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Laparoscopic Total Mesorectal Excision

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Abstract

Since the introduction of Total Mesorectal Excision (TME), two minimally invasive techniques have been developed and are currently used together with the classic open approach: laparoscopy and robotic surgery. The adoption of laparoscopy in colorectal oncologic surgery has not been fast and various factors have contributed to curb the change. Nevertheless, short-term benefits such as reduced length of stay, blood loss, and pain are now widely recognized as benefits of minimally invasive surgery.

In contrast to laparoscopy, the expansion of robotic surgery has been more expedited. However, there is currently no scientific evidence of an advantage with this approach for rectal cancer surgery, while several studies have shown a considerable increase of OR time and costs.

This manuscript aims to summarize the history of laparoscopic colorectal surgery, describe the current techniques for laparoscopic TME and review the results of the published principal studies.

Keywords: Rectal cancer; Laparoscopic surgery; Robotic surgery; Laparoscopic total mesorectal excision

Introduction

Total Mesorectal Excision (TME) was first described by Prof. Heald in 1982 and is still considered the optimal surgical treatment for rectal cancer [1]. However, since the original presentation, two new techniques were developed and are currently used together with the classic open approach: laparoscopy and robotic surgery. In addition, Transanal TME and Transanal Minimally Invasive Surgery (TAMIS) are used in selected cases and, though valuable, have limited indications. The aim of this publication is to describe the evolution of laparoscopic colorectal surgery with particular focus on laparoscopic treatment of rectal malignancies.

Development of laparoscopic colorectal surgery

The first laparoscopic cholecystectomy was performed in Germany by Erich Muhe on September 12, 1985 [2]. That milestone operation that began the era of minimally invasive surgery; six years passed before Moises Jacobs *et al.* in Miami reported in 1991 the first laparoscopically assisted colectomy [3]. The subsequent adoption and development of laparoscopic colorectal surgery was slow when compared to other abdominal procedures. Various factors have presumably contributed to this gradual shift from an open to a minimally invasive approach.

Lack of anatomical landmarks for laparoscopic surgery: The different view of the operative field offered by the laparoscopic camera changed the way surgeons were looking at the anatomy. Surgeons had to adapt to the closer and bi-dimensional view of the planes and of the anatomical structures. Therefore, critical anatomical references had to be identified by the first adopters of this new technique in order to reduce the risk of vascular and visceral injuries [4-6].

Lack of standardized techniques: The traditional lateral-to-medial approach used in open procedures starts with the mobilization of the colon, followed by the ligation of the vessels. With the laparoscopic technique, early division of the vascular pedicle and dissection along the avascular retromesocolic plane may help identifying and respecting delicate anatomical structures such as the duodenum, the ureter, the gonadal vessels and the hypogastric plexus during TME [7]. A medial-to-lateral dissection was first proposed by Milson in 1994. However, it wasn't until 2004 that a consensus was achieved by The European Association of Endoscopic Surgeons (EAES) to recommend the medial-to-lateral approach [8-10].

Limited availability of advanced instruments: The variety of instruments now available for retraction, dissection and stapling have facilitated substantially to operating deep in the pelvis and, in particular, contributed to the evolution of laparoscopic TME. Back in the 1990's, the surgical

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armamentarium was still limited. Ultrasonic technology with its advanced tissue dissection and hemostasis was first described by Amaral JF in 1994 [11]. However, ultrasonic shears did not become commercially available until 1998, and a similar evolution was followed by electrosurgical energy systems for vessel sealing [12].

Oncologic concerns: Initial suspicion of high incidence of port site metastases has raised concerns about the oncologic safety of laparoscopic colorectal surgery. At the inception of oncologic colorectal laparoscopy, a number of studies reported cases of wound recurrence at port site [13-15]. This culminated with a small case series, published by Berends *et al.* reporting a 21% incidence rate [16]. As a consequence, many authors recommended abandoning laparoscopic colorectal procedures for cancer, except within controlled, clinical studies [17,18]. Possible explanation included intraoperative trauma and contamination during specimen extraction, but also embolization of exfoliated cells due to intraabdominal gas flow. This speculation was corroborated by experimental models showing possible increased tumor dissemination and implantation with pneumoperitoneum [19]. Subsequent randomized trials have not found any difference in wound recurrence between laparoscopy and open colorectal procedures, confirming the oncologic safety of this technique [20,21].

Absence of structured training programs in colorectal surgery: Standardization and quality of training has the potential to improve safety and outcomes in surgery. In addition, structured tutoring and teaching may aid in the adoption of new techniques. In an interesting survey published by Moloo *et al.*, lack of formal training was one of the main reasons cited by surgeons not offering laparoscopic colon resections [22]. Advanced training has an even stronger relevance for rectal cancer surgery that is technically demanding, requires advanced laparoscopic skills, and has a steep learning curve [23-25].

The lack of diffusion of specific laparoscopic training programs could contribute to explaining the slow adoption of this technique for the cure of rectal cancer. The rate of TME performed laparoscopically in the United States from 2007-2009 was, in fact, still under 10% [26]. All the lessons learned from the history of laparoscopic colorectal surgery fostered a quicker adoption of robotic surgery and the standardization of the technique for robotic TME [27]. However, currently there is no evidence that robotic-assisted surgery confers an advantage for rectal cancer treatment, and is associated with a longer operative time and increased costs. Randomized control trials and systematic reviews have confirmed equal results with regards to oncologic and functional outcomes [28].

Techniques for laparoscopic TME

While there remains variability amongst institutions and individual surgeons, there are several important elements that are vital to performing an effective laparoscopic TME for rectal cancer.

Positioning: Appropriate positioning is the initial crucial step for successful TME. The patient should be placed in the modified lithotomy position. The table is then positioned into steep Trendelenburg (25 degrees to 30 degrees) with left side up (10 degrees to 15 degrees). It is important to remember that prolonged positioning can lead to neuropraxia of the lower or upper limbs; if case time exceeds three hours, then a break from positioning should be given.

Port placement: Correct placement of ports can vary by institution. Each surgeon typically has a personal variation in their port placement. They should be placed in an area that allows the surgeon to visualize the pathology, decrease restrictions of movement, and provides the surgeon a comfortable position. Three options for port placement are pictured below:

Figure 1 with this port placement described by Plasencia *et al.*, the surgeon and the assistant work on opposite sides, providing freedom of movement for each. This mimics open surgery and allows an active role for the assistant. Ports are one hand-width apart, preventing collisions. With the camera in the epigastric region, the whole abdomen can be easily visualized. The 12 mm port within the right lower quadrant/suprapubic area can be extended into a Pfannenstiel incision for extraction. One disadvantage of this port layout is that depending on patient's body habitus- it can make the splenic flexure mobilization and access to the deep pelvis difficult.

Figure 2 from Morino et al. [29] while similar to Figure 1, this arrangement provides an extra port in the suprapubic area that can serve as both an extraction site or as stapler port for ultra-low cancers.

Figure 3 this configuration allows the assistant to operate with two hands. The camera is able to descend deeper into the pelvis for improved view of the TME field. However, three people are needed to operate and the second assistant can restrict motion of the operating surgeon.

Preferred approach to dissection: The classical approach to TME has been a lateral-to-medial dissection. In open surgery, with the assistant and the surgeon on opposite sides, it was the most logical way to perform the dissection. By developing a medial-to-lateral approach, Milsom et al. revolutionized the laparoscopic procedure [9,21]. The advantages of medial-to-lateral were first seen in 2003 in an RCT, where it was found to be quicker, less expensive, and had similar oncologic results [30].

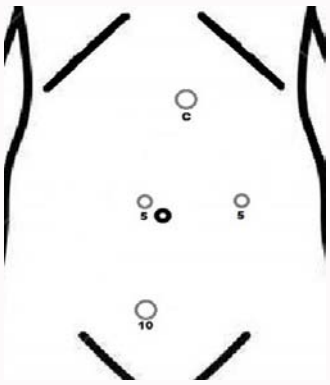

Figure 1: Port placement described by Plasencia et al.

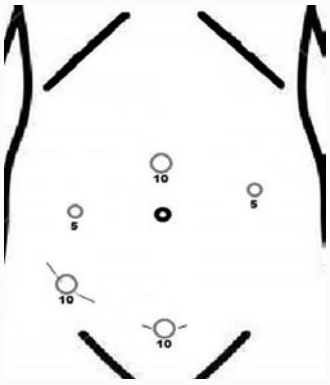

Figure 2: Port placement described by Morino et al. [29].

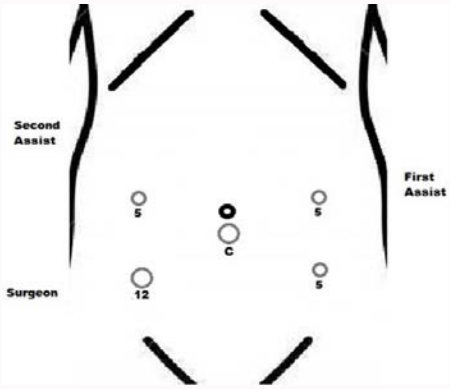

Figure 3: This configuration allows for dissection to be carried out on either side.

In a retrospective cohort study of the two approaches, Hussain *et al.* found "the [medial to lateral] approach increases the lymph node harvest, gives comparable CRM clearance, similar length of hospital stay and complications" [31]. A large meta-analysis in 2019 demonstrated decreased length of stay, decreased operating time and decreased morbidity [32]. Handling of the vessels and their origins are more easily approached. Additionally, by dissecting them out, lymph node harvest is more complete and with stapling devices, the origin of the artery has a more appropriate angle for division. The medial approach also allows the surgeon to visualize how well the mobilized colon will eventually reach into the pelvis. Once in the appropriate plane, the retroperitoneal structures can be identified more efficiently. Approach from the medial helps the colon remain fixed and keep tension to facilitate the dissection. There is also less manipulation of the tumor and simulates the classic "no touch" technique originally described by Turnbull [33]. This also facilitates less tumor metastasis via the blood stream [34]. The lateral-to-medial approach, on the contrary, can be utilized if the distal colon and rectum are adherent to the abdominal or pelvic wall with a foreshortened mesentery. In these types of situations, mobilizing the distal portion laterally can then facilitate the medial-to-lateral dissection. In a patient with very thick retroperitoneal fat, starting laterally may also help medial dissection. One must be careful to avoid entering the posterior renal space, which is a common mistake. In 2004, the European Association for Endoscopic surgery (EAES) formally identified it as the recommended approach for laparoscopic colorectal resection [8].

Once in the presacral plane, the dissection is usually carried in a posterior fashion with a medial-to-lateral approach. It provides appropriate visualization of the ureter and iliac vessels, as well as exposing the lateral borders of the rectum. The nerves and sacral veins also come into the field of view. By continuing this dissection, coning is avoided and prevents the resection from having positive margins [35]. Preservation of the TME is essential and has been shown to be equivalent to the open technique. With these advantages, it is clear why the medial-to-lateral approach has become standardized in the laparoscopic TME.

Visualization: With the development of new high-definition camera systems, laparoscopic visualization has allowed extremely precise dissection. Nerve preservation and identification of the mesorectal plane is better visualized then with an open technique. Helping to visualize the deep pelvis and overcome the technical dilemmas give laparoscopy an advantage. The ability to see the whole operative field, record differences in technique and critique the dissection, gives laparoscopy a method of standardizing techniques and quickly advancing the education of those interested in the field [36]. Developing teaching videos will also help propagate the use of laparoscopy in residency programs. Another addition to laparoscopy includes ICG9, which has been developed to evaluate blood flow to the planned areas for anastomosis.

Pitfalls: Laparoscopic surgery is a technically challenging operation that takes significant skill. Performing a complete TME is the essential part of the operation. Obesity, male sex and patients with prior surgery are all at increased risk for intraoperative injuries, incomplete TME, positive CRM and failed anastomosis [37]. Increased adipose tissue reduces peritoneal space and decreases the field of view in the low pelvis. Obesity is thus associated with higher conversion rates, increased operative time, and increased morbidity and mortality [38,39]. Prolonged surgery with laparoscopy decreases its benefit and increases risk of peripheral nerve injury due to extended patient positioning. Despite these shortcomings, laparoscopic surgery has been proven to be safe and provides successful oncologic outcomes.

Published trials in laparoscopic rectal surgery

A number of studies and trials have been published comparing the feasibility and outcomes of laparoscopic rectal surgery to the open and, more recently, robotic technique. Completeness of TME was an important indicator for an effective oncologic procedure considered in all of these studies.

Beginning with the MRC CLASICC trial, a randomized controlled trial published in 2005, the investigators began to demonstrate the benefits of a laparoscopic approach to TME [40]. This trial randomized 794 patients with colon and rectal cancers (526 laparoscopic, 268 open) from 1996 to 2002. Primary short-term endpoints were positivity rates of circumferential and longitudinal resection margins, proportion of Dukes' C2 tumors, and in-hospital mortality. Specifically, 253 and 128 of these patients underwent surgery for rectal cancer. Within the laparoscopic cohort, there was a 34% conversion rate to open technique, with this group experiencing more postoperative morbidity than either open or laparoscopic resections (59%, 37%, 32% respectively, $p<0.05$). Length of Stay (LOS) was two days shorter in the laparoscopic group (median 11 *vs.* 13 days, $p<0.05$). For patients undergoing rectal surgery, rates of positive Circumferential Radial Margin (CRM) in laparoscopic and open surgery were 14% and 16%, respectively. Importantly in patients undergoing Low Anterior Resection (LAR), this trial showed that the rate of positive CRM was 12% in the laparoscopic group, as compared to 6% in open group; these values did not rise to statistical significance. Interestingly, TME was performed 10% more in the laparoscopic group, which the authors postulated could be due to laparoscopy offered an easier approach to this technique.

The three-year follow-up data from the MRC CLASICC trial was subsequently published, confirming the safety of the laparoscopic approach on long-term survival [41]. Among the patients who underwent LAR and Abdominoperineal Resection (APR), there was no significant difference in three-year Overall Survival (OS) between the two approaches; specifically, 66.5% for open and 74.6% laparoscopic for LAR. Considering the previous finding of an increase in positive CRM in patients undergoing laparoscopic LAR, this long-term data demonstrated no differences in local recurrence rate for LAR (7.8% laparoscopic, 7% open) or APR (15.1% laparoscopic, 21.1% open) [42,43]. This early trial highlighted the importance of the learning curve associated with laparoscopic rectal surgery and was presumably the cause of the high conversion rate.

One randomized trial investigated the laparoscopic and open approaches in patients after neoadjuvant chemo-radiation in mid- and low- rectal cancers (within 9 cm of anal verge). The COREAN trial was conducted in three tertiary institutions in South Korea, accruing 340 patients (170 in each group) with T3N0-N2 rectal adenocarcinoma [44]. In this non-inferiority trial, short-term outcomes assessed CRM, quality of TME, lymph node harvest, time to return of bowel function, perioperative complications, pain, and quality of life scores. Procedures were performed by six to eight weeks after completion of chemo radiation. Prior to being accepted to the trial, seven surgeons, all of whom had performed a median of 75 laparoscopic colorectal surgeries previously, were required to submit video of a laparoscopic rectal surgery to a committee for approval of their technique, including quality of TME and preservation of autonomic nerves. Only two patients were converted from laparoscopic to open, and were included in the laparoscopic group for analysis.

All oncologic outcomes were similar between the two groups including lymph node harvest, proximal/distal/radial margins, rate of positive CRM, and macroscopic TME quality. Time of surgery was significantly longer with laparoscopy (mean 197 min *vs.* 245 min). They also had a similar rate of perioperative complication, although superficial wound drainage was significantly increased in the open group (11 *vs.* 2, p<0.05). Laparoscopy was associated with various short-term benefits. Patients who underwent a minimally invasive approach had significantly shorter time to return of bowel function, time to normal diet, and required significantly less IV morphine *via* patient-controlled analgesia pump. Lastly, quality of life scores, using QLQ-C30, showed significantly better physical functioning and less fatigue in the laparoscopic resection (LR) group , as compared to open resection (OR), three months postoperative. Oncologic safety was confirmed by the follow-up data. Median follow-up times were 46 and 48 months for open and laparoscopic approach, respectively. There was no significant difference in three-year Disease-Free Survival (DFS), OS, or local recurrence rates. Interestingly, the long-term follow-up showed similar quality of life between the two groups, similar to other comparative trials [45].

COLOR II was a non inferiority, multi-institutional, phase III clinical trial comparing laparoscopic and open approaches to rectal cancer [46]. To be included in this trial, surgeons were required to provide videos of five laparoscopic TMEs, demonstrating satisfactory oncologic technique. The primary endpoint was three-year local recurrence rate. Six hundred and ninety nine patients were randomized to laparoscopic approach and 345 to open. Similar to the results from the COREAN trial, operative time for the laparoscopic approach was significantly longer (240 *vs.* 188 min, p<0.0001). The study also demonstrated less intraoperative blood loss (200 *vs.* 400 mL, p<0.0001), a reduction in LOS by 1 day (8 *vs.* 9 days, p<0.05) and return of bowel function one day earlier with the laparoscopic approach (2 *vs.* 3 days, p<0.00001). From the oncologic standpoint, the number of lymph nodes harvested, distal margin, and rate of positive CRM (10%) were all similar between the two approaches. The three-year follow-up data of the COLOR II trial was later published, demonstrating a similar local recurrence rate (5%) and OS (86.7% LR, 83.6% OR) [47]. However, the trial showed that patients with low rectal cancers had a significant reduction in recurrence rate after laparoscopic surgery (3.8% *vs.* 12.7% - p<0.05), as well as an increase in DFS in patients with stage III disease via the laparoscopic approach (64.9% *vs.* 52% - p<0.05).

Two RCTs were unable to demonstrate the non inferiority of the laparoscopic approach, the AlaCaRT Trial and ACOSOG Z6051 Trial [48,49]. Performed in the New Zealand and the USA/Canada, respectively. Primary endpoints of these trials were completeness of TME, as well as distal and circumferential radial margins. The ALaCaRT trial accrued 237 patients in the open arm and 238 for laparoscopic approach. All patients had T1-T3 rectal cancers within 15 cm of the anal verge. Non-inferiority was set as a difference of 8%, with an accepted success rate of 90% for open TME. ACOSOG Z6051 used a non-inferiority cutoff of 6%, and accrued 222 patients in the open arm and 240 in the laparoscopy arm with stage II and III rectal cancer (T1-3, N0-N2) within 12 cm of the anal verge, after neoadjuvant chemotherapy. These studies confirmed various short-term findings demonstrated in prior studies. However, in ACOSOG Z6051, there was a success rate (complete TME and negative margins) of 86.9% in open versus 81.7% in laparoscopy, failing to meet the non-inferiority cutoff upon analysis. Similar results were obtained in ALaCaRT study with only 82% of laparoscopic resected specimens being considered successful compared to 89% of the open group.

Nevertheless, the two-year follow-up studies of each trial showed similar outcomes in DFS and local recurrence between laparoscopy and open surgery, differing from the short-term outcomes reported in their initial results [50,51]. In ACOSOG Z6051, though the analyses for DFS and recurrence were under-powered, the authors compared for superiority, demonstrating no statistical difference between the two groups in these important categories. At two years, DFS was 79.5% and 83.2% for LR and OR (with similar rates at four years), respectively. At two years, local recurrence rates were 2.1% and 1.8%, respectively, for LR and OR. Distant metastasis rates were also similar between the two groups, 14.6% LR and 16.7% OR. Similarly, ALaCaRT showed no statistical difference in DFS and OS, with local recurrence rates of 5.4% and 2.3% in the laparoscopic and open groups, respectively. These trials failed to clearly demonstrate the non inferiority of a laparoscopic approach, but the subsequent follow-up confirmed similar oncologic outcomes for surgeons experienced in laparoscopic rectal surgery.

With the increased adoption of robotic surgery in rectal surgery, a multicenter RCT comparing laparoscopy to robotic surgery was conducted: The ROLARR trial [52] (Robotic *vs.* Laparoscopic Resection for the Rectal Cancer). The primary end point in this trial was conversion to open laparotomy. Secondary end points included circumferential resection margin positivity and sexual/bladder function. Forty surgeons across 29 international institutions participated, with ultimately 471 patients randomized. The study demonstrated no statistically significant difference in conversion rate (8.1 *vs.* 12.2% p=0.16), positivity of CRM, complication rates, or effects on quality of life at six months postoperative. Surprisingly, this study demonstrated an overall conversion rate for laparoscopy of about 10%, which was significantly lower than those seen in previous trials, which further weakened the argument in favor of robotic surgery. Only after a subgroup analyses, a difference in conversation rate was found in men, obese patients, and those undergoing LAR as compared to APR (4.7 *vs.* 11.9%, p=0.007). The authors speculate that this may actually highlight the differences within the procedures themselves, with the oncologic portion of the APR being performed through the perineum, reducing the complexity of the laparoscopic dissection. Similar to previous studies in robotic surgery, OR times and costs were increased in the robotic group, with the authors ultimately concluding that robotic surgery does not confer a specific

advantage in rectal cancer surgery.

Conclusion

Standardization and quality of training in laparoscopic colorectal surgery plays a fundamental role in improving oncologic safety and outcomes in surgery. In addition, structured tutoring and teaching may help the adoption of new techniques. In an interesting survey published by Moloo et al. [22], lack of formal training was one of the main reasons cited by surgeons not offering laparoscopic colon resections. Advanced training has an even stronger relevance for rectal cancer surgery that is technically demanding, requires advanced laparoscopic skills and has a steep learning curve [23-25]. The rate of TME performed laparoscopically in the United States in the period 2007-2009 was, in fact, still under 10% [26].

The lessons learned from the history of laparoscopic colorectal surgery helped foster a quicker adoption of robotic surgery and the standardization of the technique for robotic TME [27]. However, currently there is no evidence that robotic-assisted surgery confers an advantage for rectal cancer treatment and is associated with a longer operative time and increased costs [53-55]. In a study by Park *et al.* at Yonsei University of Seoul, comparing long-term oncologic outcomes of robotic *vs.* laparoscopic surgery for rectal cancer, no significant differences were found in the five-year overall disease-free survival and local recurrence rates between robotic and laparoscopic surgical procedures. However, the patient's mean payment for robotic surgery was approximately 2.34 times higher than laparoscopic surgery [56]. Randomized control trials and systematic reviews have demonstrated similar results with regards to oncologic and functional outcomes with both techniques; the ROLARR trial only showed a possible advantage in a selected group of male obese patients [52].

Nevertheless, both of these approaches are helping propagate minimally invasive surgery and will continue to complement each other and stimulate the research of new technologies. Next-generation robotic platforms might overcome current limitations and prove robotic TME to be cost-effective; however, currently the routine use of robotic rectal surgery for cancer remains controversial and cannot be adopted as the standard of care [28]. Laparoscopic TME will remain an important tool in the field of oncologic colorectal surgery because of its reduction in short-term morbidity, oncologic effectiveness, and broad availability.

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