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Laparoscopy in the Management of Colorectal Cancer

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1. Introduction

Since the introduction of laparoscopic surgery, minimally invasive techniques have been widely used for benign and malignant diseases. [1, 2] Although many surgeons perform laparoscopic colectomy for benign diseases, its application for colorectal malignancy had slow progress because of oncological considerations. [3] Over time, many randomized controlled trials have been published comparing open to laparoscopic surgery for colorectal cancer, which show that in experienced hands, competent oncology resections can be performed the results are equivalent to open surgery [4-7]. However, the results of the minimally invasive surgery for rectal cancer have not been thoroughly investigated and large multicenter randomized trials are underway.

Large number of randomized controlled trials comparing laparoscopic to open surgery for colon cancer have established better short-term results - less pain, shorter length of stay, faster return of bowel function and equivalent oncological outcomes [2-5]. Laparoscopic rectal surgery is still developing with promising short-term benefit, although depending on the skills and techniques of the surgeon [6]. Surgery of rectal cancer requires more technical skills (total mesorectal excision, low pelvic anastomosis), many fear that the oncological principles could be compromised during laparoscopic resection. In addition to oncological concerns, the widespread of laparoscopic surgery for colorectal cancer is impeded by the significant learning curve.

Hand-assisted techniques introduced in the 1990s were an attempt to overcome some of these limitations and provide an overlap between open and laparoscopic techniques and the transition from open to minimally invasive surgery for many surgeons [1, 8]. Acceptance of minimally invasive procedures by patients and surgeons led to the development of new technologies to ease the laparoscopic approach. The introduction of single incision laparo-

scopic surgery (SILS) devices has allowed fewer cuts. [9] The clinical application of endoscopic natural orifice transluminal surgery (NOTES) in colorectal disease is not yet fully accepted, but it was possible great advances in instrumentation and improving techniques for specimen extraction after laparoscopic colectomy [12].

2. Systemic benefits

Basic science studies have demonstrated the better preservation of oncological and immunological functions after laparoscopic surgery before trials on humans [7-9], thus giving hope for better long-term oncologic outcome. Tumor cells are found in systemic blood circulation and in the peritoneal fluid immediately after surgery and if they survive may avoid the immunological defense of the organism. The surgical trauma causes immunological alterations and the organism might be vulnerable during the postoperative period [7-9]. Laparoscopic surgery causes lesser trauma and therefore less effect on the immune system, decreases the proliferation stimuli for cancer cells and neoangiogenesis [7-9, 11]. The changes can last shortly after the operation, but some are observed after months or longer [11]. These potential advantages do not provide better long-term outcomes in human trials, although some report better oncological results after laparoscopic surgery in terms of longer cancer-related survival and less tumor recurrences [10-14].

The rate of conversion to open surgery is still very high, as demonstrated by three multicenter prospective trials - the NCI Clinical Outcomes of Surgical Therapies (COST; 21%), Colon Cancer Laparoscopic or Open Resection (COLOR; 17%), and the Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASICC; 29%) [15, 16]. This could be due to more precautionous behavior of the surgeons and their inexperience.

A meta-analysis from 2006 demonstrated intriguing results. It includes 1134 patients after colectomy in two periods – 1996-2000 and 2000-2004. Laparoscopic colectomy was introduced as an option only in the second period. The authors found that 3-year overall survival decreased in the latter, while the overall survival of patients after open colectomy remained the same over the two periods. [17]

Intracorporeal anastomosis for right laparoscopic colectomy improved patient outcome compared with patients who underwent extracorporeal anastomosis. There is found faster recovery of nutrition, faster recovery of intestinal function, and shorter hospitalization. However, there was no difference in average surgery time between the two groups.

According to the differences in age, gender, BMI, ASA class, or abdominal surgical history, in laparoscopic colectomy with extracorporeal anastomosis (laparoscopic-assisted colectomy), the bowel is externalized through a lateral mini-incision. With this approach, bowel mobilization and ligation of vessels is usually laparoscopic, whereas resection of the specimen and creation of the anastomosis is extracorporeal. On the other hand, in laparoscopic right colectomy with intracorporeal anastomosis (totally laparoscopic colectomy), bowel mobilization, ligation of vessels, resection of the specimen, and creation of the anastomosis are totally intracorporeal.

Regarding oncological radicality, there are significant differences in the number of lymph nodes removed. An average of 19 lymph nodes from the intracorporeal group and 14 lymph nodes from the extracorporeal group are reported to be removed. In the literature, some authors have reported no differences in safety, whereas others noted that the only advantage was a smaller incision. On the other hand, other studies affirmed the safety of intracorporeal anastomosis, with the same complication rate as for extracorporeal anastomosis. Because intracorporeal anastomosis is considered more difficult, only a few surgeons have used this kind of technique; however less mobilization is required, and less tension is applied to the bowel and mesentery because the bowel does not need to reach the anterior abdominal wall for externalization. [11] Furthermore, the excessive tension on the mesentery during the mobilization is associated with an increased risk of mesenteric or portal vein thrombosis. Concerning surgical times, there is not a significant difference in surgical time between the two groups. Patients in the intracorporeal group had a shorter hospitalization duration. In some cases, the hospitalization duration was longer possibly because of age (43.2% of patients in the intracorporeal group and 33.4% in the extracorporeal group were over 80 years old). Our results showed a significantly shorter average hospitalization stay in the intracorporeal group. These data agree with a recent Spanish study, although this difference was not significant ($P = 0.5424$) because hospitalization duration is influenced by many patient factors. On the other hand, we found that 71.4% of patients in the intracorporeal group went home within 7 d, and 54.7% of patients in the extracorporeal group went home within this period. [20, 21] Patients in the intracorporeal group and extracorporeal group went home within 7 d. Concerning the recovery of intestinal function, our results found significantly shorter average times for resumption of gas evacuation after 3 d in the intracorporeal group compared to after 3.8 d in the extracorporeal group. Bowel movements occurred after an average of 4.9 d in the intracorporeal group. In the intracorporeal group, the nasogastric tube was removed after 1.8 d, whereas it was removed after 3 d in the extracorporeal group. This difference can be explained by an increased percentage of paralytic ileus in the second group, which is due to the traction of the right colon and terminal ileum through the mini-incision on the pancreas and duodenum. This approach allowed a more rapid recovery of liquid and solid nutrition consumption. [25-27] There are met some major complications, which included severe anemia, occlusion, anastomotic dehisces, and enterocutaneous fistulae. There were no significant differences between the two groups.

In conclusion, our study clearly shows that laparoscopic right colectomy with intracorporeal anastomosis improves patient outcome. Intracorporeal anastomosis resulted in faster recovery of nutrition consumption, faster recovery of intestinal function, and shorter hospitalization duration. The higher number of lymph nodes removed seems to be related to vascular division as the first surgical step as a rule. This confirms that a mini invasive approach improves patient outcome.

3. Port site metastasis

The early trials of laparoscopic colectomy have established high rate of tumor recurrence near the port wounds, which was considered a serious drawback of the new approach. The etiology

is unclear, although some authors suggest poor surgical technique and tumor biology as a probable cause. The reported rate in the early trials reached 21%. Recent trials (Hughes *et al.*, 1603 patients, [15] found the rate to be 0.68%. Fleshman *et al.* [5] reported results based on the NCI COST trial, which demonstrated comparable rates for open and laparoscopic surgery after 5- and 8-year follow up (0.5% and 0.9%, respectively). The Barcelona trials had similar outcome after a median follow-up of 95 months [7]. The European randomized controlled study, the Colon Cancer Laparoscopic or Open Resection (COLOR) trial (2009) established after 53-month median follow-up that the port site metastasis rate was 0.4% after open (n=542) and 1.3% after laparoscopic colectomy (n=534). [19] The location of the recurrences was near the extraction port (n=2) and near the trocar sites (n=5) [5]. Recent studies do not report such high recurrence rates.

Proper training and the use of safe oncologic techniques are essential in the prevention of port site metastases. Such safe techniques are the routine use of wound protectors, less instrument exchange, avoidance of direct trauma to the tumor, avoidance of inadvertent desufflation.

4. Enhanced recovery after surgery

The approach employs a multimodal perioperative care pathway with the aim of attenuating the stress response to surgery and accelerating recovery [21]. Implementation of enhanced recovery protocols has led to improved outcomes across a range of different specialties including reductions in postoperative morbidity and hospital stay [61-65]. The fundamental premise of ERAS is the incorporation of evidence-based practice. It would seem to follow therefore that the evolution of enhanced recovery guidelines should be dynamic, allowing modifications of certain aspects of the program as new data becomes available. Some authors have advocated a rigid adherence to the ERAS protocol, citing study data that demonstrates a proportional relationship between deviation from the protocol and increased morbidity [61]. However, as evidence for components of the ERAS protocol change, it may be that a more flexible and individualised approach should be considered.

5. Perioperative fluid administration

Traditionally, patients undergoing major colorectal surgery have received liberal volumes of intravenous fluids [49]. Excess intravenous fluid during and after surgery has been associated with delayed gut function and increased complication rates [50, 51]. Fluid restriction has been proposed as a possible method of improving recovery and reducing postoperative complications. Brandstrup *et al* [58] found that randomising patients undergoing elective colorectal surgery resection to a restricted fluid protocol reduced cardiopulmonary and wound morbidity. MacKay *et al* [59] found no difference in recovery of gastrointestinal function or time to discharge with postoperative fluid restriction while using a conservative intra-operative protocol. Goal directed fluid therapy *via* oesophageal Doppler (OD) monitoring offers an

opportunity to individualise peri-operative fluid administration. OD provides a real time representation of haemodynamic function, and has been shown to be comparable with other methods for estimating cardiac output such as LIDCO. A number of studies have shown that goal-directed fluids reduce morbidity, critical care admissions, and hospital stay [62]. It is not clear however whether these benefits are still significant within an enhanced recovery protocol. Other goal-directed techniques employ central venous oxygen saturation (ScvO₂) as a surrogate for mixed venous oxygen saturation. ScvO₂ is related to tissue oxygenation and so can be used to titrate oxygen and fluid therapy, particularly in the immediate postoperative period. This approach requires central venous access which is not always available as some groups have developed a less invasive approach to monitoring. While a number of different fluid protocols have been proposed, the optimal approach is still unclear.

6. Evolving postoperative analgesia

Epidural analgesia was considered central to early ERAS protocols, since it reduces the endocrine-mediated stress response [53, 54], and improves postoperative intestinal function [55]. Epidural analgesia also provides superior pain control to systemic opiates, particularly in the first 24-36 h after surgery [56]. Data on the effect of epidural analgesia come predominantly from studies in open surgery while the benefits in laparoscopic surgery are less clear. Levy *et al* [65, 66] performed a meta-analysis to address this question but concluded that there was a paucity of quality data. The authors subsequently performed a study in which patients were randomised to receive epidural, spinal or patient-controlled opiate analgesia following elective laparoscopic colorectal resection. They demonstrated a significantly longer hospital stay, time to return of bowel function and duration of nausea in the epidural group. Intrathecal morphine has been proposed as an alternative [67]. A meta-analysis provides encouraging results in patients undergoing abdominal surgery; reduced post-operative pain in the first 48 h and significantly reduced opiate consumption compared with systemic opiates [68]. Transversus abdominus plane blocks have also been gaining in popularity although comparative data is still lacking [69]. Epidurals can cause vasodilatation and hypotension [70], resulting in excess fluid challenges, third space shift and fluid overload. As studies emerge demonstrating benefits of alternative analgesic techniques, it does raise the question: Should epidural analgesia be the standard technique for all colorectal resections? Perhaps a more individualised approach dependent on the procedure, use of laparoscopy and placement of incisions should be considered. In this way more patients may be able to avoid potential complications while maintaining adequate analgesia and facilitating early mobilisation.

7. Laparoscopic and open surgery in enhanced recovery

The adoption of laparoscopic techniques within colorectal surgery came at a similar time to the introduction of "fast-track" surgery. Early studies examining the effect of laparoscopic surgery showed clear superiority in short term outcomes when compared with open surgery

using traditional recovery technique [63, 64]. Patients undergoing laparoscopic surgery have reduced in-patient stays, less morbidity and improved postoperative pain [65, 66]. What is less clear is how much of the benefit is attributable to laparoscopy and how much is an effect of differing perioperative care pathways. Since these early trials there have been a number of small trials comparing laparoscopic and open colorectal surgery within an enhanced recovery setting with conflicting results [55-61]. Most recently a four-armed randomised study of patients undergoing either open or laparoscopic surgery, in an enhanced recovery or standard recovery programme was performed. They demonstrated a significantly faster recovery time following colonic surgery in those patients undergoing laparoscopic procedures within an ERAS programme. What is clear is that there are still a number of areas within the enhanced recovery protocol where the evidence-base continues to change. The relative contributions of different facets of the protocol also remain to be determined. While this is the case we should accept a flexible approach to facilitate the adoption of techniques supported by randomised data. There may also be scope for a degree of individualisation to reflect the wide range of patients and procedures to which enhanced recovery is now being applied. [70]

8. Laparoscopic colectomy

After the initial description in 1991, several reports of laparoscopic colectomy (LC) for colorectal cancer were described. Significant concerns regarding this approach surfaced when minimally invasive techniques applied to colorectal malignancy lead to increased surgical complications and worse cancer outcomes compared to conventional open approaches. An early report, using minimally invasive techniques for benign colorectal disease, showed a significantly high rate of serious complications (18%), including inadvertent enterotomies, intraoperative hemorrhage, anastomotic leaks, and pelvic abscesses. When LC was used to treat colorectal cancer, several papers noted early wound or trocar site recurrences, including one case series documenting a 21% rate. With a less than 1 percent wound implantation rate for open surgery, serious concerns were raised as to the possibility that poor oncologic results were due to a combination of poor technique and abnormal distribution of malignant cells secondary to pneumoperitoneum. Further concerns that laparoscopic techniques may be problematic to cancer patients arose when some studies demonstrated statistically significant worse cancer-specific survival in patients who had conversion from laparoscopic to open surgery. Moloo et al. described decreased survival at 2 years of 76% from 87% for all stages ($P = 0.02$) of colorectal cancer collected from a prospective database of 377 consecutive laparoscopic patients. In the same cohort, at 5 year followup, there was a trend toward decreased overall survival in converted patients (61.9% versus 69.7%, $P = 0.077$). Chan et al. showed an increased local recurrence rate at 3 year followup of 9.8% in the laparoscopically converted group as compared to 2.8% in open patients ($P = 0.03$). The oncological concerns raised in early reports provided a compelling argument to study the question of oncologic equivalence between the open and laparoscopic approach to colorectal cancer in a controlled fashion.

In the early 1990s, several multicenter prospective randomized controlled trials comparing laparoscopic and open surgery for colorectal cancer were initiated. Ultimately, seven large-scale trials compared laparoscopic and open colectomy for colon carcinoma and examined short-term and long-term outcomes. These trials included the Clinical Outcomes of Surgical Therapies (COST) trial funded by the National Cancer Institute in the United States, the Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASICC) trial in the United Kingdom, the Colon Cancer Laparoscopic or Open Resection (COLOR), a multicenter European trial, the Barcelona trial, and several others [20–26]. The main focus of these trials was oncologic outcomes, but short-term outcomes, quality of life, and safety were also evaluated. The CLASICC trial was the only large trial that also evaluated MIS in rectal cancer. Though modest in early studies, the short-term patient-related advantages of laparoscopic surgery have now been confirmed and are significant over the open approach. The Minimally Invasive Colorectal Resection Outcomes (MICRO) review identified 22 randomized controlled trials and 66 cohort series for benign and malignant colorectal disease [27]. Laparoscopic colectomy results in significantly lower pain scores and analgesia requirements, estimated blood loss, return of bowel function, and length of stay. Numerous other trials, including the COST, COLOR, and CLASICC trials, examining short-term outcomes following laparoscopic colectomy for colorectal cancer have confirmed these findings [20–26, 28]. Several studies have also identified a decreased rate of postoperative morbidity including fewer wound infections [21, 23, 27, 29]; this was recently reinforced by a large trial from the National Surgical Quality Improvement Program (NSQIP) database of over 10,000 patients identifying decreased incidence of wound infection following laparoscopic colectomy (9.5% versus 16.1%, $P < 0.001$) [30]. Quality of life has been assessed in several trials and results varied from no difference to favoring improved quality of life in laparoscopic colectomy [31].

The initially cited oncologic concerns of laparoscopic colectomy for colorectal cancer were later dispelled when surgeons trained in appropriate laparoscopic oncologic resection performed operations in the trial setting. Major trials, including the COST, CLASICC, and COLOR trials, examined tumor specimens and reported long-term data on recurrence and survival. The surgical specimens were evaluated, and parameters such as lymph node yield, circumferential resection margins, and longitudinal margins were quantified. No trial identified statistically significant differences in lymph node yield [20–26] or resection margins [20, 22, 26]. This initial evidence allayed some concerns regarding oncologic resections, but the long-term measures for recurrence and survival were still unknown. Trial data matured, and more evidence accumulated confirming similar recurrence patterns and rates between laparoscopic and open colectomy. Local recurrence, distant recurrence, and wound or port site metastases were the same between groups [4, 5, 7, 24, 32–34]. Disease-free and overall survival in long-term follow-up (up to 7 years) is equivalent [4, 5, 7, 32–34]. The concern that conversion from laparoscopic to open surgery in patients with colon cancer may lead to worse oncologic outcomes was not seen when 5-year COST trial data showed no statistical difference in these two groups.

Despite evidence demonstrating improved short-term outcomes of laparoscopic colectomy and oncologic equivalence, widespread implementation of this technique was slow. The lack of formalized training, outside single-day laparoscopic training courses, and the significant

learning curve for straight laparoscopic techniques likely represented significant barriers to adoption. As hand-assisted laparoscopic surgery grew in popularity, a more widespread adaptation with fewer conversions to open surgery occurred in part due to a shorter learning curve with this technique. Three randomized controlled trials have been performed to compare a hand-assisted technique to a laparoscopic technique including patients with both benign and malignant disease, all demonstrating decreased rates of conversion to open surgery [35–37]. A recent meta-analysis compiling 13 studies demonstrated decreased operative times and decreased open conversion rates with a hand-assisted approach [38]. There were no differences in short-term clinical outcomes or oncologic resection results. A recent study by the Mayo Clinic prospectively analyzed the use of hand-assisted surgery in a minimally invasive colorectal practice and found that when applied to a center performing large volumes of laparoscopic surgery, hand-assisted techniques were responsible for more complex procedures to be done laparoscopically [39]. This technique is a minimally invasive approach that has been helpful for surgeons to transition from open to laparoscopic colectomy, especially if they have had little previous laparoscopic experience. Moreover, this technique has allowed a MIS approach in patients otherwise not previously considered candidates (obese, adhesions).

As surgeon experience increased and as more studies demonstrated that laparoscopic colectomy for benign and malignant disease is an acceptable alternative to open surgery, the overall ratio of laparoscopic to open colectomies in the United States has increased. A recent analysis from 2000 through 2004 demonstrated an increasing incidence of laparoscopic colectomy from 3% to 6.5% nationally with increased rates of laparoscopic approaches in urban centers and teaching hospitals [40]. A separate study and database of patients from 2004 through 2006 identified over 32,000 patients, of which 34% underwent laparoscopic colectomy [41]. This trend toward increased laparoscopy has also been influenced by public knowledge and patient demand for this approach, as well as improved and formalized laparoscopic training in residency programs.

The short-term advantages of laparoscopic surgery over the open approach are confirmed. The minimally invasive approach is characterized by lower pain score and analgesia requirement, estimated blood loss; earlier return of bowel function and shorter length of stay (Minimally Invasive Colorectal Resection Outcomes (MICRO), [20]. The postoperative recovery of pulmonary function is quicker after laparoscopic colectomy. None of the randomized trials have observed significant increase in the anastomotic leakage rate [2-5]. Several studies demonstrated the decreased rate of postoperative morbidity and less wound infections [2-7]. Quality of life after laparoscopic surgery has been evaluated in several trials and the results varied from similar to better QoL than after open surgery [21].

In 2008 Lacy et al. reported the long-term outcomes of Barcelona trial (median follow-up 95 months). The overall survival rate was higher in the laparoscopic (64%) group when compared with the open group (51%) with no statistically significant difference ($p < 0.07$). Laparoscopic group demonstrated higher cancer-related survival and lower cancer recurrence in ($p < 0.07$ for both). The differences in survival and recurrences between the open and laparoscopic groups were observed for III stage tumors, with significantly better results in terms of overall-survival, cancer-related survival and chances of being free of recurrence. Results for stage I and II did

not show any statistical difference. The conclusion is that in a dedicated laparoscopic center, LAC may result in a long-term survival benefit compared with OC, particularly in advanced cases". This oncological advantage can be explained by a preserved cellular immunity, attenuated stress and inflammatory response. [7]

These results seem encouraging and lead the way for laparoscopic surgery, although in a 2007 study by Fleshman (5-year follow-up, COST trial) the data did not demonstrate significant difference in the 5-year overall survival, 5-year disease-free survival, and recurrence rates between the two groups. The pattern of recurrence is also similar. [5] In 2007 Bonjer et al. reported meta-analysis, based on 3-year follow-up data from Barcelona, COST, COLOR and CLASSIC trials. No significant difference in 3-year survival, 3-year disease free survival or tumor recurrence rates between study groups was observed. Analysis by stages did not show any statistical difference in survival between both groups [16].

The hand-assisted laparoscopic surgery is a potential way to decrease operative time and maintain the benefits of the minimally invasive approach. The type of laparoscopic surgery allows introducing a hand through special device in the abdominal cavity, while preserving pneumoperitoneum. This provides proprioception and tactile feedback and ability to perform manual dissection and retraction. A study by Marcell [8] reported the results after multicenter randomized trial. The hand assisted sigmoidectomy group had significantly shorter operative time by 30-minutes when compared with straight laparoscopic group. Both groups had similar short-term outcomes. There were no differences in time to bowel function, pain scores, narcotic use, or time to bowel function. Conversion to open surgery was also significantly less for the hand-assisted group. Incision length was significantly longer for the hand-assisted group, but the difference was small. The authors concluded that hand-assisted surgery results in significantly shorter operative time, while maintaining similar outcomes as straight laparoscopic surgery [17]. Hand-assisted surgery allows to perform more complex procedures and to operate on patients with adhesion or obesity.

9. Laparoscopy for rectal cancer

The use of laparoscopic approach in the treatment of rectal cancer has led to increase of surgical complications and worse cancer outcomes in comparison to the open surgery [6] strong statement to make, may be phrase it differently. Several papers reported increased rate of port-site recurrences, reaching up to 21% [3]. The same parameter for the open approach is 1%. Those results might be explained by poor surgical technique and abnormal distribution of cancer cell due to the pneumoperitoneum [7]. The cancer-specific survival was significantly lower after conversion to open surgery [8, 9].

Based on the data of a prospective trial, including 377 laparoscopic patients [22] the survival decreased from 87% to 76% at 2 years for all stages of colorectal cancer. After a 5-year follow-up the overall survival decreased in converted patients. The local recurrence also proved to be higher: 9.8% and 2.8% for the laparoscopic and open groups, respectively. Several large trials were initiated in the 1990 (Clinical Outcomes of Surgical Therapies (COST) [21] in the

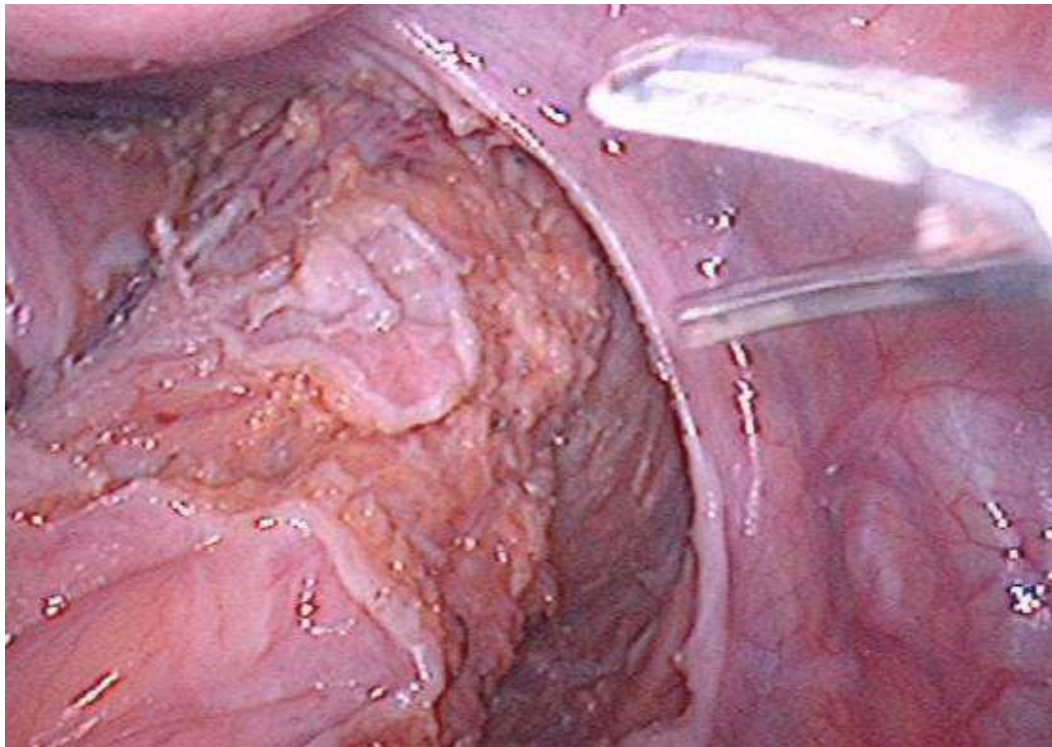


Figure 1. Laparoscopic resection of rectal cancer –anterior mobilization of the rectum

USA, the Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASSIC) [6] in the United Kingdom, Colon Cancer Laparoscopic or Open Resection (COLOR) in Europe and the Barcelona trial) [15]. Those trials evaluated laparoscopic and open colectomy for colon carcinoma and examined short-term and long-term outcomes, as well as short-term outcomes, quality of life and safety. Only the CLASSIC trials evaluated minimally invasive surgery for rectal cancer.

The potential benefits of laparoscopic rectal surgery are known and were proven by meta-analysis of studies of non-randomized trials – shorter time of bowel function restoration, shorter length of stay [22]. A characteristic advantage of the laparoscopic surgery is that it provides unobstructed view to the entire surgical team and magnified view of the operating field, thus allowing more accurate dissection. The pneumoperitoneum helps to open the planes of dissection of the mesorectum. The limitations of the laparoscopic rectal surgery are the unsure data on oncological safety [2-5], the concerns about inadequate oncological distant dissection, anastomotic leakage, technical challenges [23, 24].

Significant difficulty poses the obtaining of adequate exposure of the rectum. The narrow pelvis in some patients may cause clashing of the instruments and poor dissection. An experience assistant is required in such cases. The CLASSIC trial reported increased rate of positive circumferential margin after laparoscopic rectal surgery (12%) in comparison to the open group (6%). The distant margin of the tumor is difficult to be identified, as it cannot be palpated. This may cause inadequate distal resection.

The use of laparoscopic stapler requires multiple firings to complete distal rectal resection. In the case of low rectal anastomoses, this increases the anastomotic leakage rate (17% below 12cm from the anal verge [11], 20% below 15cm [23]. The leakage rate after open total mesorectal dissection varies from 4% to 11% [25, 26]. Future improvement of the stapler technology is required.

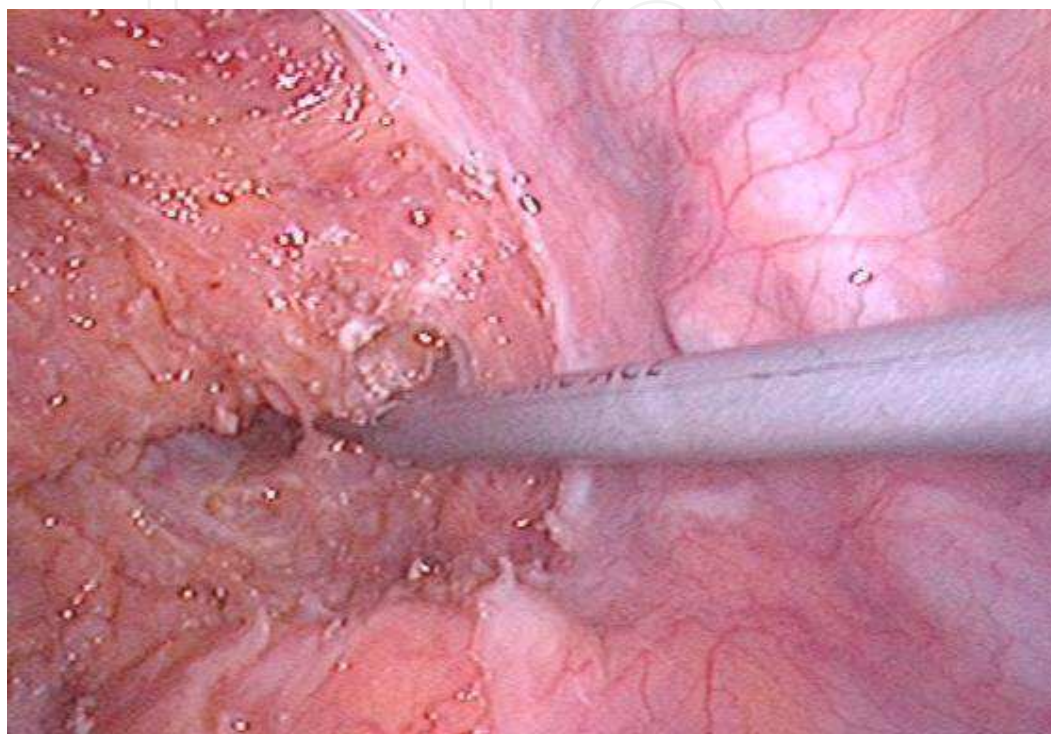


Figure 2. Lymph node dissection in laparoscopic rectal cancer resection

The proven benefits of laparoscopy noted in colon cancer surgery including decreased intraoperative blood loss, smaller length of incision, less postoperative pain, faster recovery of intestinal function, and shorter length of hospital stay likely also apply to rectal cancer surgery [37]. In RCTs the mean operative time for open surgical resection of rectal cancer ranged from 106 to 284 min compared to 120 to 245 min for laparoscopic resection. As expected, duration of operation was significantly longer in the laparoscopic group compared to the open group in 6 of the 8 RCTs [7, 22, 31, 38-40]. Similar results were reported in RCTs of open *vs* laparoscopic resection for colon cancer. Zhou *et al* [24] reported both shorter open and laparoscopic operative times compared to other trials with no significant difference between the two operative approaches (120 min *vs* 106 min for laparoscopic *vs* open resection respectively, $P = 0.051$). However, no details were provided on tumor stage, conversion rate, or whether the analysis was performed on an intent-to-treat basis. Araujo *et al* [25] was the only RCT to demonstrate significantly shorter operative times with laparoscopic compared to open resection (228 min *vs* 284 min respectively, $P = 0.04$). However, they attributed these results to fact that the surgical team performing laparoscopic APR was the same whereas open APR was often performed by different surgical teams. In addition, extraction of the specimen from the

perineum likely decreased operative time because there was not an abdominal incision to close. Two meta-analyses included operative time as an outcome of interest. Aziz *et al* [17] included 22 studies comparing laparoscopic *vs* open rectal cancer resection in 2071 patients and found that operative time was significantly increased with the laparoscopic group as compared to the open group with a weighted mean difference (WMD) of 40.18 (95% CI, 26.46-56.13). Gao *et al* [26] performed a meta-analysis of short-term outcomes after laparoscopic resection for rectal cancer based on 11 studies and included 643 patients which reported no difference in operating time between open and laparoscopic approaches with a WMD of 1.59 [1.2-1.98]. Intraoperative blood loss was significantly less for the laparoscopic group compared to the open group in 4 of 6 RCTs and ranged from 20 mL to 321.7 mL and from 92 mL to 555.6 mL in the laparoscopic and open groups respectively [31, 35, 38, 40]. Araujo *et al* [25] did not specifically report on the amount of intraoperative blood loss but there was no statistically significant difference in the need for blood transfusions between the two groups which was attributed to the fact that in an APR the majority of blood loss occurs during the perineal portion of the case which is the same regardless of surgical access.

A recent Cochrane review by Breukink *et al* [41] evaluating the safety and efficacy of elective laparoscopic TME for the resection of rectal cancer found that in the majority of studies blood loss was reduced with the laparoscopic approach although this did not translate to fewer blood transfusions. Length of incision was measured in 3 of 8 RCTs and ranged from an average of 5 cm to 10 cm with the laparoscopic approach compared to an average of 19.1 cm to 22 cm with the open approach [7, 38, 40]. Seven of the 8 trials reported a conversion rate which ranged from 0%-34% [7, 38-40]. Conversion to the open approach was commonly defined as length of incision greater than the size needed for tumor extraction or premature abdominal incision to allow improved mobilization. In the majority of studies conversion to open surgery was required because of local tumor invasion or difficult dissection in a narrow pelvis although bulky tumor, dilated small bowel, dense adhesions, bleeding, rectal perforation, difficulty mobilizing the splenic flexure, failure to identify or injury to the ureter, ischemia of the descending colon, and anastomotic failure were also cited. Breukink *et al* [41] reported that 36 of 48 studies assessed conversion and showed a highly variable rate ranging from 0% to 33%. However, they report that the lack of consensus in the definition made results difficult to interpret. In addition, surgeon experience and patient selection criteria were often not mentioned. Two trials reported particularly high rates of conversion. Ng *et al* [37] had a conversion rate of 30.3% but they did not routinely perform preoperative staging with computed tomography scans and therefore frequently converted after diagnostic laparoscopy. Twelve of the 23 patients randomized to laparoscopic surgery were converted to open due to local tumor invasion, bulky tumor, or dilated small bowel which may have been recognized by preoperative imaging. In the CLASICC trial the conversion rate for laparoscopic resection of rectal cancer was reported at 34% and attributed to excessive tumor fixation and uncertainty of tumor clearance [6]. Surgeon learning curve may account for this high rate of conversion as evidenced by the fact that the overall rate of conversion dropped by year of study from 38% in year one to 16% in year six. However, consistent with several non-randomized reports, in the CLASICC trial patients converted to open resection had a higher operative mortality compared to patients in the laparoscopic or open groups (9% *vs* 1% *vs* 5% respectively) [6].

Conversion was also associated with worse oncologic outcomes in nonrandomized comparative and descriptive studies [46].

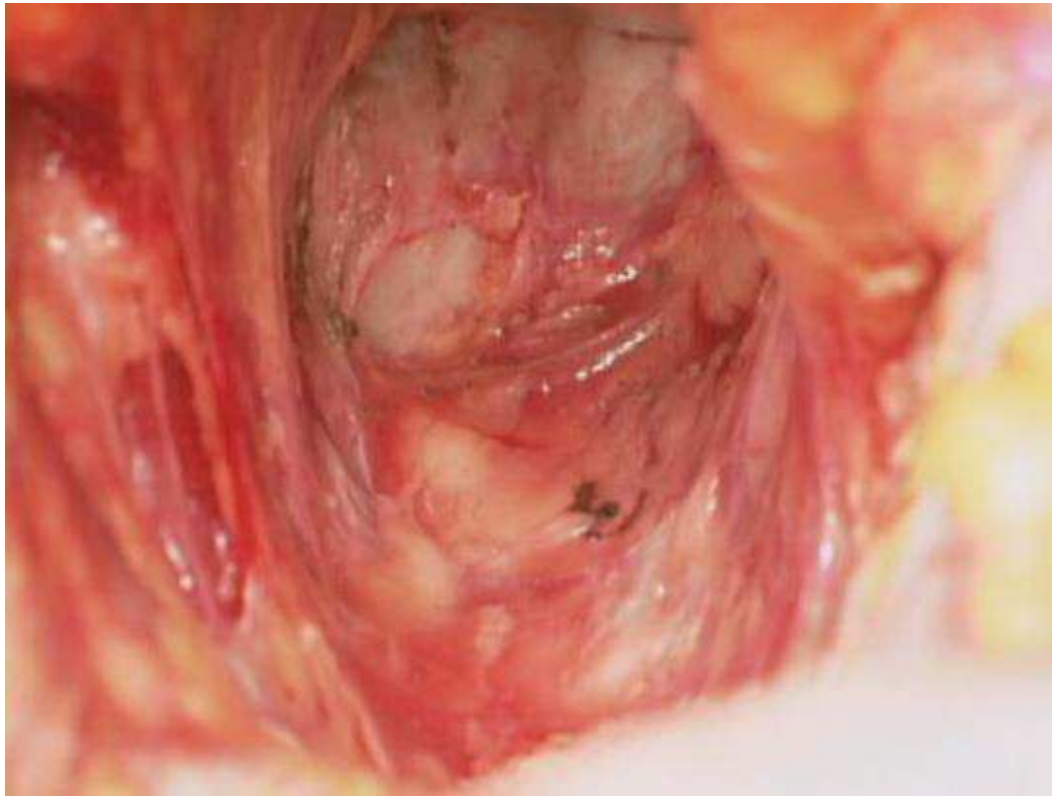


Figure 3. Total mesorectal excision after laparoscopic rectal resection

10. Short-term oncologic outcomes

While the number of lymph nodes retrieved can vary based on age, gender, tumor site, use of pre-operative radiation, and tumor grade, the extent and quality of surgical resection can also have an impact on the number of nodes collected and is therefore often considered a surrogate marker of the oncologic completeness of the resection [37]. The American Joint Committee on Cancer recommends that at least 12 lymph nodes be examined in patients with rectal cancer to confirm the absence of nodal involvement by the tumor [34]. In addition, a number of studies have reported that the number of lymph nodes examined may be associated with patient outcome [25, 26]. Six of the 8 RCTs reported the mean number of lymph nodes retrieved with a range of 5.5 to 17 nodes in the laparoscopic group compared to 11.6 to 18 nodes in the open group [22, 31, 34]. In 4 of the 6 trials the number of lymph nodes isolated was not significantly different based on surgical approach. Araujo *et al* [25] reported a significantly lower yield of lymph nodes with laparoscopic rectal resection compared to open resection (5.5 *vs* 11.9 respectively, $P = 0.04$). They suggested that laparoscopy offered better dissection and accuracy due to better visualization and exposure of structures with less manipulation of the mesorec-

tum especially in a narrow pelvis. Four of the 8 RCTs reported the use of pre-operative chemoradiation. In these trials, the mean number of lymph nodes retrieved ranged from 5.5 to 17 nodes in the laparoscopic group and from 11.6 to 18 nodes in the open group [31, 34, 38, 40]. Some authors [37] found that in the 17 trials that reported the number of lymph nodes retrieved, the mean number of nodes was 10 for the laparoscopic group and 12 for the open group ($P = 0.001$) with the majority of trials reporting a median of 11 or fewer nodes obtained. In 9 of these 17 trials, both groups were treated with preoperative radiation therapy and reported a mean of 10 lymph nodes harvested in the laparoscopic group and 11 in the open group. One of the greatest concerns of laparoscopic TME is that obtaining a complete oncologic resection will be more difficult. Involvement of the circumferential or distal margin is one of the most important prognostic factors in rectal resection with TME and can lead to an increase in local recurrence and a reduction in survival. Radial margins of less than 2 mm are associated with a local recurrence rate of 16% compared to a significantly reduced local recurrence rate of 6% with margins greater than 2 mm [27]. Six of the 8 RCTs reported the involvement of the CRM and no difference was found by surgical approach [7, 31, 38-40, 45]. In the majority of trials the rate of CRM involvement was less than 5%. Patients with positive radial margins often had tumor invading the pelvic side wall or adjacent structure and were frequently converted from a laparoscopic to an open procedure [39]. In the CLASICC study, the only multicenter trial, a positive CRM was identified in 14 of 97 (14%) patients with open surgery and in 30 of 193 (16%) patients with laparoscopic rectal resection [6]. Of patients undergoing anterior resection, the CRM was positive in 16 of 129 (12%) individuals in the laparoscopic group and in 4 of 64 (6%) individuals in the open group. While there is a non-significant higher positivity of the CRM in the laparoscopic anterior resection group, this is once again likely due to the fact that the learning curve was not completed before the start of this study. Two RCTs reported on distal margin status and the incidence of distal margin positivity was not significantly different between the two surgical approaches and in fact was 0% [3, 31]. All 3 meta-analyses and the Cochrane review by Breukink *et al* [41] found no difference in positive margins based on surgical access.

11. Postoperative course

Less postoperative pain, faster recovery of intestinal function, and shorter length of stay are important benefits of laparoscopic colorectal surgery. Only 3 of 8 RCTs compared the exact amount of post-operative pain medication and 2 of these studies reported a significant reduction in analgesic use in the laparoscopic group [39, 40, 45]. Zhou *et al* [24] did not quantify the exact usage of pain medication, but found no significant difference in the number of days parental analgesics were necessary (4.1 *vs* 3.9 in the open and laparoscopic groups respectively). Resumption of bowel function was usually reported on post-operative days 3 to 5 and ability to tolerate a solid food diet was reported on post-operative days 3 to 6 [7, 31, 35, 39, 40, 45]. In the majority of RCTs earlier bowel movements and diet advancement was reported with the laparoscopic approach. The return of bowel function and reduction in wound pain was thought to contribute to earlier discharge after laparoscopic surgery. While in a majority of

trials, the length of stay was not significantly different between surgical approaches, there was a trend toward decreased length of stay with laparoscopic rectal surgery. Breukink *et al* [41] found that laparoscopic TME resulted in earlier return of normal diet, less pain, less narcotic use and a shorter hospital stay.

12. Complications

Rectal cancer surgery is associated with a high rate of morbidity and mortality. Post-operative mortality in RCTs ranged from 1%-4% and demonstrated no statistically significant difference based on surgical approach. The rate of post-operative complications ranged from 6% to 69% and with the exception of Zhou *et al* [24] did not differ significantly between laparoscopic and open groups. Wound infection and urinary tract infection accounted for the majority of perioperative complications in both groups. There was a higher incidence of wound infection with the open approach however this did not reach statistical significance. Breukink *et al* [41] found no difference in morbidity between the laparoscopic and open groups although there was a trend toward lower morbidity with laparoscopic TME. Aziz *et al* [17] found no difference in perioperative morbidity between the 2 groups while Gao *et al* [26] found that the overall morbidity rate of the laparoscopic group was significantly lower than that of the open group. Anastomotic leak is the most serious complication after sphincter sparing rectal cancer resection especially with neoadjuvant chemoradiation. In addition, development of an anastomotic leak is reported to be associated with decreased long-term survival and higher rates of local recurrence after curative resection for colorectal cancer [39-43]. Operative expertise and selective diversion in high risk patients has resulted in a anastomotic leak rate of 1%-17% in most published series studying laparoscopic resection for rectal cancer [29, 30]. Consistent with reports from non-randomized comparative trials, RCTs demonstrated no significant difference in the incidence of anastomotic leak between the laparoscopic and open technique for the resection of rectal cancer. While the incidence of perioperative morbidity was not different based on surgical access, fewer patients had long-term complications with laparoscopic rectal cancer resection compared to the open approach. Adhesion related bowel obstruction was the most common longterm morbidity. With a median follow-up of greater than 9 years, Ng *et al* [37] found that adhesion-related obstruction requiring hospitalization (18.9% *vs* 2.7%) and reoperation (6.8% *vs* 0%) was higher in the open group. They report a cumulative probability of adhesion-related bowel obstruction at 10 years of 20.5% in the open group and 3.9% in the laparoscopic group. [45] Data on long-term complications was not separated by site of disease but the overall occurrence of incisional hernia (7.9% *vs* 10.9%, $P = 0.32$) and reoperation for adhesions (1.1% *vs* 2.5%, $P = 0.30$) was not statistically difference between laparoscopic and open resection. Long-term studies need to be done to determine if laparoscopy decreases the incidence of intra-abdominal adhesion formation by reduced surgical trauma, less tissue handling, and smaller incisions.

13. Long-term outcomes

The initial reports of the long-term outcomes after laparoscopic surgery for rectal cancer were discouraging. Several randomized trials report of the rate of positive circumferential radial margin in the laparoscopic group in comparison to the open group (12-5.9% and 6-4.2%, respectively). The 3-year follow-up did not establish higher local recurrence rate – 7.0% and 7.8%, respectively. The local recurrence rate after laparoscopic and open abdomino-perineal resection were 15.1% and 21.1%, respectively. The overall disease-free survival rate was also similar after laparoscopic and open anterior resection 70.9% and 70.4% and APR – 49.8% and 46.9%. Other data demonstrated 5-year disease survival reaching 83.7% for laparoscopic and 80.4% for open surgery. According to a meta-analysis of 20 laparoscopic rectal cancer studies between 1993 and 2004, including over 2000 patients, there is no significant difference in the number of harvested lymph nodes [22]. Despite the encouraging results, the laparoscopic rectal surgery could be fully evaluated only after long-term results are available. The ongoing studies are the American College of Surgeons Oncology Group (ACOSOG) Z6051 trial from the U.S.; the COLOR II trial from Europe, Canada, and Asia; and the Japanese Japan Clinical Oncology Group (JCOG) 0040 trial.

A number of the clinical trials were performed to determine the safety and feasibility of the laparoscopic approach for rectal adenocarcinoma and therefore the data we have for long-term outcomes is limited [5]. Braga *et al* [48] found no difference in local recurrence (4.0% in the laparoscopic group vs 5.2% in the open group, $P = 0.97$), overall five-year survival, or disease free five-year survival based on surgical approach. With a median follow-up of 87.2 mo in the laparoscopic group and 90.1 mo in the open group, Ng *et al* [45] demonstrated that after curative resection, the probability of five-year survival was 75.2% vs 76.5% for laparoscopic vs open APR respectively ($P = 0.20$). In addition, stage-by-stage comparison for the two groups showed no statistical difference. There were no port site recurrences and overall recurrence rates were not significantly different between the two groups (laparoscopic 20% vs open 25%, $P = 0.60$). Despite the higher rate of circumferential margin positivity in patients undergoing laparoscopic anterior resection in the CLASICC trial, there was no difference in local recurrence, three-year overall or three-year disease free survival between the two approaches (open OS 66.7% and laparoscopic OS 74.6%, $P = 0.17$; open DFS 70.4% and laparoscopic DFS 70.9%, $P = 0.72$; open LR 7.0% and laparoscopic LR 7.98%, $P = 0.70$) [6]. In addition, there was no significant difference in the rates of local recurrence, three-year overall survival, or three-year disease-free survival in patients undergoing laparoscopic vs open APR [12]. However, the sample size is small and therefore larger studies are needed for conclusive results. Ng *et al* [37] published results of a randomized trial of laparoscopic vs open anterior resection for upper rectal cancer with a median follow-up of 9 years. No difference in local recurrence, overall survival, or disease-free survival was reported. Although these studies suggest comparative oncologic outcomes between laparoscopic and open rectal cancer resection, they include small sample sizes and are almost all are single institution studies, highlighting the need for large, multi-center RCTs to provide confirmatory data. With a mean follow-up of 35 mo for both groups, overall local recurrence was not statistically different between the 2 groups (laparoscopic 7% vs open 8%, $P = \text{NS}$). Eleven studies provided sufficient data to compare overall

survival. Overall survival was 72% for patients undergoing laparoscopic rectal cancer resection and 65% for open resection at an average of 4.4 years ($P = 0.5$). Subset analysis by [36] demonstrated no significant difference between laparoscopic and open rectal cancer resection in terms of local recurrence (laparoscopic 7.2% vs open 7.8%, $P = 0.46$), development of distant metastases (laparoscopic 13.5% vs open 9.1%, $P = 0.60$), or cancer-related mortality (laparoscopic 9% vs open 10%, $P = 0.16$). While, this data is encouraging, it is no conclusive.

14. Hybrid and hand-assisted laparoscopic rectal surgery

Some authors have introduced a new method of hybrid rectal surgery, aiming to combine the benefits of open and laparoscopic approach. The colonic mobilization is performed laparoscopically, while the rectal dissection is performed through a Pfannenstiel incision. A retrospective review established significantly longer hospital stay after hybrid procedures than after open procedures [27].

Another method is the hand-assisted laparoscopic surgery. A special access device for the hand is introduced in the abdomen. Compared with fully open techniques this method provides shorter operative time. High ligation of vessels, splenic flexure takedown, and lateral mobilization may be accomplished in a shorter period time with a hand-assisted technique. In hand-assisted laparoscopic surgery, rectal exposure and dissection can be either performed directly through the incision using the open techniques or laparoscopically with manual assistance [28]. This method combines the excellent laparoscopic view and the dissection techniques in open surgery and provides tactile sensation.

By performing distal rectal division directly through the incision using the open surgical staplers, hand-assisted laparoscopic rectal surgery may result in a lower anastomotic leakage rate.

15. Summary

After rigorous evaluation the laparoscopic surgery for colon cancer has become the gold standard. Laparoscopic colon resection for cancer, in experienced hands, can be performed safely and reliably with many short-term benefits to the patients while resulting in at least equivalent long-term outcomes as open surgery, which is supported by level 1 data. In conclusion, RCTs have demonstrated that laparoscopy does not adversely affect cancer related survival in patients with adenocarcinoma of the colon. Concerns about the technical difficulty of TME may have contributed to the exclusion of rectal cancer patients from most of these large multicenter RCTs resulting in little data on oncologic outcomes with laparoscopic rectal cancer resection. Laparoscopic rectal dissection is technically more demanding than open and constraints of a narrow pelvis may result in difficulty assessing and obtaining adequate surgical margins. However, there are several proposed benefits of laparoscopic rectal resection. A clear and magnified view of the pelvis provided by the improved optics of laparoscopy may aid sharp

dissection for TME and assist in identification of vital pelvic structures including the ureters and autonomic nerves. In addition, pneumoperitoneum may separate the parietal and visceral fascia of the mesorectum facilitating dissection in this plane. Laparoscopic rectal cancer resection has a steep learning curve but increased experience with both open and laparoscopic TME will lead to shorter operating times and decreased morbidity. Current data suggests that laparoscopic rectal cancer resection may benefit patients because of reduced blood loss, earlier return of bowel function, and shorter hospital length of stay. Concerns that laparoscopic rectal cancer surgery may compromise short-term oncologic outcomes including number of lymph nodes harvested and CRM positivity do not appear to be supported by the available literature. However, there is a paucity of data concerning long-term oncologic outcomes and complications with laparoscopic rectal cancer surgery. There are two large, multicenter RCTs that are currently being conducted: the COLOR II trial in Europe and the ACOSOG-Z6051 trial in the United States. Both of these studies are comparing the laparoscopic and open approach for treatment of resectable rectal cancer. Results from these trials will provide information on the long-term outcomes of laparoscopic rectal cancer resection and are eagerly awaited. In view of the lack of level one data on oncologic outcomes, laparoscopic TME for locally advanced, curable rectal cancer should only be performed within the confines of a RCT.

Other potential, but less conclusively demonstrated benefits include better preservation of cell-mediated immune function and reduced tumor cell proliferation. Although a similar level of evidence does not yet exist for the laparoscopic rectal surgery for cancer, the evidence to date suggests that it is likely that the ongoing large randomized trials will demonstrate clinical benefits of laparoscopic rectal cancer surgery. New devices for minimizing of the abdominal trauma are being developed. The steep learning curve, cost and difficult training are still hindrance to the wide use of laparoscopic colon surgery.

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