Laparoscopic surgery for rectal cancer: The state of the art

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Abstract

At present time, there is evidence from randomized controlled studies of the success of laparoscopic resection for the treatment of colon cancer with reported smaller incisions, lower morbidity rate and earlier recovery compared to open surgery. Technical limitations and a steep learning curve have limited the wide application of minimally invasive surgery for rectal cancer. The present article discusses the current status of laparoscopic resection for rectal cancer. A review of the more recent retrospective, prospective and randomized controlled trial (RCT) data on laparoscopic resection of rectal cancer including the role of trans-anal endoscopic microsurgery and robotics was performed. A particular emphasis was dedicated to mid and low rectal cancers. Few prospective and RCT trials specifically addressing laparoscopic rectal cancer resection are currently available in the literature. Improved short-term outcomes in terms of lesser intraoperative blood loss, reduced analgesic requirements and a shorter hospital stay have been reported but the follow-up time period is too short in all these studies and the few RCT trials currently available do not draw any definitive conclusions. On the basis of available data in the literature, the minimally invasive approach to rectal cancer surgery has some short-term advantages and does not seem to confer any disadvantage in term of local recurrence. With respect to long-term survival, a definitive answer cannot be given at present time as the results of RCT trials focused on long-term survival currently ongoing are still to fully clarify this issue.

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INTRODUCTION

Proven advantages of the short-term and similar long-term oncological outcome of laparoscopic surgery (LPS) for colorectal cancer when compared to open surgery have facilitated its wide diffusion[1]. The adoption of the laparoscopic approach for the management of rectal cancer has been more limited and controversial and is still considered investigational in the United States. This has been due to several concerns: the fact that laparoscopic total mesorectal excision (TME) has obvious technical difficulties: it mandates dissection to the pelvic floor; it is technically
FEASIBILITY AND SHORT-TERM OUTCOMES

The feasibility of any laparoscopic procedure is reflected by the associated conversion rate. Figures ranging from 0 to 33% have been reported in the scientific literature[1,6-17]. This great variability in terms of conversion rate should be attributed to different variables such as the type of operation, distance of the tumor from the anal verge, previous surgeries, fixity of the tumor, experience of the surgical team or single surgeon, surgical volume of the center and the related learning curve. The UK MRC CLASICC trial is the only multicenter randomized controlled trial (RCT) published on rectal cancer. All the participating surgeons were required to have completed only 20 laparoscopic colorectal resections before entering in the study and thus had not gone through the whole learning curve before starting the study. Therefore, the data from this trial might be biased in the results of the intention-to-treat analysis which seem to support this hypothesis, reporting an initial phase with a conversion rate of 45% which declined to 15% in the last year of the study[1]. Different figures were reported when high volume centers or single experience centers were involved in a RCT trial to be a safe alternative to a conventional stapler. This latter stapling device has been recently reported in a prospective randomized trials specifically focusing on mid to low rectal cancers. However, this study was limited into care in common daily practice remains unclear. The safety of laparoscopic rectal cancer surgery has been extensively reported in the literature. In a recent Cochrane review of 4424 patients from 48 studies comparing laparoscopic vs open TME for rectal cancer, Breukink reported no significant differences in morbidity and mortality rate with several short-term advantages in favour of laparoscopic resection such as less blood loss, quicker return to normal diet, less pain as measured by narcotic use and reduced length of hospital stay[18]. On the other hand, a longer operating time and higher cost of the surgical procedure have been reported by a recent meta-analysis focused on the management of rectal cancer[18-21]. Some caution and criticism is recommended in the interpretation of these data as the majority of the studies included in the meta-analysis were small series or case-control studies and only three RCT trials. Moreover, in one of the three RCT analyzed in the meta-analysis, the distance of the tumor from the anal verge was not reported making it possible that recto-sigmoid cancer was also included[18]. These tumors generally behave similarly to colon cancer but have great technical differences in their management. Nevertheless, more recently data from non-randomized comparative studies and RCT trials including the CLASICC MRC RCT, trial reported no differences in term of overall morbidity and mortality despite a trend toward a lower wound infection rate reported by other RCTs and most comparative series as shown in Table 1.

In particular, no differences of anastomotic leak rate have been reported between the LPS and open group. Data from CLASICC RCT reported a 10% leakage rate in the LPS and 7% in the open group. Similar findings were reported in comparative studies and the majority of non-randomized series showing either similar or lower anastomotic leak rates with figures ranging from 3.5% to 16.8%; it was most commonly reported to be approximately 10% as it emerged in two recent reviews and a meta-analysis on this subject[19-21]. This is a relevant issue in terms of safety and in favor of laparoscopic rectal surgery which has been previously hypothesized to increase the anastomotic leak rate of coloanal Anastomosis following TME. In fact, transection of the rectum in the deep pelvis and anastomosis are considered two limiting factors due to the technical limitations of the currently available staplers which require multiple firing with possible increase of anastomotic leak[22]. A virtual simulation recently published in the literature has shown that the current stapler has to go through the iliac bone in order to achieve a 90° angle at the levator ani[23]. This situation could be partially overcome by the insertion of a conventional stapler through a supra-pubic port or alternatively by the insertion of a dedicated curved stapler. This latter stapling device has been recently reported in a RCT trial to be a safe alternative to a conventional stapler to secure the distal rectum during low anterior resection (LAR) in mid to low rectal cancers. However, this is the only study currently available in the literature on this subject and due to the high cost of the stapling machine[24] and the fact that differences in the devices are relatively minor factors that could affect leakage rates[18-21], further RCT studies are needed to justify the routine use of a curve stapler or supra-pubic port during laparoscopic TME.

PORT SITE METASTASIS

The actual overall incidence of port-site metastasis is a rare event and is about 0.1% from reviews and meta-analysis on this subject[19-21]. This figure is comparable to that of
wound recurrence following open surgery\textsuperscript{25,26}. According to these findings, port-site metastasis is not an inherent drawback of LPS for rectal cancer.

**ONCOLOGICAL OUTCOME**

The current evidence for laparoscopic resection for rectal cancer is based mainly on several case series, case-matched studies and non-randomized studies, the majority of which have a relatively short follow-up period. Only a few randomized studies are available in the literature. To our knowledge, only 6 studies have been published so far on rectal cancer only. An additional RCT trial was also published, but in this study, recto-sigmoid tumor were considered with different technical and functional consideration when compared to low and mid rectal tumors\textsuperscript{27}. The results of the aforementioned studies are influenced by different factors such as tumor height, experience of the surgical team, surgical approach (i.e. TME vs abdominoperineal amputation of the rectum) and use of neoadjuvant chemoradiation. In particular, many series report results for selected patients with early stage tumors reasonable given the technical issues of laparoscopic manipulation of neoplasms. However, such reports are not useful in making generalizations about the appropriateness of the technique for all patients with rectal cancer.

With respect to lymph nodes harvested intraoperatively, with the exceptions of Strohlein et al\textsuperscript{28} who reported a difference in favor of open surgery (laparoscopic 13.5%/open access 16.9; \(P = 0.001\)) and Lujan who reported a difference in favor of laparoscopic TME in a RCT trial\textsuperscript{3}, all the other comparative series and RCT trials analyzed in the present review reported no difference in the mean numbers of lymph-nodes harvested with laparoscopic or open rectal cancer resection, which varied considerably from 5 to 23\textsuperscript{25-27,31,32}. Moreover, concerns have been recently raised by West et al\textsuperscript{30} about an adequate distal resection margin and a cylinder without a waist both for low anterior and abdominoperineal resection. Lateral and distal margins are critical components of oncological proctectomy. Heald et al\textsuperscript{3} and Quirke et al\textsuperscript{31} demonstrated the need to achieve a wide lateral (radial) margin in order to avoid local recurrence of the neoplasm in the pelvis. In non randomized comparative studies, laparoscopic and open excision for rectal cancer were found to be equivalent in achieving distal and radial margins\textsuperscript{8-10,13,14}. Different results were obtained when only RCT trials were considered. In single RCT center experience, good results were obtained with figures ranging between 1 and 4% involvement of radial and distal margin with no difference in respect to laparoscopic and open surgery\textsuperscript{13,14}. When a RCT multicenter trial is considered, laparoscopic anterior resection resulted in a higher rate of radial margin involvement when compared to open resection (6% open vs 12% for LPS; \(P = 0.19\)) although this difference failed to reach statistical significance\textsuperscript{7}. These latter data, however, referred to a center where surgeons are not solely dedicated to rectal surgery and have not completed their learning curve of laparoscopic rectal resection before starting the trial. Due to the mentioned findings, a trial promoted by the American College of Surgeons Oncology Group (ACOSOG) is currently ongoing. This trial will only consider patients with mid and low position, stage II and III rectal cancer. Operations will only be performed by surgeons who demonstrate expert abilities in both laparoscopic and colon rectal surgery before enrolling patients. Moreover, a more recent report analyzing data from the CLASICC RCT trial showed no impact of the high rate of radial margin involvement observed in the laparoscopic group on local recurrence rate\textsuperscript{33}. In addition, results from other recent non randomized series found no differences in radial margins involvement between the laparoscopic and open group\textsuperscript{30,14}.

**Local recurrence**

Local recurrence is a key indicator of oncological adequacy in rectal cancer surgery which varies dramatically among surgeons, the surgical technique being a major determinant. In open surgery, the standard for local recurrence has been set by Heald et al\textsuperscript{3} who reported a 4% local recurrence rate following LAR of the rectum with TME with a 10 years follow-up. According to these findings, in order for the laparoscopic approach to rectal cancer to be widely accepted, the proof of oncological equivalence is of paramount importance. Although most series and RCTs excluded T4 lesions and adopted neoadjuvant chemoradio-

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**Table 1 Short-term outcome after laparoscopic total mesorectal excision in randomized controlled trials and comparative series**

| Author          | Mortality | Mortality | Wound infection rate (%) | Leak rate (%) |
|-----------------|-----------|-----------|--------------------------|---------------|
|                 | Open LPS  | Open LPS  | Open LPS                 | Open LPS      |
| Lujan et al\textsuperscript{3} (TME) | 33        | 33.7      | 2.9                      | 1.9           | 0               | 12              | 6               |
| Braga et al\textsuperscript{3} (LAR/TME) | 40        | 29        | 0                        | 13            | 0               | 12              | 5               |
| Ng et al\textsuperscript{3} (APR)   | 52.1      | 45.1      | 2                        | 8.3           | 0               | NA              | NA              |
| Strohlein et al\textsuperscript{3} (LAR/TME) | NA        | NA        | 3.3                      | 5.3           | 4.5             | 15.3            | 10              |
| Gouvas et al\textsuperscript{8} (LAR/TME) | 36        | 63        | 0                        | 31            | 9               | 10              | 16              |
| Jayne et al\textsuperscript{8} (TME/APR/LAR) | 37        | 40        | 5                        | 12            | 13              | 7               | 10              |
| Laurent et al\textsuperscript{8} (TME/APR) | 37.7      | 32        | 0.2                      | 2.6           | NA              | NA              | 12.9            | 11.8            |
| Staudacher et al\textsuperscript{10} (TME) | 27.8      | 29.6      | 0                        | 13.9          | 4.6             | 12.6            | 14.8            |
| Ruillier et al\textsuperscript{31} (TME) | 11.6      | 21.9      | 0                        | 3.1           | NA              | NA              | -               | 0               |
| Zhou et al\textsuperscript{32} (TME)   | 12.4      | 6.1       | 0                        | 0             | NA              | NA              | 3.4             | 1.2             |

LPS: Laparoscopic surgery; TME: Total mesorectal excision; LAR: Low anterior resection; APR: Abdominoperineal resection.
diation for locally advanced rectal cancer, data from large series report local recurrence rates after laparoscopic TME ranging between 2.9% and 7.7%, with a mean recurrence rate of about 5% with no significant differences between laparoscopic and open resection as shown in Table 2. Different figures are reported when laparoscopic abdominopereineal resection (APR) is considered. A higher local recurrence rate is in fact reported following laparoscopic APR when compared to laparoscopic sphincter saving surgery[6,14,38-39]. Local recurrence rates after LPS varied considerably from 0 to 25% with contrasting results in series. When only comparative studies are considered, the majority of the studies found no differences in term of local recurrence rates between laparoscopic and open rectal resection[35-37] with the exception of two early comparative studies which demonstrated higher recurrence rates compared with open surgery but the difference was not significant[14,38]. In particular, Fleshman et al[14] reported a 19% recurrence rate in LPS vs 14% in open group while Feliciotti et al[38] found a 20.8% and 18.2% recurrence rate in laparoscopic and open groups respectively. This difference however, failed to reach statistical significance in both studies.

Data from CLASICC MRCT trial showed a 15.1% local recurrence rate following LPS abdominoperineal excision and a 21.1% local recurrence rate following open APR[18]. Araujo, comparing laparoscopic vs open APR in a RCT trial, reported a 0% local recurrence rate following laparoscopic APR and a 15.4% local recurrence after conventional surgery. However, the study was a small series of only 13 patients per group[6]. Similar findings were also reported by Ng et al[19] who reported a 5% local recurrence rate after laparoscopic APR vs 11% local recurrence rate after open APR.

A significantly higher local recurrence rate was also observed after curative open APR when compared to conventional anterior resection. Wibe et al[20] in a prospective, cohort study involving 47 hospitals and 2136 patients reported a 15% local recurrence rate after APR vs 10% following LAR (P = 0.008). Similar findings were also reported by Heald et al[21] who found a 33% and 1% local recurrence rate after APR and conventional anterior resection of the rectum respectively. The higher incidence of local recurrence after APR compared to LAR with sphincter salvage could be ascribed to the higher prevalence of T4 disease and the higher incidence of positive radial margin which usually requires sphincter ablation and use of neoadjuvant therapy[22-24].

Long-term outcome

Long-term survival data following laparoscopic resection of the rectum are scanty in the literature. The majority of long-term outcome data refer to a single surgeon experience series or comparative studies and only five RCT studies focusing on this subject are currently available with different length of median follow-up period with figures ranging from 33.1 to 87.2 mo[2,3,6,33]. Data from these series reported no difference in terms of local recurrence, overall and disease free survival between groups. Similar findings of overall and disease free survival are reported by small comparative series but the follow-up time period is too short in all these studies to draw any conclusions[4,13,34,38]. In contrast, Laurent et al[21] reported a better survival rate in laparoscopic stage III tumors with no difference in term of local recurrence and cancer-free survival between laparoscopic and open surgery with similar quality of surgery in a mono-centric comparative study with over 400 patients with mid and low rectal cancer. A better survival rate in patients with stage III tumor was also reported by Lacy et al[22] in a RCT trial in patients with colon cancer and by Morino et al[23] in a prospective comparative study which focused on patients with extraperitoneal rectal cancer treated with laparoscopic or open surgery. More recently, Law et al[24] reported in a comparative monocenter series with a median follow-up of 34 mo in patients with stage II and III rectal cancer, a 5 year actuarial survival of 71% in the laparoscopic group compared to a 59% survival rate in the open group, also identifying laparoscopy as one of the independent significant factors associated with better survival at the multivariate analysis.

The positive impact of the laparoscopic approach on survival is still unclear. Supporting evidence of the beneficial oncological role of laparoscopy includes its impact on surgical stress response, cellular immunity, cytokine release,

### Table 2 Local recurrence rates after laparoscopic rectal cancer surgery

| Author/year | Operation | No. of patients | Follow-up (mo) | Local recurrence rate (%) |
|-------------|-----------|-----------------|---------------|--------------------------|
| Hartley et al[10] (2001) | TME | 21 | 38 | 5 | 4.5 |
| Laurent et al[11] (2009) | LAR/TME | 238 | 52 | 3.9 | 5.5 |
| Bretagool et al[12] (2005) | TME | 50 | 18 | 0 | NA |
| Fleshman et al[13] (1999) | APR | 42 | 23.8 | 19 | 14 |
| Araujo et al[14] (2003) | APR | 13 | 47.2 | 0 | 15.4 |
| Ng et al[15] (2008) | APR | 51 | 87.2 | 5.9 | 4.2 |
| Law et al[16] (2006) | LAR/TME | 98 | 23 | 4.9 | 3.3 |
| Staudacher et al[17] (2007) | TME | 108 | 27.6 | 6.4 | 5.1 |
| Leroy et al[18] (2004) | TME | 102 | 36 | 6 | NA |
| Milson et al[19] (2009) | TME/LAR | 103 | 42 | 5 | NA |
| Jayne et al[20] (2005) | TME/APR | 128 | 36.8 | 11.4 | 14.05 |

LPS: Laparoscopic surgery; TME: Total mesorectal excision; LAR: Low anterior resection; APR: Abdominopereineal resection.
intraoperative tumor manipulation and blood transfusion rate. Moreover, during the early postoperative period, laparoscopic patients seem to display decreased levels of pro-inflammatory and vascular endothelial growth factor (VEGF) compared to open surgery.

In summary, based on the available data in literature, the mini-invasive approach to rectal cancer surgery does not seem to confer any disadvantage in terms of local recurrence. With respect to long-term survival a definitive answer cannot be drawn at present and the results from the RCT trials focused on long-term survival currently ongoing are needed.

GENITOURINARY FUNCTION
Bladder and sexual function are recognized complications of open TME, resulting from injury to the autonomic nerves. The real incidence of such complications following laparoscopic TME is still an unresolved issue due to controversial and limited data in the international literature. In a small series of laparoscopic TME including only 7 patients, Watanabe et al. reported no genitourinary dysfunction and only 9.5% erectile dysfunction. Similarly Rullier et al. reported only 3.1% long-term bladder dysfunction in patients who underwent laparoscopic intersphincteric resection. On the other hand, Quah et al. reported a significant increase of impotence or retrograde ejaculation in sexually active men after laparoscopic rectal surgery. Similar findings were reported by Jayne et al. in the only RCT trial available in the literature on this issue. In this RCT trial, more than 50% of both men and women reported no sexual activity. Among the sexually active patients, the authors found no difference in bladder function between the laparoscopic and open group while in erectile and overall sexual function, only men perceived a significant decrease of their overall level of sexual function after laparoscopic TME when compared to open. No difference in overall sexual function was observed in women. The authors attributed the poorer sexual function observed in the laparoscopic group to the fact that TME was more commonly performed in the laparoscopic than open group. Moreover, TME and conversion to open were identified as independent predictors of postoperative male sexual function at multivariate analysis.

Currently, it remains unclear how the mini invasive approach to rectal surgery affects genitourinary function. This is not only because the limited available data show conflicting results, but mainly because different criteria and methods of measurements have been adopted. Future studies with the possible use of urodynamics and standard questionnaires are warranted.

TRANS-ANAL ENDOCOSCOPIC MICROSCUGERY
Trans-anal endoscopic microsurgery (TEM), a technique initially developed for the excision of benign polyps not amenable by endoscopic resection, has recently gained a place in the universe of the mini invasive approach to rectal cancer. However, the widespread acceptance of TEM has been a very slow process due to its elevated starting cost and, most of all, for its limited caseload in non-specialized centers. Only recently in fact, TEM has been proposed as an alternative safe and successful approach to major surgery in particular for well differentiated T1 rectal tumors and carcinoid tumors while controversy still exists in the treatment of more advanced tumors like poor differentiated T1 or T2. Moreover, TEM might be employed for non curative intent or pain relief in advanced tumors in patients with severe co-morbidities which preclude a major resection or in the salvage resection of local recurrence. The main advantages of TEM are less blood loss, reduced operating times, shorter postoperative length of stay, less use of analgesia during postoperative course, earlier recovery and lower rate of major complications. The occurrence of major complications in the case of TEM is mainly represented by perforation with entry in the peritoneum; occurrence of a recto-vaginal fistula and hemorrhage with figures ranging from 0 to 28% has been reported in a recent review by Middleton et al. However this great variability is mainly influenced by the surgeon or team experience and hospital caseload.

When compared to traditional trans-anal excision, TEM provides several advantages such as better visualization, higher likelihood of achieving clear resection margins, lower recurrence rates and a higher rate of clear resection margins. The main disadvantage of TEM is a significant change in continence in particular with respect to ano-rectal dysfunctions such as tenesmus and fecal soilage measured either by manometry or surveys. These symptoms seem to be significantly ameliorated or return to preoperative levels at 6 wk to 3 mo following the operation with minimal impact on clinical incontinence.

With respect to oncological outcome, comparative series and RCT trials reported recurrence rates and long-term survival similar to those with open resection for T1 rectal cancer. However, when more advanced tumors are considered, local recurrence rates significantly increase to 14% for PT2 cancer and to 20% in patients with PT3 lesions as reported in a recent meta-analysis by Suppiah et al. which includes 28 studies. With respect to T2 tumors, in which management using TEM is the object of major controversy in the literature, recently Tsai et al. in a large prospective study with 269 patients with a mean follow-up of 49.5 mo. This result is in accordance with the reported 6% to 80% local recurrence rate for T2 tumors in previous TEM series. Different results were reported by Lezoche et al. who reported a 5% recurrence rate in both study arms and a similar distant metastasis rate (5% in each arm) after a median follow-up period of 56 mo in 40 patients preoperatively staged UT2NO who had preoperative neoadjuvant chemoradiation and were randomized to TEM or laparoscopic resection.

In conclusion, TEM is a safe and effective technique for curative resection with good short- and long-term outcomes when used for benign tumors, select T1 adenocar-
cinoma, carcinoid tumors or when adopted for palliative resection and salvage surgery for a more advanced tumor stage in patients medically unfit or unwilling to undergo radical resection. However, some criticism is required in the analysis of data on oncological outcome as the majority of available data come from retrospective series with a significant patient and tumor heterogeneity and with different surgical indications.

ROBOTICS

The wide diffusion of the mini-invasive approach to rectal cancer has been hampered mainly by the availability of nonwristed instruments which make the operation technically demanding, especially while working in the confined space of the pelvis and in particular during the maneuver of transecting the rectum and fashioning the anastomosis. Recently, a hybrid technique has been introduced named as “robotics”[62-66]. This technique has the potential to overcome the obstacles of the standard laparoscopy by introducing wristed instruments which allow the surgeon to regain the two lost degrees of freedom. The value of using six degrees of freedom is of particular relevance when operating in a confined space such as the pelvis[63,64]. Moreover, the three-dimensional visualization offered by the robot provides a better visualization of depth in the pelvis to the surgeon. In addition, the higher magnification of the robotic camera system might be helpful in the identification and preservation of small anatomic structure like pelvic autonomic nerves. The potential advantages of robotics in confined spaces are well known by urologists and in a recently published consensus statement it is estimated that robotics prostatectomy in the United States has a penetration of 60% with more than 50,000 prostatectomies performed in 2007[65].

The experience of the adoption of robotics in rectal cancer surgery is, however, very limited[62-64] mainly because of the high cost of robotic platform and most of all by its costs of maintenance. The current available data from the literature show that robotic TME is feasible and safe with similar conversion, morbidity and mortality rates when compared to laparoscopic TME. Moreover, no differences were observed in the number of lymph-nodes harvested intraoperatively and to the distal margin involvement at the specimen analysis when compared to conventional laparoscopy[64,65]. Operative time is increased by the use of robotics probably due to the need for splenic flexure mobilization and high ligation of the inferior mesenteric artery and vein which mandate the repositioning of the robot and its operating arms. However, a totally robotic surgery technique for rectal cancer has recently been developed using a six-port system including a camera port to perform rectal cancer surgery from the splenic flexure to the pelvic diaphragm in one setup[67]. This technique was successfully adopted in 45 patients with very low conversion rate (2.2%).

At the present time, laparoscopic proctectomy is not yet cost-effective over standard laparoscopy, as it emerged in a comparative study by Delaney who reported his experience on a very small series with only six patients with different types of operations[68]. A more accurate visualization of pelvic nerves has been now advocated by the use of robotics with potential advantages on genitaliourinary function. Future RCT on this subject will clarify this point.

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