred significantly higher total hospital charges than the laparoscopic approach, with a mean difference of $24 890 per case [71]. If all the rectal cancers diagnosed each year in the U.S.A. were operated on by the robotic approach, the additional yearly national expenditure would be $1.12 billion.

The Robotic assisted *vs* laparoscopic assisted resection for rectal cancer (ROLARR) trial is the first international, multicenter, prospective RCT comparing the robotic approach with standard laparoscopy for the curative resection of rectal cancer [72]. A total of 471 patients were randomized into two groups: 234 patients undergoing conventional laparoscopic proctectomy and 237 undergoing robotic proctectomy. While the final results have yet not been published, the robotic approach has failed to demonstrate superiority, relative to any oncological parameter or to any measure of morbidity or mortality, over the laparoscopic approach [73]. At present, the additional time and expense involved in robotic rectal cancer resection cannot be justified.

Single-incision laparoscopic surgery

Some of the proven major advantages of conventional multiport laparoscopy (CML) over the open approach are reductions in pain, length of stay, wound complications, and improved cosmesis. Single-port laparoscopic surgery (SILS) may further enhance the advantages of CML by performing the entire procedure through a single incision in the abdominal wall, thus minimizing surgical trauma. SILS represents the next evolutionary step in minimally invasive surgery, towards a totally scar-free procedure; however, in this technique, the laparoscopic working ports are all introduced through the single incision, which contradicts the basic 'triangulation' rule of laparoscopy. This method requires advanced laparoscopic skills when compared with CML, added complexity, and poorer ergonomics, while early studies have also reported a longer operating time than with CML.

SILS has introduced several new, inherent, technical and ergonomic problems beyond CML, which include lack of triangulation, camera and instrument clashing and 'sword fighting', inline viewing, and instrument crowding at the port site. Those issues may be challenging, even in the hands of experienced laparoscopic surgeons. The restricted visibility, with affected range of movements, may result in inadequate dissection and mobilization and increase the risk of inadvertent injury. Those obstacles are even more significant in colorectal surgery, where the surgical field is even wider. Several alterations have been offered to try and overcome the inherent shortcomings of SILS, including different lengths of instruments and camera, curved and articulated instruments, and specialized SILS ports, as well as clever endo-retractors [74].

SILS colectomy was first reported in 2008 by Remzi *et al*. and has since gained great popularity among colorectal surgeons [75]. The learning curve for SILS colectomy spans between 30 and 60 cases, according to various reports [76, 77]. As surgeons have accumulated more experience with the SILS platform, operating times have shortened and became comparable with CML [78]. In some reports, the mean operating times of SILS have been reportedly even shorter than CML [79]; however, this may suggest a reporting bias, as SILS is being performed by select, highly qualified laparoscopic surgeons. Most colorectal procedures have been described using the SILS approach, including proctectomy, total abdominal colectomy and reversal of Hartman's procedure.

Several randomized, clinical trials and several meta-analyses have been published comparing the SILS approach with the CML approach for colon cancer [78–84], with ever increasing evidence of equality between the two approaches in terms of safety and feasibility. SILS has been shown to be superior to CML in terms of intra-operative blood loss, return of bowel function, hospital stay, and incision length. There have also been some early indications that oncological results are comparable with standard laparoscopy [79, 84]. As stated earlier, the majority of reported studies were conducted by highly specialized and experienced laparoscopic colorectal surgeons, thus a recommendation for routine use of SILS in colorectal surgery cannot be made. In addition, due to the long learning curve, special attention should be paid to qualifying the mainstream colorectal surgeons before widespread application of SILS for colorectal cancer.

Natural-orifice transluminal endoscopic surgery

Natural-orifice translumenal endoscopic surgery (NOTES) represents the next evolutionary step in minimal invasiveness, as the procedure involves gaining access to the peritoneal cavity and performing the procedure via intentional puncture of the gastric wall, the rectum, vagina or urinary bladder. There have been several reports of feasible and successful NOTES procedures, including transvaginal and transgastric NOTES cholecystectomy, NOTES appendectomy, and transgastric NOTES splenectomy. The most notable NOTES procedure to demonstrate real advantages over the 'gold-standard' approach for treatment of achalasia is the peroral endoscopic myotomy (POEM) procedure. POEM involves using standard, flexible endoscopic instruments to gain access to the submucosal plane in the mid-esophagus, and dissect caudally up to the gastroesophageal junction. A myotomy is then performed on the inner hypertrophied muscular layer of the lower esophageal sphincter using electocautery, while preserving the external esophageal sphincter. Upon completion of the myotomy, the endoscope is withdrawn and the mucosal defect is closed using endoscopic clips. This approach has been met with great enthusiasm and acceptance. Inoue has recently published his experience with 1000 achalasia patients treated via POEM, and this approach is currently being clinically performed worldwide in specialized centers, with good results [85–88].

While POEM shows real potential as a NOTES procedure replacing the conventional approach, other NOTES procedures are still in their infancy. The use of the transvaginal approach may be more feasible in specific localized procedures, such as cholecystectomy, since the procedure may be performed head-on, using standard laparoscopic instruments. The transgastric approach for cholecystectomy is more complex, since it necessitates the use of an articulating endoscopic camera—such as a scope—to allow for enhanced visualization of the operative field. There is also a need for flexible endoscopic instruments to achieve the necessary range of movements and required operative maneuvers. While theoretically feasible, visualization of the operative field is still compromised and can be confusing, and the flexible instruments lack the robustness to allow for adequate retraction and safe dissection. The endoscopic hemostatic clips are also quite cumbersome and not reliable enough for sealing large vessels, and thus are not reproducibly applied in a safe and quick manner.

Most NOTES procedures focus on a localized operative area. When moving to a wider operative field, such as in colorectal surgery, the limitations of NOTES are even more problematic.

Preliminary feasibility studies have been conducted in human cadaver models, aiming to perform NOTES transanal radical sigmoidectomy. Whiteford *et al.* were able to perform a sigmoid colon resection with *en bloc* lymphadenectomy and primary anastomosis in three male human cadavers [89]. Their procedural steps included luminal suture occlusion of the sigmoid colon, followed by transrectal bowel division, entry through the mesorectum into the pre-sacral space, *en bloc* mobilization of the sigmoid colon mesentery off the retroperitoneum, with high ligation of the superior hemorrhoidal artery. The sigmoid colon is then delivered transanally with extracorporeal division of the colon, and creation of a stapled, end-to-end colorectal anastomosis.

Pelvic dissection of the mesorectum is quite feasible and has been widely described and successfully performed by several colorectal surgeons as a part of the transanal TME (TaTME) procedure for rectal cancer: however, once the operative field extends superiorly, the major hurdle in performing an adequate oncological colorectal resection via the transanal approach is overcoming the acute angle at the sacral promontory and performing proximal dissection and mobilization of the splenic flexure, the descending colon and the sigmoid with adequate oncological takedown of the inferior mesenteric artery (IMA). While there have been a few cases reported of NOTES TME, the degree of proximal dissection beyond the peritoneal reflection is quite questionable at this point. As such, the 'pure NOTES' colectomy is currently in stagnation and not ready for wide application by colorectal surgeons, until further technological developments allow overcoming the aforementioned obstacles.

While 'pure NOTES' remains a goal yet to be achieved, the quest for that end allows for further expansion of the limitations of convention and development of 'hybrid NOTES' techniques that may allow for less-invasive and more advantageous alterations to current procedures. Hybrid NOTES involves the use of one or more transabdominal laparoscopic trocars for assistance in performing key steps such as retraction, mobilization, and control and division of major vessels, while some major parts of the procedure are performed using the natural orifice approach.

Natural-orifice specimen extraction

The easiest adaptation of a natural-orifice technique in colorectal surgery is the natural-orifice specimen extraction (NOSE), including transanal, transrectal, or transvaginal extraction of the resected specimen, which allows for avoidance of the abdominal wall incision. There have been several reports of NOSE in colorectal surgery, which initially appears to be safe and theoretically superior to conventional laparoscopy with regard to reduction in wound complications and post-operative pain; however, this needs to be further evaluated in large, prospective, controlled trials [93–97].

In 2006, Person *et al.* were the first to describe a totally laparoscopic TME with transanal extraction of the specimen, combined with creation of colonic *J*-pouch and colo-anal anastomosis [98]. In 2008, Lacy *et al.* performed a hybrid mini-laparoscopic and transvaginal resection of a sigmoid adenocarcinoma [90]. Sylla *et al.* have meanwhile performed NOTES transanal rectosigmoid resection with TME in 32 fresh human cadavers, using the transanal endoscopic microsurgery (TEM) platform. The TME was successfully performed using transanal dissection alone or with laparoscopic or transgastric endoscopic assistance [91]. Sylla and Lacy subsequently described a transanal endoscopic rectal resection with total mesorectal excision using the TEM platform performed in a 76-year-old woman with a T2N2 rectal cancer treated with neoadjuvant chemoradiation [92]. This, as well as additional work by other surgeons, eventually led to the development of the currently increasingly popular TaTME.

Transanal total mesorectal excision

The basic principle of oncological resection of rectal cancer, first advocated by Bill Heald, relies on complete mesorectal excision by means of dissecting the avascular plane around the mesorectal fascia. Violation of the mesorectal surface may harbor the risk of incomplete removal of malignant tissue and thus increase risk of local and distal recurrence. There is a pressing need for a true oncological resection via a minimally invasive approach while performing a highly demanding dissection in the pelvis, and motivated colorectal surgeons approach the mesorectal excision from the other end and perform a 'bottom-up' dissection.

The roots of TaTME could be found in the form of the combined transabdominal-transanal (TATA) approach for the surgical management of low-lying rectal cancers, and also in the form of transanal endoscopic surgery (TES) [99–101]. The TATA approach was described in 1982, to aid the distal part of dissection during open proctectomy. The first description of totally laparoscopic TATA with transanal extraction of the specimen was by Person *et al.* in 2006 [98].

The variants of TES are transanal endoscopic operation (TEO) and transanal minimally invasive surgery (TAMIS). TES has the advantage of improved access, exposure, and visualization of proximal early rectal tumors, and allowance of full-thickness resection and local control of tumors, with excellent oncological and functional outcomes. The TaTME builds on TES by using the above-mentioned advantages to precisely dissect the tissue planes and perform a full-thickness rectal dissection, while the TME is encompassed and performed 'from the bottom-up'. The TaTME approach allows early and precise definition of the distal resection margin, while the enhanced optics and pneumo-dissection allow for easy identification of the pre-sacral space and recto-vaginal or recto-prostatic plane, which may allow for better quality of the TME and reduced incidence of positive resection margins. As described earlier, this approach is particularly helpful in patients with anticipated difficult of dissection in the pelvis, such as male patients, or those with a narrow or deep pelvis, obesity, bulky prostate, or low-lying rectal tumors.

There has been an explosive increase in interest in the TaTME approach from several groups around the world, with very encouraging initial results in respect of completeness of TME and free resection margins (Table 1) [102–111].

A meta-analysis has recently been published, of seven studies comparing 303 patients who underwent laparoscopic TME with 270 patients undergoing TaTME [112]. The TaTME group had a significantly higher rate of complete mesorectal excision than the laparoscopic TME group (83.4% *vs* 73.4%; OR = 1.75; $P = 0.04$) and a lower rate of positive CRM (OR = 0.39; $P = 0.02$): however, no differences were noted in the number of lymph nodes harvested, distal resection margins (DRM), or positivity of DRM. Perioperatively, the TaTME group experienced shorter operating times (23 minutes shorter; $P < 0.01$), lower conversion rates ($P = 0.02$), and significantly lower rates of post-operative complications ($P = 0.03$). The length of hospital stay, rate of anastomotic leakage and re-admission rates showed no differences between the two groups. A limitation of this meta-analysis was that two of the seven studies performed a TATA TME, where conventional instruments, rather than dedicated transanal surgical platforms, were used to perform the perianal dissection. Furthermore, in those two studies, the perianal TME dissection involved only the distal TME; however, a subgroup analysis of the remaining five studies has shown similar conclusions with regard to circumferential resection margins and operating time, and marginal benefit for the TaTME approach for the macroscopic quality of the TME ($P = 0.05$).

Penna *et al.* recently reported the short-term clinical and oncological outcomes for 720 TaTME cases from an international multicenter registry, 88% of which were performed for rectal cancer [113]. The rate of complete TME was 85%, an additional 11% had near-complete TME, while major TME defects were reported in 4% of the cases. The CRM-positive rate was 2.4% and the DRM-positive rate was 0.3%. The abdominal

Table 1. Transanal total mesorectal excision (TaTME) initial results: details of the largest series of TaTME reported to date. Data show very encouraging results with regard to completeness of TME and free resection margins

Series	Number of Patients	LN (mean)	TME completeness	Free margins
de Lacy *et al.* [102]	20	15.9	100%	100%
Rouanet *et al.* [103]	30	13	100%	84.6%
Atallah *et al.* [104]	20	22.5	89.5%	90%
Chouillard *et al.* [105]	16	17	100%	100%
Velthuis *et al.* [106]	25	14	96%	96%
Fernandez-Hevia *et al.* [107]	37	14.3	91.9%	100%
Tuech *et al.* [108]	56	12	84%	94.6%
Veltcamp Helbach *et al.* [109]	80	14	88%	87.5%
Hüscher *et al.* [110]	102	20	97.1%	94.6%
Lacy *de al* [111]	140	14.7	97.1%	93.7%

portion was most commonly performed laparoscopically (in 82.4% of cases), followed by SILS (13.9%). Several risk factors for incomplete TME and positive resection margins have been identified on multivariate analysis, including positive CRM on staging magnetic resonance imaging (MRI), low rectal tumor <2 cm from the ano-rectal junction, and laparoscopic transabdominal posterior dissection to <4 cm from the anal verge.

There is increasing evidence that TaTME can be safely performed—with perioperative morbidity comparable to laparoscopic TME—with some good indications of superiority in terms of completeness of TME and reduced resection margin positivity. This approach is especially appealing in low rectal cancer-, male-, or obese patients: however, there is a need for well-designed and executed randomized, controlled trials to compare TaTME with laparoscopic TME. The COLOR III trial has been designed to address some of those points. The primary endpoint of the study is the CRM positivity, while secondary endpoints include completeness of mesorectum, sphincter-saving procedures, short-term morbidity and mortality, local recurrence, disease-free and overall survival at 3 and 5 years, as well as quality of life [114]; however, there is also a need to accurately delineate the indications, assess the cost-effectiveness and standardize the TaTME procedure, in addition to continuing to establish training platforms for colorectal surgeons for this technique to allow for wider adoption.

Conclusions

During the last two decades, advances in the surgical treatment of colorectal cancer have drastically evolved into a more minimally invasive approach. The advantages to laparoscopy are indisputable. The rate of evolution of different techniques and approaches reflects the accelerated rate of technology development in medicine and in general.

The field of minimally invasive medicine is going to evolve and broaden beyond our imagination. What we know now to be the 'cutting edge' in minimally invasive surgery will probably be obsolete within a decade or two; however, the abundance of techniques and technology should not defer the primary goal we have as physicians—patients' safety. New techniques should undergo adequate and thorough, well controlled, scientific investigation to better delineate true benefits and define accurate indications. We believe that the future of minimally invasive colorectal surgery is bright, but should be approached with caution and wisdom.

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