



Rectal cancer—state of art of laparoscopic versus open surgery

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Abstract: Since its introduction, laparoscopy has gained more and more consent in colorectal surgery, even if its role in rectal cancer surgery is still controversial and widely debated. The aim of this study is to present the ongoing situation of laparoscopic surgery for rectal cancer by a review of current literature. We performed a systematic search in the electronic databases (PubMed, Web of Science, Scopus, EMBASE) according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. We limited the search until 31 March 2017 and used the following search terms in all possible combinations: rectal cancer, laparoscopy, minimally invasive and open surgery. A total of 66 articles were include in this review, of which 38 were non-randomized trials, 8 were randomized controlled trials (RCTs) performed in a single center, 5 were multicentric RCTs and 15 were meta-analyses. Laparoscopic approach resulted in a faster and better recovery after surgery and has been proven to be equivalent in terms of short-terms outcomes comparing to the open approach. Nevertheless, the findings concerning oncologic safety of minimally invasive approach are still controversial. This should give the rationale to perform new meta-analyses based on the last evidences produced. Moreover, even more multicentric RCTs studies, hypothetically designed on new pathological outcomes, should be performed to finally assess if laparoscopy is a valid choice for the treatment of rectal cancer.

Keywords: Rectal; cancer; laparoscopy; open surgery; review

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Introduction

Since its introduction, laparoscopy has gained more and more consent in colorectal surgery, becoming the Gold Standard for the surgical treatment of colon cancer (1). On the contrary, its role in rectal cancer surgery is still controversial and widely debated. In fact rectal cancer surgery results more technically difficult than the colonic one, due to the narrow space of the pelvis, which gets laparoscopic surgery particularly challenging. For this reason laparoscopic rectal surgery gets performed only in specialized centers worldwide.

In the last decade accumulating evidence has demonstrated that recovery after laparoscopy is faster and

better, moreover laparoscopic rectal resection has been proven equivalent to the traditional technique in terms of short-terms outcomes. Nevertheless, its oncologic safety remains unclear and doubts about pathologic outcomes are still open and worsened by new evidence reported by the most recent international studies. With this study we aim to present the ongoing situation of laparoscopic treatment for rectal cancer by reviewing the current literature.

Materials and methods

To identify all possible studies regarding the comparison between laparoscopic and open rectal resection for rectal cancer and to make the state of art of laparoscopic rectal

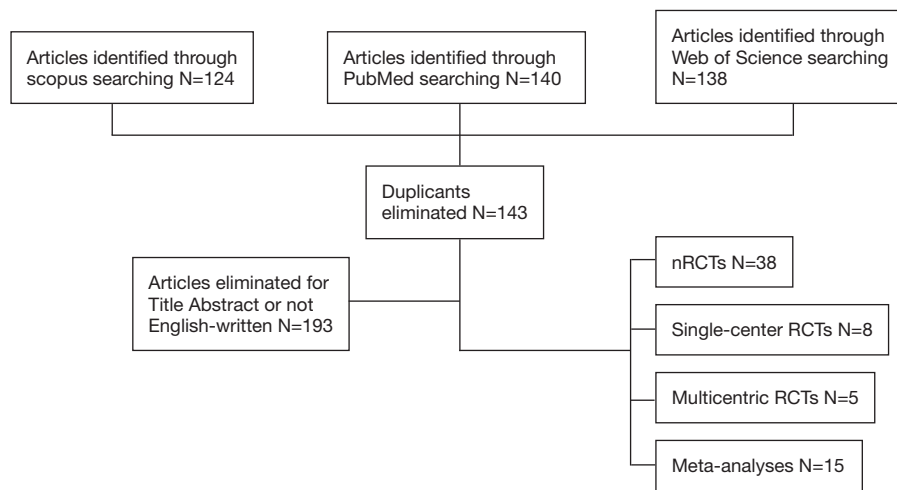


Figure 1 Studies' exclusion according to PRISMA. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

resection, we performed a systematic search in the electronic databases (PubMed, Web of Science, Scopus, EMBASE) according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (2). We limited the search until 31 March 2017 and used the following search terms in all possible combinations: rectal cancer, laparoscopy, minimally invasive and open surgery. We included only English-written articles comparing laparoscopic surgery to the open technique for rectal cancer treatment.

Results

The search produced 402 articles; 143 were duplicates and were removed. Two independent Authors evaluated the remaining articles excluding the ones that were not pertinent (not comparing laparoscopy to the traditional technique in rectal cancer treatment) or not English-written. Reviews were excluded too resulting in 66 articles, of which 38 are non-randomized trials, 8 are randomized controlled trials (RCTs) performed in a single center, 5 are multicentric RCTs and 15 are meta-analyses (*Figure 1*).

Articles included in this review have been divided in four categories: non RCTs, single-center RCT, multicentric RCTs, meta-analyses; and chronologically ordered in *Tables 1-4*.

Discussion

Rectal cancer is a worldwide disease that constitutes one-third of colorectal cancers (67) and whose incidence has

increased significantly in the last decades (68). The main treatment for rectal cancer is the surgical resection, which results have drastically improved since the introduction of total mesorectal excision (TME).

Thanks to accumulating evidence indicating that laparoscopic treatment of colon carcinoma is considered equivalent to the open technique, the laparoscopic technique is widely accepted and performed in the treatment of colon carcinoma. On the contrary, the role of laparoscopy in the treatment of rectal cancer is still not clear. Laparoscopic rectal surgery is more difficult than colonic one, due to the narrow space of pelvic cavity and the oncological safety remains unclear. Therefore, laparoscopy in rectal cancer is still not recommended as the gold standard treatment by international guidelines.

Anyhow the open approach too presents several limitations, especially in terms of oncologic outcomes, as it has been demonstrated by Rickles *et al.* (69) who reported a 22% less risk of positive circumferential resection margin (CRM) after laparoscopic surgery compared to an open approach.

All these reasons led to the current interest of surgeons towards new techniques, such as the use of robotics, transanal approach (taTME) or the combination of laparoscopy and transanal approach for rectal cancer surgery.

During the last decade many studies have been performed to prove the safety and feasibility of laparoscopic-assisted resection for rectal cancer. In order to demonstrate the non-inferiority of the laparoscopic approach against the open

Table 1 Non-randomized trials on rectal cancer resection

Author	Title	Year	Journal	Type	Patients	Lap	Open
Fleishman <i>et al.</i> (3)	Laparoscopic versus open abdominoperineal resection for cancer	1999	<i>Diseases of the Colon & Rectum</i>	Retrospective	194	42	152
Leung <i>et al.</i> (4)	Laparoscopic-assisted abdominoperineal resection for low rectal adenocarcinoma	2000	<i>Surgical Endoscopy</i>	Study-control	59	25	34
Anthuber <i>et al.</i> (5)	Outcome of laparoscopic surgery for rectal cancer in 101 patients	2003	<i>Diseases of the Colon & Rectum</i>	Retrospective	435	101	334
Feliciotti <i>et al.</i> (6)	Long-term results of laparoscopic versus open resections for rectal cancer for 124 unselected patients	2003	<i>Surgical Endoscopy</i>	Retrospective	86	52	34
Hu <i>et al.</i> (7)	Comparative evaluation of immune response after laparoscopic and open total mesorectal excisions with anal sphincter preservation in patients with rectal cancer	2003	<i>World Journal of Gastroenterology</i>	Retrospective	45	20	25
Wu <i>et al.</i> (8)	Laparoscopic versus conventional open resection of rectal carcinoma: a clinical comparative study	2004	<i>World Journal of Gastroenterology</i>	Retrospective	36	18	18
Morino <i>et al.</i> (9)	Laparoscopic versus open surgery for extraperitoneal rectal cancer: a prospective comparative study	2005	<i>Surgical Endoscopy</i>	Retrospective	191	98	93
Law <i>et al.</i> (10)	Laparoscopic and open anterior resection for upper and mid rectal cancer: an evaluation of outcomes	2006	<i>Diseases of the Colon & Rectum</i>	Retrospective	265	98	167
Lelong <i>et al.</i> (11)	Short-term outcome after laparoscopic or open restorative mesorectal excision for rectal cancer: a comparative cohort study	2007	<i>Diseases of the Colon & Rectum</i>	Retrospective	172	104	68
Veenhof <i>et al.</i> (12)	Laparoscopic versus open total mesorectal excision: a comparative study on short-term outcomes: a single-institution experience regarding anterior resections and abdominoperineal resections	2007	<i>Digestive Surgery</i>	Retrospective	100	50	50

Table 1 (continued)

Table 1 (continued)

Author	Title	Year	Journal	Type	Patients	Lap	Open
Staudacher <i>et al.</i> (13)	Laparoscopic versus open total mesorectal excision in unselected patients with rectal cancer: impact on early outcome	2007	<i>Diseases of the Colon & Rectum</i>	Retrospective	187	108	79
Mirza <i>et al.</i> (14)	Long-term outcomes for laparoscopic versus open resection of nonmetastatic colorectal cancer	2008	<i>Journal of Laparoendoscopic & Advanced Surgical Techniques</i>	Retrospective	92	54	38
Ströhlein <i>et al.</i> (15)	Comparison of laparoscopic versus open access surgery in patients with rectal cancer: a prospective analysis	2008	<i>Diseases of the Colon & Rectum</i>	Prospective	389	114	275
Yu <i>et al.</i> (16)	Laparoscopic versus open total mesorectal excision for the middle-lower rectal cancer: a clinical comparative study	2009	<i>Chinese Journal of Gastrointestinal Surgery</i>	Retrospective	198	93	105
González <i>et al.</i> (17)	Laparoscopic versus open total mesorectal excision: a nonrandomized comparative prospective trial in a tertiary center in Mexico City	2009	<i>The American Journal of Surgery</i>	Prospective	56	28	28
Gouvas <i>et al.</i> (18)	Laparoscopic or open surgery for the cancer of the middle and lower rectum short-term outcomes of a comparative non-randomised study	2009	<i>International Journal of Colorectal Disease</i>	Retrospective	88	45	43
Khaikin <i>et al.</i> (19)	Laparoscopic versus open proctectomy for rectal cancer: patients' outcome and oncologic adequacy	2009	<i>Surgical Laparoscopy Endoscopy & Percutaneous Techniques</i>	Retrospective	82	32	50
Koulas <i>et al.</i> (20)	Evaluations of laparoscopic proctocolectomy versus traditional technique in patients with rectal cancer	2009	<i>Journal of the Society of Laparoendoscopic Surgeons</i>	Retrospective	117	57	60
Laurent <i>et al.</i> (21)	Laparoscopic versus open surgery for rectal cancer: long-term oncologic results	2009	<i>Annals of Surgery</i>	Retrospective	471	238	233
Baik <i>et al.</i> (22)	Laparoscopic versus open resection for patients with rectal cancer: comparison of perioperative outcomes and long-term survival	2011	<i>Diseases of the Colon & Rectum</i>	Case-matched controlled prospective	162	54	108

Table 1 (continued)

Table 1 (continued)

Author	Title	Year	Journal	Type	Patients	Lap	Open
McKay <i>et al.</i> (23)	Improved short-term outcomes of laparoscopic versus open resection for colon and rectal cancer in an area health service: a multicenter study	2011	<i>Diseases of the Colon & Rectum</i>	Retrospective	545	157	388
Gunka <i>et al.</i> (24)	Long-term results of laparoscopic versus open surgery for nonmetastatic colorectal cancer	2011	<i>Acta Chirurgica Belgica</i>	Retrospective	145	75	70
Siani <i>et al.</i> (25)	Laparoscopic versus open total mesorectal excision for stage I-III mid and low rectal cancer: a retrospective 5 years analysis	2012	<i>Il Giornale di Chirurgia</i>	Retrospective	60	30	30
Jefferies <i>et al.</i> (26)	Oncological outcome after laparoscopic abdominoperineal excision of the rectum	2012	<i>Colorectal Disease</i>	Retrospective	41	16	25
Kellokumpu <i>et al.</i> (27)	Short- and long-term outcome following laparoscopic versus open resection for carcinoma of the rectum in the multimodal setting	2012	<i>Diseases of the Colon & Rectum</i>	Retrospective	191	100	91
Seshadri <i>et al.</i> (28)	Laparoscopic versus open surgery for rectal cancer after neoadjuvant chemoradiation: a matched case-control study of short-term outcomes	2012	<i>Surgical Endoscopy</i>	Retrospective	144	72	72
Kang <i>et al.</i> (29)	The impact of robotic surgery for mid and low rectal cancer: a case-matched analysis of a 3-arm comparison—open, laparoscopic, and robotic surgery	2013	<i>Annals of Surgery</i>	Retrospective	330	165	165
Lujan <i>et al.</i> (30)	Laparoscopic versus open surgery for rectal cancer: results of a prospective multicentre analysis of 4,970 patients	2013	<i>Surgical Endoscopy</i>	Prospective	4,405	1,387	3,018
Wilson <i>et al.</i> (31)	Laparoscopic colectomy is associated with a lower incidence of postoperative complications than open colectomy: a propensity score-matched cohort analysis	2014	<i>Colorectal Disease</i>	Retrospective cohort study	37,249	15,643	21,606
Moghadamyeghaneh <i>et al.</i> (32)	Outcomes of open, laparoscopic, and robotic Abdominoperineal resections in patients with rectal cancer	2015	<i>Diseases of the Colon & Rectum</i>	Retrospective	17,496	4737	12759

Table 1 (continued)

Table 1 (continued)

Author	Title	Year	Journal	Type	Patients	Lap	Open
Midura <i>et al.</i> (33)	The effect of surgical approach on short-term oncologic outcomes in rectal cancer surgery	2015	<i>Surgery</i>	Retrospective	8,272	2,337	5,935
Dural <i>et al.</i> (34)	The role of the laparoscopy on circumferential resection margin positivity in patients with rectal cancer: long-term outcomes at a single high-volume institution	2015	<i>Surgical Laparoscopy Endoscopy & Percutaneous Techniques</i>	Retrospective	579	266	313
Cho <i>et al.</i> (35)	Minimally invasive versus open total mesorectal excision for rectal cancer: long-term results from a case-matched study of 633 patients	2015	<i>Surgery</i>	Retrospective	633	211	422
Kim <i>et al.</i> (36)	Long-term outcomes of laparoscopic versus open surgery for rectal cancer: a single-center retrospective analysis	2015	<i>The Korean Journal of Gastroenterology</i>	Retrospective	307	131	176
Zaharie <i>et al.</i> (37)	Laparoscopic rectal resection versus conventional open approach for rectal cancer - a 4-year experience of a single center	2015	<i>Journal of BUON</i>	Retrospective	172	29	143
de Jesus <i>et al.</i> (38)	The circumferential resection margins status: a comparison of robotic, laparoscopic and open total mesorectal excision for mid and low rectal cancer	2016	<i>European Journal of Surgical Oncology</i>	Retrospective	241	41	200

Table 2 Single center randomized trials on rectal cancer resection

Author	Title	Year	Journal	Type	Patients	Lap	Open
Araujo <i>et al.</i> (39)	Conventional approach x laparoscopic abdominoperineal resection for rectal cancer treatment after neoadjuvant chemoradiation: results of a prospective randomized trial	2003	<i>Revista do Hospital das Clínicas</i>	Prospective	28	13	15
Zhou <i>et al.</i> (40)	Laparoscopic versus open total mesorectal excision with anal sphincter preservation for low rectal cancer	2004	<i>Surgical Endoscopy</i>	Prospective	171	82	89
Braga <i>et al.</i> (41)	Laparoscopic resection in rectal cancer patients: outcome and cost-benefit analysis	2007	<i>Diseases of the Colon & Rectum</i>	Prospective	168	83	85

Table 2 (continued)

Table 2 (continued)

Author	Title	Year	Journal	Type	Patients	Lap	Open
Pechlivanides <i>et al.</i> (42)	Lymph node clearance after total mesorectal excision for rectal cancer: laparoscopic versus open approach	2007	<i>Digestive Diseases</i>	Prospective	73	34	39
Ng <i>et al.</i> (43)	Laparoscopic-assisted versus open abdominoperineal resection for low rectal cancer: a prospective randomized trial	2008	<i>Annals of Surgical Oncology</i>	Prospective	99	51	48
Lujan <i>et al.</i> (44)	Randomized clinical trial comparing laparoscopic and open surgery in patients with rectal cancer	2009	<i>Surgical Endoscopy</i>	Prospective	204	101	103
Liang <i>et al.</i> (45)	Effectiveness and safety of laparoscopic resection versus open surgery in patients with rectal cancer: a randomized, controlled trial from China	2011	<i>Journal of Laparoendoscopic & Advanced Surgical Techniques</i>	Prospective	343	169	174
Ng <i>et al.</i> (46)	Laparoscopic-assisted versus open total mesorectal excision with anal sphincter preservation for mid and low rectal cancer: a prospective, randomized trial	2014	<i>Surgical Endoscopy</i>	Prospective	80	40	40
Fujii <i>et al.</i> (47)	Short-term results of a randomized study between laparoscopic and open surgery in elderly colorectal cancer patients	2014	<i>Surgical Endoscopy</i>	Prospective	200	100	100

Table 3 Multicentric randomized trials on rectal cancer resection

Author	Title	Year	Journal	Type	Patients	Lap	Open
Guillou <i>et al.</i> (48)	Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicenter, randomized controlled trial	2005	<i>Lancet</i>	Prospective	794	526	628
van der Pas <i>et al.</i> (49)	Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial	2013	<i>Lancet Oncology</i>	Prospective	1,103	739	364
Kang <i>et al.</i> (50)	Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial.	2014	<i>Lancet Oncology</i>	Prospective	340	170	170
Fleshman <i>et al.</i> (51)	Effect of laparoscopic-assisted resection versus open resection of stage II or III rectal cancer on pathologic outcomes: the ACOSOG Z6051 randomized clinical trial	2015	<i>JAMA</i>	Prospective	462	240	222
Stevenson <i>et al.</i> (52)	Effect of Laparoscopic-Assisted Resection versus open resection on pathological outcomes in rectal cancer: the ALaCaRT randomized clinical trial	2015	<i>JAMA</i>	Prospective	475	238	237

RCT, randomized controlled trial.

Table 4 Meta-analyses on rectal cancer resection

Author	Title	Year	Journal	Patients	Lap	Open
Aziz <i>et al.</i> (53)	Laparoscopic versus open surgery for rectal cancer: a meta-analysis	2006	<i>Annals of Surgical Oncology</i>	2,071	909	1,162
Gao <i>et al.</i> (54)	Meta-analysis of short-term outcomes after laparoscopic resection for rectal cancer	2006	<i>International Journal of Colorectal Disease</i>	643	285	358
Bonjer <i>et al.</i> (55)	Laparoscopically assisted versus open colectomy for colon cancer: a meta-analysis	2007	<i>Archives of surgery</i>	1,765	796	740
Anderson <i>et al.</i> (56)	Oncologic outcomes of laparoscopic surgery for rectal cancer: a systematic review and meta-analysis of the literature	2008	<i>European Journal of Surgical Oncology</i>	2,178	1,403	1,775
Gong <i>et al.</i> (57)	A meta-analysis of clinical outcomes after laparoscopic operation for rectal cancer	2010	<i>Chinese Journal of Gastrointestinal Surgery</i>	2,850	1,145	1,705
Ohtani <i>et al.</i> (58)	A meta-analysis of the short- and long-term results of randomized controlled trials that compared laparoscopy-assisted and conventional open surgery for rectal cancer	2011	<i>Journal of Gastrointestinal Surgery</i>	2,095	1,096	999
Huang <i>et al.</i> (59)	Laparoscopic-assisted versus open surgery for rectal cancer: a meta-analysis of randomized controlled trials on oncologic adequacy of resection and long-term oncologic outcomes	2011	<i>International Journal of Colorectal Disease</i>	1,033	–	–
Ng <i>et al.</i> (60)	Long-term oncologic outcomes of laparoscopic versus open surgery for rectal cancer: a pooled analysis of 3 randomized controlled trials	2012	<i>Annals of Surgery</i>	278	136	142
Trastulli <i>et al.</i> (61)	Laparoscopic versus open resection for rectal cancer: a meta-analysis of randomized clinical trials	2012	<i>Colorectal Disease</i>	1,544	841	703
Arezzo <i>et al.</i> (62)	Laparoscopy for rectal cancer reduces short-term mortality and morbidity: results of a systematic review and meta-analysis	2013	<i>Surgical Endoscopy</i>	4,539	2,087	2,452
Ahmad <i>et al.</i> (63)	A systematic review and meta-analysis of randomized and non-randomized studies comparing laparoscopic and open abdominoperineal resection for rectal cancer	2013	<i>Colorectal Disease</i>	454	248	206
Vennix <i>et al.</i> (64)	Laparoscopic versus open total mesorectal excision for rectal cancer	2014	<i>The Cochrane Database of Systematic Reviews</i>	4,224	–	–
Zhang <i>et al.</i> (65)	Laparoscopic versus open surgery for rectal cancer: a systematic review and meta-analysis of randomized controlled trials	2014	<i>Asian Pacific Journal of Cancer Prevention</i>	3,045	1,804	1,241
Jiang <i>et al.</i> (1)	Laparoscopic versus open surgery for mid-low rectal cancer: a systematic review and meta-analysis on short- and long-term outcomes	2015	<i>Journal of Gastrointestinal Surgery</i>	3,678	–	–
Chen <i>et al.</i> (66)	Laparoscopic versus open surgery for rectal cancer: a meta-analysis of classic randomized controlled trials and high-quality nonrandomized studies in the last 5 years	2017	<i>International Journal of Surgery</i>	4,353	2,251	2,102

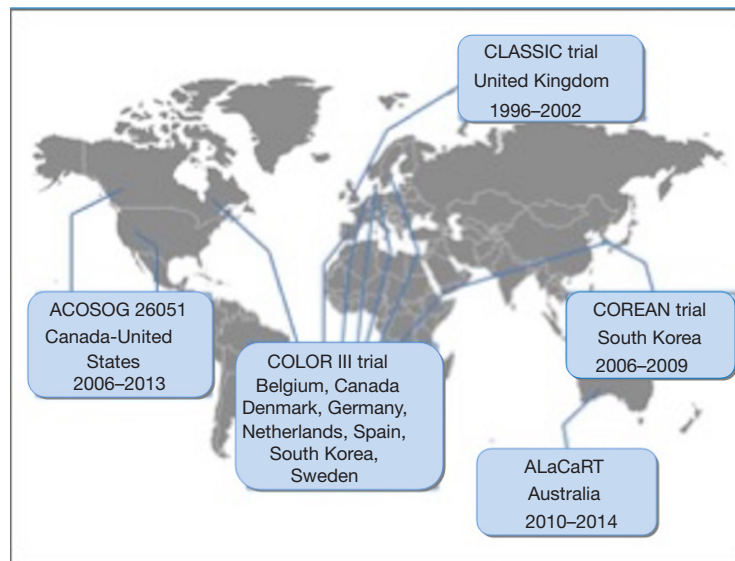


Figure 2 Multicentric studies designed and performed all over the world in the last 20 years.

surgery, Authors all over the world have compared the two techniques in terms of short- and long-term outcomes.

Most of these studies are non-randomized comparative (3–20) trials (NRCTs) (21–38). The findings of these studies were extremely encouraging, showing the non-inferiority of laparoscopy compared to the open technique in terms of oncological outcomes (like disease-free survival and local recurrence) and intraoperative and postoperative factors. Moreover the laparoscopic group presented advantages regarding antibiotic and analgesic therapy, early mobilization, hospital stay, intraoperative blood loss, resuming oral nutrition, bowel transit resumption, postoperative complications and wound complications, concluding that laparoscopic resection for rectal cancer is feasible, safe and effective.

To collect more accurate evidence about short- and long-term outcomes after laparoscopic surgery for rectal cancer compared to open surgery, a large number of randomized control trials (RCTs) have been produced in the last few years (39–47). Most of these studies focused on postoperative morbidity, length of hospital stay, quality of life, long-term survival, and local recurrences, finding no significant difference between the groups.

For an example, a recent study was developed by Ng *et al.* (43) who performed a single-center, prospective, randomized trial on 80 patients with mid and low rectal cancer, focusing on oncologic outcomes (in particular quality of the TME specimen, circumferential resection

margin (CRM) involvement, and number of lymph nodes removed), which were found similar between both groups.

The results assessed with these randomized trials seem to suggest that laparoscopic surgery for rectal cancer could improve short-term results while not jeopardizing the oncological outcomes compared with open surgery. The major limitation of these studies is that, being single-centered they are based on an exiguous number of patients.

To reach a wider number of patients multicentric studies have been designed and performed all over the world in the last 20 years (*Figure 2*).

In the CLASICC trial (48) 794 patients with colorectal cancer from 27 UK centers were enrolled to be treated by either laparoscopic or open surgery. Primary short-term end-points were positivity rates of circumferential and longitudinal resection margins and in-hospital mortality. In the CLASICC trial, regarding the cancer of the rectum, no significant difference in CRM positivity was detected in patients who underwent a rectal resection in both laparoscopic and open group. CRM positivity, instead, was significantly greater in laparoscopic than in the open surgery group for patients who underwent anterior resection. It is important to highlight that positive CRM is a strong predictor of both local recurrence and overall survival, since it is associated with a high rate of local recurrence and poor morbidity and mortality for rectal cancer patients (69). As a first conclusion, at the time of its first publication, the impair short-term outcomes after a laparoscopic approach

in an anterior resection of the rectum did not justify its routine use. Further studies about long-term outcomes of patient enrolled in the CLASICC trial, have been recently published focusing on the local recurrence, overall survival and disease-free survival (70,71). No significant differences between the laparoscopic and open approach were found in local recurrence, overall survival and disease-free survival after 3, 5 and 10 years follow-up. However, it is worth mentioning that the CLASICC trial (48) enrolled not only patients with rectal cancer but also patients with colon cancer, which may cause confusion on conclusions about rectal cancer.

Two other multicentric studies, aimed to compare laparoscopic and open surgery in patients with rectal cancer, were the COLOR II trial (49) and the COREAN trial (50), enrolling respectively 1,103 patients with rectal cancer within 15 cm from the anal verge and 340 patients with II and III mid- and low rectal cancer. Both studies demonstrated similar results in oncologic outcomes, disease-free survival and recurrence, confirming the safety and feasibility of the laparoscopic approach for rectal cancer. COLOR II trial was performed in 30 centers and hospitals from eight countries from 2004 to 2010. As expected, blood loss and recovery resulted better after the laparoscopic approach, even if it was connected to longer operative time. In terms of safety, completeness of the resection, positive CM (<2 mm) and median tumor distance to distal resection margin did not differ significantly between the groups. Also morbidity and mortality within 28 days after surgery were similar. So the authors concluded that laparoscopic surgery resulted in similar safety to open surgery and associated to a better recovery, if performed in selected patients treated by skilled surgeons.

The COREAN trial (50) was performed in three centers from 2006 to 2009 in South Korea. Its conclusions were similar to the COLOR II trial (49): although surgery time was longer in the laparoscopic group, no significant difference was found in the involvement of the CRM, macroscopic quality of the TME specimen, number of harvested lymph nodes, and perioperative morbidity, once again stating the efficacy and safety of laparoscopic rectal resection.

More recently, two multicentric studies have been published, introducing controversial conclusions about the non-inferiority of laparoscopic surgery compared with open surgery. In the ALaCaRT Randomized Clinical Trial conducted between 2010 and 2014, 475 randomized patients with T1–T3 rectal adenocarcinoma, underwent either laparoscopic [237] or open [238] rectal resection (52). The

primary end point was several oncological factors selected to an adequate surgical resection. A successful resection was achieved in 194 patients (82%) who underwent laparoscopic surgery and 208 patients (89%) who received open surgery. CRM was clear in 93% of patients in the laparoscopy group and in 97% who underwent open surgery. Distal margin was clear in 99% of cases in both groups, and TME was complete in 87% of patients in the laparoscopic surgery group and 92% in the open surgery group. Based on these findings the Authors concluded that, among patients with T1–T3 rectal tumors, there was not sufficient evidence to establish the non-inferiority of laparoscopic surgery compared to open surgery, so the choice of a laparoscopic approach for a patient with rectal cancer should be made with caution.

Similar evidence was found by Fleshman *et al.* in the ACOSOG Z6051 randomized clinical trial (51). A multicenter randomized trial enrolling patients from 35 institutions across United States and Canada, between 2008 and 2013. A total of 486 patients with a stage II or III rectal cancer within 12 cm from the anal verge were randomized after neoadjuvant therapy to receive a laparoscopic [240] or an open [222] resection. The aim of the study was to assess whether laparoscopic resection was not inferior to open resection, based on pathologic and histologic evaluation of the resected specimen. Successful resection occurred in 81.7% of laparoscopic resection cases and 86.9% of open resection cases and did not support the non-inferiority. These results too do not support the use of laparoscopic resection in patients with stage II or III rectal cancer.

It's important to notice that the chosen outcome to assess the efficacy of laparoscopic surgery in rectal cancer was a composite of a CRM greater than 1 mm, distal margin without tumor, and completeness of TME. This combination of short-terms outcomes has been arbitrarily chosen by the Authors and it still has to be proven its real impact on recurrence and long-term survival. So, both studies share the main limitation: the non-inferiority of laparoscopy compared to open surgery is based on the combination of completeness of TME and the positivity of CRM which, as short-terms outcomes, are only predictors of local recurrence. Long-terms outcomes are needed to define laparoscopy inferior compared to the traditional approach.

Moreover, although the results of the comparison between laparoscopy and open technique in terms of successful resection do not support the non-inferiority of laparoscopy, taken singularly, CRM and TME in the ALaCaRT trial are very close to be significant ($P=0.06$) and

Table 5 Oncologic outcomes on multicentric randomized trials on rectal cancer resection

Author	Protocol	Countries	Years	Number of patients	Distal margin	Completeness of TME	CRM	Long-term recurrence
Guillou <i>et al.</i> (48)	CLASICC	UK	1996–2002	794	Yes	No	Yes	Yes
van der Pas <i>et al.</i> (49)	COLOR II	Belgium, Canada, Denmark, Germany, Netherland, Spain, South Korea, Sweden	2004–2010	1,103	Yes	Yes	Yes	Yes
Kang <i>et al.</i> (50)	COREAN	South Korea	2006–2009	340	No	Yes	Yes	Yes
Fleshman <i>et al.</i> (51)	ACOSOG Z6051	United States, Canada	2008–2013	486	Yes	Yes	Yes	No
Stevenson <i>et al.</i> (52)	ALaCaRT	Australia	2010–2014	475	Yes	Yes	Yes	No

CRM, circumferential resection margin; TME, total mesorectal excision.

then equivalent in open and laparoscopic surgery.

Finally both studies do not take under consideration short-terms outcomes, like recovery, which has been worldwide demonstrated faster and associated with a lower rate of incidence of complications after laparoscopic surgery.

In the past 10 years meta-analytic studies have been performed to be able to give definitive results by pooling together a wide number of patients. Studies before the publication of ACOSOG and ALaCaRT protocols (51,52) stated the non-inferiority of laparoscopy compared to the open approach for rectal resection. Although their optimistic conclusions, we must underline how these studies share some limitations. Many of them, in fact, included non-RCT studies in the analysis that can lead to misleading results due to a selection bias.

The most recent meta-analytic study (72) has been published in February 2017, including ASOCOG and ALaCaRT trials (51,52), as well as 12 other unique RCTs with a total of 4,034 patients.

Including ALaCaRT e ACOSOG (51,52) the Authors came to the conclusion that the risk for achieving an incomplete mesorectal excision is significantly higher in patients undergoing laparoscopic rectal resection compared to the open technique, dampening the enthusiasm in support of laparoscopy for rectal surgery.

In conclusion, due to its impressive outcomes in terms of post-operative recovery and low rate of complication, laparoscopy has been seen for many years as the answer for rectal surgery. For the first time, after decades of certain advantages of laparoscopy, we are now witnessing the questioning of its equivalence to the traditional technique in terms of oncologic outcomes (Table 5). So the answers is yet to be found: to assess if the results of ongoing multicentric

RCTs have a real impact on the disease-free and overall survival of patients undergoing rectal surgery performed with laparoscopic technique, thus we will have to wait for their long-term results. Only in the next future, in fact, we will be able to assess if the failure of laparoscopy in these trials in terms of pathologic outcomes will bring to an actual increase of recurrence and mortality, alongside a shortage of the disease-free survival. This should give the rationale to perform new meta-analyses based on the new evidence produced. Moreover, even more multicentric RCTs studies, hypothetically designed on new pathological outcomes, should be performed to finally assess if laparoscopy is a valid choice for the treatment of rectal cancer.

Furthermore, the controversial findings we are facing could be explained by the fact that TME is challenging at baseline, working in the deep pelvis, with rigid instruments, from angles that require complicated maneuvers results even more difficult. It is possible that future developing of instruments, the introduction of different technologies such as robotics and the introduction of new techniques like taTME will improve efficacy of minimally invasive techniques and exceed the limitations of laparoscopy (12).

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Footnote

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