



A narrative review of rectal cancer surgery: is there a role for laparoscopy?

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Background and Objective: There is well established evidence supporting the use of laparoscopy in colon cancer, however its initial adoption for surgical treatment of rectal cancer was limited due to oncologic concerns. More recently, robotic surgery and transanal total mesorectal excision (taTME) have emerged as alternative minimally invasive techniques to address the challenges of laparoscopy in the pelvis. This literature review investigates the current status of laparoscopy for the treatment of rectal cancer.

Methods: A literature review was performed using PubMed to identify relevant studies investigating the use of laparoscopy in rectal cancer through November 2022. The review focused primarily on randomized controlled trials, large single center, population studies and meta-analyses. Studies were excluded if they did not include a laparoscopic surgery group or if they were not exclusive to rectal cancer.

Key Content and Findings: Inconclusive results of randomized controlled trials on noninferiority of laparoscopy *vs.* open surgery based on composite pathologic outcomes raised initial concerns while follow-up data have not revealed any differences in long-term oncologic outcomes. Since these trials, numerous institutional and population-based studies have supported the use of laparoscopy in rectal cancer. However, there is substantial data supporting the increasing use of robotic surgery as an alternative to laparoscopy while the role of taTME remains controversial.

Conclusions: Laparoscopy is a safe and effective surgical technique for the treatment of rectal cancer. As more surgeons are preferably trained in robotics, this technology has the potential to supplant the use of laparoscopy. However, until robotic systems are more readily available and financial costs are addressed, laparoscopy remains an acceptable minimally invasive option in well trained hands.

Keywords: Rectal cancer; laparoscopy; surgery

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Introduction

Background

Colorectal cancer (CRC) is the third most common malignancy in the United States, with 44,580 new cases of rectal cancer reported in 2022 (1). Though the rate of CRC cancer in people over the age of 50 has steadily declined

over the last decade largely due to improvements in screening, the incidence among persons ages 20–49 between 1992 and 2016 has nearly doubled. This rise has primarily been driven by the disproportionately increased rates of rectal cancer over colon cancer (2). With the growing number of young adults afflicted with this disease, strategies to limit recurrence and improve survival remain paramount.

Rationale and knowledge gap

The introduction of laparoscopy in colorectal surgery revolutionized surgical decision making and post-operative outcomes (3), but its adoption into rectal cancer has been limited due to concerns surrounding surgical quality, recurrence and oncologic outcomes. Local recurrence rates for rectal cancer dramatically decreased with the adoption of total mesorectal excision (TME) first described by Heald in 1982 (4), and the subsequent emphasis on histopathologic assessment of circumferential resection margin and TME completeness (5). Proper TME and adequate circumferential resection margins have now become the cornerstones of quality in rectal cancer surgery. The bony confines of the pelvis, particularly in the obese and male populations, challenge the surgeon's ability to meet these quality metrics. There have been ongoing advances in surgical technology to attempt to overcome these challenges. At this time, the best surgical approach to rectal cancer is still under debate.

Objective

In this review, we present the current evidence for laparoscopy in rectal cancer when compared to the open technique and alternative minimally invasive approaches, namely robotic surgery and transanal TME (taTME). This article is in accordance with the Narrative Review reporting checklist (available at: <https://ales.amegroups.com/article/view/10.21037/ales-22-80/rc>).

Methods

A literature review was performed using PubMed to identify relevant studies investigating the use of laparoscopy in rectal cancer through November 2022. The following search terms in various combinations were used: “rectal

cancer”, “laparoscopy”, “laparoscopic surgery”, “minimally invasive surgery”, “open surgery”, “robotic surgery”, and “transanal total mesorectal excision”, “taTME”. The review focused primarily on randomized controlled trials, large single center, population studies and meta-analyses. Studies were excluded if they did not include a laparoscopic surgery group or if they were not exclusive to rectal cancer (*Table 1*).

Laparoscopy vs. open surgery—results of randomized controlled trials

The first randomized controlled trial to investigate the role of laparoscopy in rectal cancer was the UK Medical Research Counsel (MRC) trial of conventional versus laparoscopic assisted surgery in colorectal cancer (CLASICC), published in 2005, which included patients with both colon and rectal cancer (6). In the rectal cancer arm (230 laparoscopic and 113 open), the investigators found no difference in morbidity or mortality between the two groups. There was no overall difference in positive circumferential margin (CRM) rates, however in patients undergoing anterior resection there was a trend towards a higher positive CRM rate in the laparoscopic group compared to the open group (12% *vs.* 6%), though this was not statistically significant. Overall, there were relatively high rates of positive CRM in both groups, 16% for laparoscopic and 14% for open surgery. Additionally, the conversion rate to open was 34%. While the results of this study raised concerns about the oncologic safety of laparoscopy in rectal cancer, both 5- and 10-year follow-up did not reveal any differences in local recurrence, overall survival or disease-free survival (7,8). The CLASICC trial carried a number of limitations. Firstly, it did not clearly define the proportion of patients with high, middle or low rectal tumors. Moreover, preoperative imaging with high

Table 1 Summary of the search strategy

Items	Specification
Date of search	8/2022–11/2022
Databases searched	PubMed
Search terms used	“Rectal cancer” [MeSH], “laparoscopy” [MeSH], “laparoscopic surgery” [MeSH], “minimally invasive surgery” [MeSH], “open surgery” [MeSH], “robotic surgery” [MeSH], “transanal total mesorectal excision” [MeSH], “taTME” [MeSH]
Time frame	1982–2022
Selection process	Included studies were searched and selected by Luca Stocchi and Michelle DeLeon

resolution magnetic resonance imaging (MRI) was not readily available or standardized at the time, and the study commenced prior to the widespread implementation of neoadjuvant chemoradiation following the results of the German Rectal Cancer Study Group in 2004 (9). These factors may have contributed to the high conversion and positive CRM rates reported in this study. With the evolution of neoadjuvant treatment and laparoscopic surgical technique, later studies more accurately reflect contemporary management of rectal cancer.

Short-term outcomes

After the CLASICC trial there were four subsequent randomized controlled trials comparing laparoscopy to open surgery in rectal cancer—the Comparison of Open versus Laparoscopic Surgery for Mid and Low Rectal Cancer After Neoadjuvant Chemoradiotherapy (COREAN) (10), the Colorectal Cancer Laparoscopic or Open (COLOR II) (11), the American College of Surgeons Oncology Group (ACOSOG) Z6051 (12), and the Australasian Laparoscopic Cancer of the Rectum Randomized Clinical Trial (ALaCart) (13). All four studies were designed to assess the non-inferiority of laparoscopic surgery compared to open surgery and excluded T4 tumors. COLOR II also excluded T3 tumors within 2 mm of the endopelvic fascia. Pertinent patient characteristics are shown in *Table 2*. Similar rates of male patients were included in each study. There were varying percentages of patients with high, middle, and low rectal tumors, with ACOSOG Z6051 having the highest proportion of low rectal tumors, defined as those located <5 cm from the anal verge. The COREAN trial did not stratify based on tumor height but only included tumors less than 9 cm from the anal verge and reported an average distance of 5.6 and 5.3 cm in the laparoscopic and open arms, respectively. Average body mass index (BMI; 24 kg/m²) and conversion rate (1.17%) were lowest in the COREAN trial. Across the four trials, there were no differences in perioperative morbidity or mortality between the two groups. All studies found that laparoscopy was associated with longer operative times, less estimated blood loss and earlier return to bowel function. However, only the COLOR II study reported a shorter length of hospital stay in the laparoscopic group (8 *vs.* 9 days, *P*=0.036), while no difference was found in the other trials. The only study to evaluate short-term functional outcomes was the COREAN trial. At 3-month follow-up, patients treated with laparoscopic technique reported less problems with

micturition, and gastrointestinal and defecation problems while no differences in sexual function were identified between the two groups (10).

Recently, Jiang *et al.* published the short-term results of a multicenter prospective randomized trial conducted in China comparing laparoscopic and open resection (14). The Laparoscopy-Assisted Surgery for Carcinoma of the Low Rectum (LASRE) trial had a 2:1 randomization design and was stratified by staging and a variety of patient related variables. A total of 1,039 patients (685 in the laparoscopic group *vs.* 350 in the open surgery group) were included. Morbidity rate was comparable between the two groups. The laparoscopic group was associated with higher rates of sphincter preservation and shorter duration of hospitalization (8 *vs.* 9 days). These short-term results favored laparoscopic surgery.

Pathologic outcomes

Most notable were the conflicting results regarding pathologic outcomes (*Table 2*). The design of ACOSOG Z6051 included the assessment of a surgical composite score (combination of TME completeness, CRM, and distal resection margin) to quantify “pathologic success”, which was viewed as a surrogate of oncologic outcomes. The ALaCart study design was modeled after the ACOSOG Z6051. It is remarkable that both studies were inconclusive in their ability to demonstrate noninferiority of laparoscopic *vs.* open technique. The authors of these trials concluded that there was not enough evidence to support the continued use of laparoscopy in rectal cancer. The COLOR II and COREAN trials found no difference in pathologic outcomes between the two groups when TME quality, CRM and distal margin were analyzed separately. The mixed results were unexpected, and much controversy ensued regarding the oncologic safety of laparoscopy in rectal cancer surgery. Acuna *et al.* (15) conducted a noninferiority metanalysis of quality of surgical resection based on assessment of CRM, plane of mesorectal excision, distal resection margin and a composite outcome referred to as “successful resection” based on the consensus of 58 worldwide experts. Based on 14 randomized controlled trials, laparoscopic resection was noninferior compared with open resection for the rates of positive CRM, incomplete mesorectum and positive distal resection margin. For the rate of “successful resection”, the comparison remained inconclusive. The authors therefore concluded that laparoscopy was noninferior to open surgery for rectal cancer in terms of individual quality of surgical

Table 2 Selected patient characteristics of randomized controlled trials comparing laparoscopic to open surgery for rectal cancer

Trial name	Year	Patient numbers, lap/open	BMI (kg/m ²), lap/open	Males (%), lap/open	Neoadjuvant CRT, lap/open	Middle rectum, lap/open	Lower rectum, lap/open	Conversion rate (%)	Pathologic outcomes	Results, lap/open	P value
COREAN (10)	2010	170/170	24.1/24.1	64.7/64.7	100/100	NR	NR	1.2	TME (% complete)	72.4/74.7	0.414
									Positive CRM (%)	2.9/4.1	0.770
									Distal margin (cm)	2.0/2.0	0.543
									Lymph nodes (total)	17/18	0.085
COLOR II (11)	2013	699/345	26.1/26.5	64.0/61.0	59/58	39.0/39.0	29.0/27.0	16.6	TME (% complete)	88.0/92.0	0.250
									Positive CRM (%)	10.0/10.0	0.850
									Distal margin (cm)	3.0/3.0	0.676
									Lymph nodes (total)	13/14	0.085
ACOSOG Z6051 (12)	2015	240/222	26.4/26.8	64.5/66.1	100/100	35.1/39.7	51.2/48.5	11.2	TME (% complete)	92.1/95.1	0.20
									Positive CRM (%)	12.1/7.7	0.11
									Distal margin (cm)	3.2/3.1	0.82
									Lymph nodes (total)	17.9/16.5	0.22
									Successful composite outcome** (%)	81.7/86.9	0.41
ALaCart (13)	2015	238/235	27.0/26.0	67.0/64.0	50/49	43.0/44.0	35.0/35.0	8.8	TME (% complete)	87.0/92.0	0.06
									Positive CRM (%)	7.0/3.0	0.06
									Distal margin (cm)	2.6/3.0	0.50
									Lymph nodes (total)	NR	NA
									Successful composite outcome*** (%)	82.0/89.0	0.38

* , TME—included complete and near complete; **, successful composite outcome defined as complete or near complete TME, negative CRM, and negative distal margin; ***, successful composite outcome defined as complete TME, negative CRM, and negative distal margin. BMI, body mass index; CRT, chemoradiotherapy; COREAN, the Comparison of Open versus Laparoscopic Surgery for Mid and Low Rectal Cancer After Neoadjuvant Chemoradiotherapy; NR, not reported; TME, total mesorectal excision; CRM, circumferential margin; COLOR II, the Colorectal Cancer Laparoscopic or Open; ACOSOG, the American College of Surgeons Oncology Group; ALaCart, the Australasian Laparoscopic Cancer of the Rectum Randomized Clinical Trial; NA, not applicable.

Table 3 Long-term outcomes of randomized controlled trials comparing laparoscopic to open surgery for rectal cancer

Trial name	Year	Patients included, lap/open	Endpoints	Results (%), lap/open	P value	Percentage difference (95% CI)
COREAN (16,17)	2014	170/170	3-year LR	2.6/4.9	NR	2.3 (–1.8 to 6.4)
			3-year DFS	79.2/72.5	NR	–6.7 (–15.8 to 2.4)
			3-year OS	91.7/90.4	NR	–1.3 (–7.4 to 4.8)
			10-year LR	3.4/8.9	0.05	NR
			10-year DFS	64.3/59.3	0.20	NR
			10-year OS	76.8/74.1	0.44	NR
COLOR II (18)	2015	699/343	3-year LR	5.0/5.0	NR	0.0 (–2.6 to 2.6*)
			3-year DFS	74.8/70.8	NR	4.0 (–1.9 to 9.9)
			3-year OS	86.7/83.0	NR	3.1 (–1.6 to 7.8)
ALaCart (19)	2018	225/225	2-year LR	5.4/3.1	NR	2.3 (–1.5 to 6.1)
			2-year DFS	80.0/82.0	NR	–2.0 (–9.3 to 5.4)
			2-year OS	94.0/93.0	NR	0.9 (–3.6 to 5.4)
ACOSOG Z6051 (20)	2019	240/222	2-year LR	2.1/1.8	0.86	NR
			2-year DFS	79.5/83.2	0.77	NR

*, 90% CI reported. CI, confidence interval; COREAN, the Comparison of Open versus Laparoscopic Surgery for Mid and Low Rectal Cancer After Neoadjuvant Chemoradiotherapy; LR, local recurrence; NR, not reported; DFS, disease-free survival; OS, overall survival; COLOR II, the Colorectal Cancer Laparoscopic or Open; ALaCart, the Australasian Laparoscopic Cancer of the Rectum Randomized Clinical Trial; ACOSOG, the American College of Surgeons Oncology Group.

resection outcomes (15). The aforementioned and more recently published LASRE trial confirmed comparable rates of complete mesorectal excision, negative CRM, distal resection margins and number of retrieved lymph nodes (14).

Long-term oncologic and functional outcomes

Long-term outcomes have since been published by all four trials, with the COREAN study having the longest follow up of 10 years (Table 3). Despite the initial concerns surrounding pathologic adequacy in laparoscopy, there were no differences in overall local recurrence, disease-free survival or overall survival between laparoscopy and open surgery in any of the studies.

The COREAN trial was the first to report long-term outcomes and found no difference in 3-year local recurrence, disease-free survival and overall survival between laparoscopy and open surgery (16). Further stratification by stage similarly did not show any differences in disease-free survival. These results are concordant with the trial's initial findings showing no difference

in pathologic outcomes between laparoscopy and open surgery. However, there were significant differences in tumor downstaging after neoadjuvant chemoradiation favoring the laparoscopic group, which may have influenced these results. Subsequent 10-year follow-up again showed no difference in local recurrence, disease-free survival or overall survival (17). To account for the differences in ypT and ypN between the two groups, a stratified multivariate analysis with adjustment for these variables was performed and continued to show no difference in the 10-year outcomes. The initial results indicating improved short-term functional outcomes in favor of laparoscopy, did not persist in long-term follow-up (10).

In the COLOR II trial, Bonjer *et al.* (18) reported no significant difference in overall 3-year local recurrence and disease-free survival rates. However, when analyzed by tumor height, they found that in the subset of patients with low rectal tumors (<5 cm from the anal verge), laparoscopy was associated with significantly decreased positive CRM rates {9% *vs.* 22% [confidence interval (CI): 23.2 to 3.0]} and local recurrence rates [4.4% *vs.* 11.7% (CI: 13.9 to 0.7)]. Furthermore, in stage III patients, they reported

decreased disease-free survival in the open group [52% *vs.* 64.9% (CI: 2.2 to 23.6)]. The authors hypothesized that these differences may be due to improved visualization with laparoscopy, and less trauma to the rectum during minimally invasive surgery (18). Quality of life follow-up at 12 months revealed no difference in micturition or sexual function between the laparoscopic and open groups (21).

In the ACOSOG Z6051 trial, Fleshman *et al.* reported no difference in 2-year local recurrence and 2- and 4-year disease-free survival rates (20). This is despite their earlier report showing that laparoscopy could not meet the criteria for non-inferiority in pathologic outcomes. They performed further multivariate analyses and found that positive CRM was the most important factor associated with local recurrence, whereas incomplete TME was not a significant determinant of any recurrence. Patients undergoing abdominoperineal resection (APR) had a higher risk of local recurrence and lower disease-free survival compared to low anterior resection (LAR) and LAR with coloanal anastomosis. Risk of recurrence consistently decreased with increasing tumor distance from the anal verge. The authors emphasize that this trial was not powered to detect differences in these secondary outcomes, therefore the results do not necessarily indicate a lack of difference between the two arms. Long-term functional outcomes of the ACOSOG Z6051 have not yet been reported.

In the ALaCart trial, Stevenson *et al.* reported no overall differences in 2-year local recurrence, disease-free survival or overall survival (19). Tumor stage, distance from the anal verge and type of operation (LAR or APR) did not influence local recurrence or disease-free survival. Similar to the findings of Fleshman *et al.* (20), a positive CRM was the only pathologic factor associated with a higher risk of local recurrence at 2 years. The authors concluded that although these results are reassuring for laparoscopy, they do not prove noninferiority and continue to favor open surgery due to pathologic differences from their earlier report. Long-term functional outcomes were recently published and showed no difference in bowel or urinary symptoms at 3 months, but less fecal incontinence, sore skin and moderate to severe urinary symptoms for men at 12 months in the open surgery group. However, when specifically analyzing the change between baseline and 12 months, there were no significant differences between groups. With regard to sexual satisfaction, there were no differences in men or women at 12 months (22).

Multiple meta-analyses have been performed confirming these long-term oncologic outcomes (23,24). The most

recent meta-analysis by Creavin *et al.* (25) analyzed 12 randomized controlled trials and included the latest long-term outcomes data from the ACOSOG Z6051 and ALaCart trials. The assessment of a combined 3,744 patients (2,133 in the laparoscopic group and 1,611 in the open group) indicated no difference in local recurrence (laparoscopic 4.4% *vs.* open 4.3%), distant recurrence (17.2% laparoscopic *vs.* 18.5% open) 5-year disease-free survival (laparoscopic 82.0% *vs.* open 76.2%) or 5-year overall survival (laparoscopic 77.3% *vs.* open 81.0%) between the two groups. In concordance with the results of Fleshman *et al.* (20), the subgroup analysis found that positive CRM was associated with worse disease-free survival, but TME quality was not. They found that achieving a successful composite score improved disease-free survival, however their study design was not powered to determine differences in composite score based on surgical approach.

Laparoscopy vs. open surgery, results of widespread implementation

The results of randomized controlled trials have spurred a more widespread adoption of laparoscopic surgery in rectal cancer. Laparoscopic rectal cancer resection in the “real world” has been tested in comparison with open surgery by several population and single institutional studies. The results of large retrospective studies are reported in *Table 4*. Sujatha-Bhaskar *et al.* assessed the pathologic outcomes and overall survival of patients from the National Cancer Database (NCDB) undergoing proctectomy between 2010 and 2014. Out of 6,313 identified cases, 53.8% underwent open surgery compared to 31.8% undergoing laparoscopic resections and 14.3% undergoing robotic proctectomy. In an intent-to-treat model, multivariate analysis demonstrated improved CRM negativity rates with laparoscopic surgery compared with open surgery. In addition, laparoscopic proctectomy was associated with a lower death hazard ratio (HR) when compared to open proctectomy [odds ratio (OR), 0.81; P=0.037]. Kaplan-Meier analysis demonstrated a statistically significant trend towards superior overall 5-year survival for robotic and laparoscopic cohorts compared with open resection (81% following laparoscopic proctectomy, 78% for robotic proctectomy, and 76% for open proctectomy; *Table 4*) (26).

Manchon-Walsh *et al.* (28) evaluated 1,513 patients with stage I–III rectal cancer undergoing laparoscopic *vs.* open surgery in Catalonia’s public hospitals from 2011 to 2012. To minimize differences between the two

Table 4 Retrospective studies comparing laparoscopic and open rectal resection

Author	Year	Study design	Patient numbers, lap/open	5-year OS (%), lap/open (P value)	5-year RFS (%), lap/open (P value)	Morbidity (%), lap/open (P value)	5-year LR (%), lap/open (P value)	5-year DM (%), lap/open (P value)
Sujatha-Bhaskar (26)	2017	Retrospective, NCDB	2,009/3,399	81/76 (0.019)	NR	NR	NR	NR
Hida (27)	2018	Propensity score-matched	482/482	*89.9/90.4 (ns)	*70.9/71.8 (ns)	30.3/39.2 (0.005)	NR	NR
Manchon-Walsh (28)	2019	Propensity score-matched	842/517	77.3/64.8 (<0.001)	NR	NR	**3.4/7.4	**9.9/7.4 (0.122)
Schnitzbauer (29)	2020	Retrospective	4,540/11,838	82.6/76.6 (<0.001)	81.8/74.3 (<0.001)	NR	NR	NR
Goto (30)	2021	Propensity score-matched	237/237	*90.5/88.6 (ns)	*78.3/71.6 (ns)	***17.7/19.8 (0.319)	*5.2/6.9 (0.165)	NR
Dehlaghi Jadid (31)	2022	Retrospective, Sweden	2,094/6,316	NR	NR	NR	2.9/3.6 (0.075)	15.6/19.6 (<0.001)

* , 3-year data; ** , 2-year data; *** , Clavien-Dindo 3 or higher. OS, overall survival; RFS, recurrence-free survival; LR, local recurrence; DM, distant metastases; NCDB, National Cancer Database; NR, not reported; ns, not significant.

groups the authors applied propensity score-matching to select two more easily comparable groups. A total of 842 laparoscopic patients were matched to 517 open surgery patients. The overall conversion rate was 13.2%. There were statistically significant differences in TME quality favoring the laparoscopy group (complete TME rates: 70.1% *vs.* 67.9%; near complete rates: 8.4% *vs.* 5.6%, $P=0.012$). However, there were no differences in positive CRM or positive distal resection margin rates between the two groups. Laparoscopy was associated with a lower rate of local recurrence and distant metastasis rates as well as decreased mortality, both at 2 years (10.8% *vs.* 17.4%, $P=0.001$) and 5 years (Table 4). On multivariate analysis the authors found laparoscopy to be an independent protective factor for local relapse at 2 years (HR, 0.44; $P=0.001$) and mortality, both at 2 years (HR, 0.65; $P=0.004$) and at 5 years (HR, 0.61; $P<0.001$). When discussing the possible causes of these differences the authors hypothesized this may be secondary to a decreased inflammatory response associated with minimally invasive surgery (28).

In another multicenter propensity score-matched cohort study in Japan, Hida *et al.* (27) analyzed 1,500 cases from 69 institutions between 2011 and 2012. Average BMI was 22 kg/m² and average distance to the anal verge was 4.6 cm. The conversion rate to open surgery was 5.2%. A propensity score to adjust for differences between the two groups was constructed using 8 different variables (age, body mass index, sex, history of abdominal operations, tumor distance from the anal verge, tumor depth, lymph node metastasis, and preoperative therapy). Based on 462 matched patients per group, laparoscopic surgery was associated with less estimated blood loss (90 *vs.* 625 mL, $P<0.001$) and lower complication rates (30.3% *vs.* 39.2%, $P=0.005$). There was no difference in positive CRM rates between the two groups, but there were more examined lymph nodes along the inferior mesenteric artery in the open group (17 *vs.* 14, $P=0.001$). No differences in 3-year local recurrence, disease-free survival or overall survival were identified, though the study was not powered to detect differences in these variables (27). More recently and again in Japan, Goto *et al.* (30) conducted a similar case-matched study utilizing propensity score matching with 6 covariates. From a base of 1,091 eligible cases of locally advanced mid to lower rectal cancer (stages II and III), 237 cases of laparoscopic surgery were extracted and compared with the same number of open counterparts. The study period ranged from 2008 to the end of 2014. As expected, the patient BMIs were comparable between the

two groups (22 *vs.* 22.5 kg/m² in the laparoscopic and open groups, respectively). Operative times were significantly longer while the length of postoperative hospital stay was significantly shorter in the laparoscopic group. There were no significant differences between groups in the incidence of postoperative complications. Three-year overall survival and relapse-free survival rates were also comparable. The authors concluded that laparoscopic surgery could be a therapeutic option for locally advanced rectal cancer (30). The results of these studies may have limited applicability to Western countries, given the high prevalence of lateral lymph node dissection, which is typical for Japan, and their low BMI when compared to Western countries.

In this respect, Schnitzbauer *et al.* (29) assessed the results on 16,378 patients undergoing rectal cancer resection in 30 centers in Germany between 2007 and 2016, 4540 of whom (27.7%) underwent laparoscopic surgery. Patients undergoing laparoscopy were associated with reduced 90-day mortality (OR, 0.658). In addition, they were associated with significantly longer overall survival and recurrence-free rates compared with open surgery, with HRs of 0.819 and 0.770, respectively ($P < 0.001$ for both). The 5-year relative survival rates were also in favor of laparoscopy (93.1% *vs.* 88.4%, $P = 0.012$) (29). Dehlaghi Jadid *et al.* (31) examined all patients with stage I–III rectal cancer undergoing abdominal surgery with curative intent using either open or laparoscopic technique in Sweden during a 7-year period between 2010 and 2016. The relationship between surgical approach and overall mortality was assessed through a noninferiority study design. An intent-to-treat analysis was used after adjustment for risk factors through propensity score matching. The study demonstrated that laparoscopic surgery was not inferior to open surgery with respect to 5-year overall survival. Multivariable Cox regression demonstrated that 5-year overall survival was higher in the laparoscopic group (HR, 0.877; CI: 0.877–0.993), with comparable 5-year local recurrence rates while metastatic disease was more frequent in the open group (31).

With respect to single center studies, Sasi *et al.* (32) performed a propensity-matched study in India. This country produces a unique cohort of patients as rectal cancer affects a much younger population and individuals are often diagnosed at a more advanced stage. For these reasons, they specifically sought to analyze the use of laparoscopy in tumors with a threatened or positive CRM. Four hundred and seventy-eight patients were included in the study, with 239 in each arm. There were no significant

differences between groups after propensity matching. The average age was 47 years, 60% of patients had low rectal tumors <5 cm from the anal verge, 83% had clinically positive nodes and 50% had a positive CRM on initial imaging. All patients received neoadjuvant therapy with either long or short-course radiotherapy \pm chemotherapy. The overall positive CRM rates were similar in both groups (5.4% laparoscopic *vs.* 6.3% open, $P = 0.697$), and this finding persisted when stratified by tumor distance from the anal verge. In the cohort of patients with preoperative imaging indicating positive or threatened CRM, there was no difference in pathologic positive CRM rates between the two groups (8.4% laparoscopic *vs.* 6.7% open, $P = 0.587$). Laparoscopic surgery was associated with decreased estimated blood loss (349 *vs.* 910 mL, $P = 0.000$), Clavien-Dindo grade 3–4 complication rates (6.7% *vs.* 12.5%, $P = 0.015$), shorter hospital length of stay (6 *vs.* 7 days, $P = 0.015$) and lower rates of anastomotic leak (1.7% *vs.* 5.9%, $P = 0.024$). The authors attribute their favorable pathologic outcomes to the technical expertise of the two participating surgeons and the high-quality MRI done before and after neoadjuvant radiotherapy which allowed for appropriate preoperative planning and anticipation of multivisceral resection if necessary (32). Longer term oncologic outcomes were not reported in this study.

To determine if the outcomes from ACOSOG Z6501 and ALaCart could be translated to a single institution experience, Ofshteyn *et al.* performed a retrospective review of patients undergoing laparoscopic proctectomy at a single institution and compared their outcomes to the ACOSOG Z6501 and ALaCart trials (33). Eighty-nine patients were included. Compared to the ACOSOG trial, they had a smaller number of low rectal tumors (24.1% *vs.* 51.2%) and fewer patients received preoperative chemoradiation (79.8% *vs.* 95%). They had a higher proportion of patients undergoing APR (25.8% *vs.* 5.8%, $P < 0.001$) and a higher conversion rate (24.7% *vs.* 11%, $P = 0.001$). Pathologic outcomes were similar except for a higher negative CRM rate in their cohort (97.8% *vs.* 87.9%, $P < 0.001$). Compared to the ALaCart trial, they had fewer patients with low rectal tumors (24.4% *vs.* 35%), but a greater proportion of patients receiving preoperative chemoradiation (79.8% *vs.* 50%). Their rate of conversion was also higher (24.7% *vs.* 9%, $P < 0.001$). Pathologic outcomes were similar except for a higher negative CRM rate (98.9% *vs.* 93%, $P = 0.047$) found in their study. Though this study had several limitations including small sample size and differences in tumor characteristics compared to the randomized

controlled trials, their data speaks to the pathologic quality that can be achieved with laparoscopy at a high volume minimally invasive center.

Multiple retrospective multicenter studies and single institutional studies from different countries have confirmed that laparoscopic surgery for rectal cancer is associated with oncologic results that are generally comparable to open surgery. The impact of patient selection is difficult to assess in such studies and could be responsible for those cases where laparoscopic surgery was associated with superior oncologic outcomes, which none of the prospective randomized trial results have shown. At this time the evidence indicates that laparoscopic surgery is an acceptable option in the surgical treatment of rectal cancer.

Will robotic surgery supplant laparoscopic surgery?

The robotic platform was approved by the FDA in 2000 and the first robotic TME for rectal cancer was described by Pigazzi *et al.* in 2006 (34). The Robotic *vs.* Laparoscopic Resection for Rectal Cancer (ROLARR) trial published in 2017 remains the largest randomized controlled trial comparing these two techniques in rectal cancer to date. The primary endpoint was the rate of conversion to open surgery. The study was powered based on an anticipated 25% conversion rate following conventional laparoscopic surgery, given the 34% conversion rate of the previously mentioned CLASICC trial, the best available evidence at the time of the original ROLARR design, and accounting for advances in surgical technique. Four hundred and seventy-one patients were randomized to either robotic or laparoscopic surgery. The overall positive CRM rate was 5.7%, showcasing the high quality of surgery attained in this study. There was no difference in the conversion rate between the two groups [12.2% laparoscopic *vs.* 8.1% robotic [unadjusted difference in proportions 4.1% (95% CI: -1.4% to 9.6%)] and no difference with respect to odds of conversion [adjusted OR, 0.61 (95% CI: 0.31 to 1.21), P=0.16]. There were no differences in any secondary outcomes including positive CRM rate, intraoperative complications, postoperative complications, 30-day mortality, bladder dysfunction and sexual dysfunction. A subgroup analysis limited to male patients indicated a statistically significant difference in conversion rates favoring robotic surgery (robotic 8.7% *vs.* laparoscopic 16%, CI: 0.1–14.6). The authors concluded that robotic

surgery does not confer any significant benefit over laparoscopy in rectal cancer. However, ROLARR ended up being underpowered based on its actual conversion rates. Another criticism of this study was that participating surgeons might have been experts in conventional laparoscopic surgery but still in their learning curve in robotic surgery, thus confounding the study results.

Since the ROLARR trial, the use of robotic surgery has continued to increase (35). Numerous studies have directly compared clinical, oncologic and functional outcomes of robotic and laparoscopic surgery. Muaddi *et al.* (36) conducted a systematic overview on clinical outcomes after rectal cancer resection based on 5 randomized controlled trials and several retrospective studies. There were no differences in rates of incomplete TME, risk of CRM involvement, number of lymph nodes harvested, risk of anastomotic leak, 30-day morbidity and mortality, estimated blood loss and hospital length of stay. However, robotic surgery was associated with a significant longer duration of surgery, reduced rate of conversion to open, and earlier return of bowel function (36). Another recent comparative review examined oncologic outcomes. The TME grade, CRM, distal resection margin, lymph node harvest and survival were found to be similar between robotic and laparoscopic surgery (37). With respect to functional outcomes, Flynn and coll. conducted a systematic review and meta-analysis based on relatively limited data from 14 different studies. Robotic resection was associated with improved male sexual function and urinary function while there were no differences in quality of life and gastrointestinal function (38). There is already substantial evidence indicating that robotic surgery for rectal cancer is associated with equivalent and in some cases improved outcomes when compared with laparoscopic surgery. The question remains on who can perform robotic surgery and how much training is required, which rekindles the older question on who can perform laparoscopic surgery. Unlike in laparoscopic *vs.* open surgery, the high-quality evidence on robotic *vs.* laparoscopic surgery consists of only one prospective randomized trial having the previously discussed important limitations. It also remains unclear if the adoption of robotic surgery will reach a ceiling given the limited number of robots available in any given hospital and their high cost of purchase and maintenance. This could leave some inevitable space for laparoscopic surgery as an alternative minimally invasive option beside the open technique that is still utilized for a substantial proportion of rectal cancer cases.

Is laparoscopic surgery less expensive than robotic surgery?

Despite clinically favorable outcomes, robotic surgery continues to be criticized because of its high societal costs (38). The price of a robotic system has been estimated between \$2 million and \$2.5 million with additional annual service charges of \$200,000 (39,40). The financial assessments in the previously discussed ROLARR trial indicated that the healthcare costs in the robotic-assisted group were higher than in the conventional laparoscopic group. Subsequent retrospective studies have similarly reported significantly increased operative time, total costs and operative costs with robotic proctectomy compared to laparoscopy (41,42). This financial burden is attributed to initial acquisition, ongoing maintenance, longer operative times and depreciation of the robotic system (42). Morelli and coll. specifically investigated the association between costs of robotic surgery and surgeon experience. They found that overall costs were significantly higher during the earlier experience in robotic surgery, while differences in costs between robotic and laparoscopic rectal resection were no longer significant when excluding earlier cases in the surgeon's learning curve (43). More recently, Ielpo *et al.* (44) analyzed 86 robotic-assisted rectal resections compared with 112 laparoscopic counterparts. They found that robotic surgery was associated with longer operative times and higher operating room costs, but no difference in total cost. They attributed this to decreased readmissions ($P < 0.001$) and a trend toward decreased conversion rates in the robotic arm ($P = 0.09$). Al-Mazrou *et al.* (45) performed a large propensity-matched study of 4,438 patients (2,219 robotic and 2,219 laparoscopic) included in the Premier Perspective database undergoing colon or rectal operations. Direct, cumulative and total costs were higher for the robotic group, but these differences decreased by \$1,269 over the study period between 2012 and 2014. This coincided with a significantly decreased incidence of wound infections, abdominal infection and respiratory complications in the robotic group during the final year of analysis. The authors concluded that decreased costs and short-term benefits become more apparent with greater use of the robotic technology and increasing surgeon expertise (45). Simianu *et al.* (46) developed a decision-analytic model to evaluate 1-year costs and outcomes of robotic, laparoscopic and open proctectomy based on data from the available literature. Based on costs adjusted to 2,017 dollars, laparoscopy was found to be the most cost-effective approach. However,

the analysis also indicated that robotic proctectomy could become cost effective if a modest reduction in cost, in the order of \$400 per patient, or a decreased length of postoperative hospital stay could be achieved (46). The data on cost effectiveness is variable depending on the study design and whether a public or private health system is analyzed (47,48). At this time, laparoscopy remains the most cost effective minimally invasive approach. However, future studies could corroborate long-term benefits potentially favoring robotic surgery, for example reduction of incisional hernia rates. In addition, technical advancements in robotic surgery and increased surgeon experience could result in further improvements in clinical outcomes and cost reduction. It is also important to point out that apart from the analyses of direct costs or societal costs, the actual reimbursement for a charge submitted by an individual health care institution to a private payer may already render robotic surgery financially advantageous in the notoriously fragmented American healthcare environment.

Will taTME supplant laparoscopic surgery?

taTME was introduced in 2010 to address the technical limitations of laparoscopy, particularly in the dissection of a low rectal carcinoma in the narrow pelvis of the obese and male populations (49). The transanal approach allows for improved visualization and mobility during dissection of the distal rectum and a direct view of the distal anorectal transection point. Initial studies reported acceptable pathologic outcomes and morbidity when compared to laparoscopy (50-52). However, a report from Norway indicated an alarming local recurrence rate of 9.5% and a short median time to recurrence of just 11 months (53). The pattern of recurrence was aggressive, characterized by rapid multifocal growth in the pelvic sidewalls which according to the authors is not typically seen after conventional surgery. The use of taTME was suspended in Norway after these initial reports. The subsequent Norwegian national audit of 157 patients undergoing taTME for rectal cancer between 2014 and 2018 reported an overall local recurrence of 7.6% (12 of 157), 8 of which were multifocal or extensive. The local recurrence rate for taTME at 2.4 years was 11.6% compared to 2.4% in the Norwegian Colorectal Cancer Registry ($P < 0.001$) (54). Anastomotic leaks requiring reoperative intervention were also higher than the national average (8.4% *vs.* 4.5%, $P = 0.047$). Local recurrences were equally distributed across all participating centers and

occurred even during the late study period. Thus, the authors do not attribute these high recurrence rates to learning curve alone. They hypothesize that the unusual pattern of recurrence may be secondary to technical factors inherent to the taTME procedure, specifically the exposure of the distal rectum to tumor during dissection. Though the rectal lumen is endoluminally closed distal to the tumor, persistent leakage of gas and transfer of tumor cells into the pelvis could account for the multi-focal pattern of recurrence. In contrast, a study from the Netherlands reported 3- and 5-year local recurrence rates at 2.0% and 4.0% with a median time of 19.2 months to local recurrence (55). Similarly, in a large multi-center observational cohort study of 767 patients, Roodbeen and coll. reported a 2-year local recurrence rate of 3%, without any cases of multi-focal regrowth (56). To evaluate for differences in learning curve, Oostendorp and coll. performed an implementation study analyzing the first ten cases in each of the 12 participating centers for a total of 120 patients (57). The local recurrence rate was 10% for this implementation cohort, with multi-focal recurrence occurring in 8 out of 12 patients. However, the local recurrence rate dropped to 5.6% in the prolonged cohort of 260 patients and was actually 4% when excluding the first 10 cases from each center. The authors concluded that high local recurrence rates and multifocal patterns of recurrence may be due to suboptimal execution rather than the technique itself. Ongoing prospective randomized trials such as the European COLOR III trial (58) and Chinese TaLaR (NCT02966483) (59) should provide high-quality evidence on both short-term and long-term outcomes of taTME compared with laparoscopic surgery. The results of taTME remain variable, its applicability focuses mainly on the lower rectum and good results come from selected centers with high volume and expertise. Further data is therefore necessary before it can be recommended as a replacement of conventional laparoscopic surgery.

Strengths and limitations

This review is an analysis of the most current evidence investigating laparoscopy in rectal cancer. We provide a synopsis and interpretation of the available literature, synthesizing the oncologic safety of laparoscopy compared to other techniques, while incorporating financial implications specific to the healthcare system in the United States. Limitations of this study are those inherent to a narrative review, specifically the retrospective design of several studies described, and subjective inclusion of studies

chosen by the authors which introduces inherent bias.

Conclusions

The data presented overall support the use of laparoscopy in rectal cancer, but this conclusion should be taken with caution. The surgeons in the referenced studies were either subject to stringent selection criteria in the randomized controlled trials or were employed at high volume institutions that are often responsible for the majority of rectal cancer care in a specific region. The application of these results to the general surgical community should be limited to those surgeons and institutions with specialized training and experience in laparoscopy for the management of rectal cancer. The evidence supporting favorable outcomes of robotic surgery continues to grow. However, when considering healthcare expenditures and timely availability of robotic systems, laparoscopy remains an acceptable option that allows patients to benefit from the advantages of minimally invasive surgery. There is ongoing uncertainty surrounding the oncologic outcomes of taTME and a lack of high-quality evidence to support its routine use as a safe alternative to laparoscopy or robotic surgery at this time. Regardless of surgical technique, the data continually show that positive CRM portends an overall worse prognosis with respect to local recurrence and disease-free survival. The best surgical approach should be one where the surgeon can confidently attain an adequate pathologic specimen, whether it be laparoscopic, open or robotic.

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Footnote

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