Conventional and/or laparoscopic rectal cancer surgery: what is the current evidence?

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Abstract: Despite many years of experience with laparoscopic procedures in rectal cancer, the superiority of minimally invasive approaches has been questioned especially in recent years. This article is a short review of the current knowledge about laparoscopic approaches in comparison to conventional modalities in patients with rectal cancer. To present the current state of the knowledge, we focused on reports that were published in the last few years and compared them to multicenter trials and meta-analyses published last year. Our analysis mainly applied to the primary end-points of these trials. We also included expert opinions that have been published in the last several months.

Keywords: laparoscopy; oncologic outcomes; open surgery; rectal cancer.

Introduction

The laparoscopic approach in abdominal surgery was introduced more than 20 years ago. Initially, the approach was used only as a diagnostic tool and in minor surgical procedures such as cholecystectomy and appendectomy. It was not surprising that after some years it was being used in more extensive procedures including colorectal surgery.

Minimally invasive procedures have become a standard in many surgical areas. In 1991, the laparoscopic resection of the colon was first described and reported [1, 2]. Currently, no one questions the superiority of laparoscopic modalities in acute and chronic cholecystitis, in hiatal hernias (Nissen procedure), or in patients with obesity (sleeve gastric resection). Their beneficial effect on short- and long-term outcomes in these patients is clear. In contrast, for 20 years, there is still a discussion on the differences between laparoscopic and open surgery for colon and rectal cancers [3]. During this period, several randomized controlled trials (RCTs) comparing short-term and late outcomes of laparoscopic and conventional procedures in colorectal cancer surgery have been published [4–8]. In the first decade since the first laparoscopic colonic resection was done, the results were similar regarding oncologic outcomes. These studies showed no differences in negative margins, similar number of harvested lymph nodes (LNs), tumor recurrence rate, and long-term overall survival (OS). In addition, the laparoscopic resection of the colon is associated with a faster recovery of bowel function, fewer analgesics used during the postoperative period, less blood loss during surgery, and shorter hospitalization.

In rectal cancer, the beneficial effect of laparoscopic procedures is still considered investigational. Some anatomical aspects of minor pelvis (innervation of urogenital organs and narrow spaces) and the need of neoadjuvant therapy in a part of patients make the surgery technically very demanding. Only proper mesorectal excision, achieving negative resection margins and autonomic nerve preservation, lead to good late oncologic and functional results.

Despite many years of experience with laparoscopic procedures in rectal cancer, the superiority of minimally invasive approaches has been questioned especially in recent years [9].

This article aimed to review the current knowledge about laparoscopic approach in patients with rectal cancer. To present the current state of the knowledge, we focused on reports that were published in last few years and compared them to multicenter trials and meta-analyses published last year. Our analysis mainly applied to the primary end-points of these trials.
**Oncological outcomes**

In the surgical oncology of rectal cancer, long-term results reflect the quality and efficacy of the whole treatment. The parameters investigated in trials include OS, disease-free survival (DFS), local recurrence (LR) rate, distant recurrence (DR) rate, number of harvested LNs, and circumferential resection margin (CRM) positivity rate. The last two variables (LNs and CRM) seem to be the most important for all surgeons because they show the quality of surgery.

**Data selection**

In this short review, we tried to show the oncologic results of laparoscopic and open procedures in rectal cancer published in systematic reviews and meta-analyses between 2008 and 2014 and in multicenter RCTs published last year. We searched the PubMed database for relevant articles. The database was looked through with the use of the terms “rectal”, “cancer”, “laparoscopy”, and “open” limited to “systematic review” and “meta-analyses” for the first period and “multicenter randomized trials” for the last year period. The search was also limited only to English language publications.

**Systematic reviews and meta-analyses**

In recent years, several meta-analyses and systematic reviews were published where the authors compared the quality of surgery and the oncological results between laparoscopic and conventional procedures in rectal cancer patients. Anderson et al. included 24 trials and analyzed 3158 patients. They found no statistical differences in odds ratio (OR; 72% for laparoscopic group and 65% for open-surgery group) and similar LR rates (7% for laparoscopic group and 8% for open-surgery group) [10].

Huang et al. reported and analyzed six RCTs, including 1033 patients (577 after laparoscopic resection and 456 after open abdomen procedures) with tumors located within 10 cm from the anal verge. They recorded no difference in relative risk (RR) for LR between groups [0.55; 95% confidence interval (CI), 0.22–1.40, p = 0.21]. Three-year OS and 3-year DFS were also similar (OS: hazard ratio (HR) 0.76, 95% CI 0.54–1.07, p = 0.11; DFS: HR 1.13, 95% CI 0.61–2.20, p = 0.64). OS was based on the results of four RCTs, and DFS was based on three RCTs [11].

In the studies of Ohtani et al. and Zhang et al. published in 2011 and 2014, the authors did not note any differences regarding CRM positivity, LNs harvested, LR, and DFS [12, 13]. Similarly, in the study of Jiang et al., the authors confirmed no significant differences as concerns LNs harvested, distal resection margin, positivity of CRM, LR and distal recurrence rates, and OS and DFS between laparoscopic and open procedures [14].

In the meta-analysis published by Ahmad et al., abdominoperineal resections (APR) done with both techniques were compared. The study included three RCTs and five non-RCTs. Based on non-RCTs, the LR rate was lower in laparoscopic APR (OR 3.205, 95% CI 1.002–10.251, p = 0.050). Such difference was not noted in RCTs (OR 2.216, 95% CI 0.580–8.468, p = 0.245). The overall (RCTs and non-RCTs) LR rate was lower in the laparoscopic APR group (OR 2.736, 95% CI 1.137–6.584, p = 0.025). The authors observed no differences in DR rates when they compared RCTs and non-RCTs separately, although the overall distance recurrence rate was significantly lower after laparoscopic APR (OR 1.994, 95% CI 1.062–3.742, p = 0.032) [15].

Arezzo et al. analyzed 27 studies and 8 RCTs (including 2659 patients). They found similar rates of CRM involvement (7.9% for laparoscopic technique and 6.9% for open procedures; RR 1.00, 95% CI 0.73–1.35 with no heterogeneity F = 0%). The authors concluded that, in rectal cancer, the short-term outcomes and oncological quality of laparoscopic techniques seem to be equal to open surgery. In selected patients with primary resected rectal cancer, comparable long-term results and oncological quality might indicate similar values of these two techniques [16].

All details of these meta-analyses are shown in Table 1.

Data from recently published meta-analyses are still inconclusive and do not give us a clear image of the beneficial effects of minimally invasive techniques in rectal cancer surgery. Summarizing only oncological data from these meta-analyses, we were unable to indicate a technique favorable to the patient. In most studies, any significant differences were found; thus, based on these results, any surgical guidelines cannot be pointed out. This means that further RCTs should be conducted or meta-analyzed to answer the question stated in the title of this paper.

**Multicenter randomized trials**

The temperature of our analysis rose when we compared the results of multicenter randomized trials, especially including the outcomes of trials published in 2015.
Table 1: Comparison of data from systematic reviews and meta-analyses.

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<tr>
<td>Anderson et al.</td>
<td>3158</td>
<td>72% vs. 65%, p = ns</td>
<td>N/A</td>
<td>7% vs. 8%, p = ns</td>
<td>13% vs. 14%, p = ns</td>
<td>5% vs. 8%, p = ns</td>
<td>1% vs. 0.6%, p = ns</td>
<td>10 vs. 11, p = 0.001</td>
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<td>Huang et al.</td>
<td>1033</td>
<td>HR 0.76, 95% CI 0.54–1.07, p = 0.11</td>
<td>HR 1.16, 95% CI 0.61–2.20, p = 0.64</td>
<td>RR 0.55, 95% CI 0.22–1.40, p = 0.83</td>
<td>N/A</td>
<td>7.9% vs. 5.4%, p = 0.63</td>
<td>0% vs. 0%</td>
<td>WMD –0.38, 95% CI –1.35 to 0.58, p = 0.43</td>
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<tr>
<td>Ohtani et al.</td>
<td>2095</td>
<td>N/A</td>
<td>OR 1.17, 95% CI 0.85–1.61, p = 0.35</td>
<td>OR 0.89, 95% CI 0.63–1.27, p = 0.52</td>
<td>OR 0.89, 95% CI 0.52–1.31, p = 0.41</td>
<td>OR 0.83, 95% CI 0.52–1.31, p = 0.41</td>
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<td>Ahmad et al.</td>
<td>454</td>
<td>RCTs: OR/WMD 1.167, 95% CI 0.403–3.377, p = 0.776; non-RCTs: OR/WMD 0.485, 95% CI 0.228–1.030, p = 0.060</td>
<td>N/A</td>
<td>OR 1.994, 95% CI 1.13–6.58, p = 0.025</td>
<td>RCTs: OR/WMD 0.696, 95% CI 0.111–4.355, p = 0.698; non-RCTs: OR/WMD 4.31, 95% CI 0.189–98.514, p = 0.36</td>
<td>RCTs: OR/WMD 0.696, 95% CI 0.111–4.355, p = 0.698; non-RCTs: OR/WMD 4.31, 95% CI 0.189–98.514, p = 0.36</td>
<td>N/A</td>
<td>RCTs: OR/WMD 2.205, 95% CI –2.554 to 6.965, p = 0.364; non-RCTs: –0.966, 95% CI –5.638 to 3.706, p = 0.685</td>
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<td>Arezzo et al.</td>
<td>10,861</td>
<td>N/A</td>
<td>RCTs + non-RCTs: 4.1% vs. 5.0%, RR 0.77, 95% CI 0.43–1.36, p = 0.366</td>
<td>N/A</td>
<td>RCTs + non-RCTs: 8.0% vs. 12.7%, RR 0.68, 95% CI 0.59–0.79, p &lt; 0.001</td>
<td>&lt;1 mm; RCTs + non-RCTs: 1.0% vs. 1.2%, RR 0.73, 95% CI 0.41–1.31, p = 0.292</td>
<td>&lt;1 mm; RCTs + non-RCTs: 1.0% vs. 1.2%, RR 0.73, 95% CI 0.41–1.31, p = 0.292</td>
<td>&lt;1 mm; RCTs + non-RCTs: 1.0% vs. 1.2%, RR 0.73, 95% CI 0.41–1.31, p = 0.292</td>
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Lap., laparoscopic procedure; Op., open abdomen procedure; WMD, weighted mean difference.
All colorectal specialists were looking forward to the results of the COLOR II study [17]. Finally, the outcomes were published in one of the most prestigious medical journals (New England Journal of Medicine). The international trial was conducted in 30 hospitals with a total number of 1044 included patients (699 after laparoscopic resection and 345 after open resection; 2:1 ratio). All patients with T3/T4 tumors within 2 mm of the endopelvic fascia (computed tomography or magnetic resonance imaging) were excluded from the study. After 3 years of follow-up, the LR rates were equal in both groups and amounted to 5.0% (difference 0.0%, 90% CI –2.6 to 2.6). The DFS rates were 74.8% in the laparoscopic group and 70.8% in the open-surgery group (difference 4.0%, 95% CI –1.9 to 1.9). The OS rates were 86.7% in the laparoscopic group and 83.6% in the open-surgery group (difference 3.1%, 95% CI –1.6 to 1.0). All details are shown in Table 2. The authors concluded that the laparoscopic approach in rectal cancer is associated with similar outcomes as the conventional approach regarding the rates of LR, DFS, and OS. We could agree with this, but after a careful analysis of the COLOR II study some details appeared that made this conclusion questionable. In the open-surgery group, the rate of patients in the UICC III and IV stage was about 2% more than in the laparoscopic group. All inclusion and exclusion criteria to the COLOR II study have been published earlier [20]. However, the most surprising difference concerned the rates of CRM involvement and LR in low rectal cancer (below 5 cm from the anal verge). In the laparoscopic group, the rate of CRM involvement was 9.0%. In the open-surgery group, the CRM positivity rate amounted to about 22% (difference –12.4%, 95% CI –23.2 to –3.0). The rate in the open-surgery group is unacceptable because it means that every fifth of all operated patients with low tumor underwent a nonradical procedure; thus, the quality of conventional surgery should be questioned. In tumors of the middle rectum (between 5 and 10 cm from the anal verge), the differences were reversed (10.0% in the laparoscopic group vs. 3.0% in the open-surgery group; difference 6.2%, 95% CI 0.1–11.2). It allowed to obtain nonsignificant differences regarding the CRM positivity rates in the whole group. Not surprisingly, the rate of CRM involvement directly influenced 3-year LR rates. In low tumors, the LR rate amounted to 4.4% in the laparoscopic group and 11.7% in the open-surgery group (difference –7.3%, 95% CI –13.9 to –0.7), and in lesions of the middle rectum, it was 6.5% in the laparoscopic group and 2.4% in the open-surgery group (difference 4.1%, 95% CI 0.7–7.5). The reversion made the differences in LR rates nonsignificant for the whole group.

The authors reported that these differences in the rate of CRM involvement might be clarified by better visualization during dissection in laparoscopic approaches, especially in the deep pelvic area. We realized that the outcomes from the COLOR II study came from specialized laparoscopic centers; however, such high rate of CRM involvement in the conventional group is quite difficult to explain. There is still a lack of trials focused more on oncologic outcomes than on technical points; therefore, the authors should be congratulated for their efforts.

The ACOSOG Z6051 is another very important multicenter randomized trial published last year [18]. The study was conducted in 35 centers in the United States and Canada and included only patients after neoadjuvant treatment (stages II and III). The main end-point was to achieve successful resection defined as some number of measurements: (a) CRM with a minimum of 1 mm of uninvolved tissue, (b) distal resection margin without tumor, (c) CRM with a minimum of 1 mm of uninvolved tissue, (d) distal resection margin without tumor.
and (c) completeness of mesorectal excision (TME). The trial was designed in the “noninferiority” model. The “noninferiority” model allows to compare two applied methods of treatment and answers if the tested method is not worse than the comparator. The authors chose 6% noninferiority margin as the clinically significant difference between the laparoscopic and conventional groups. A successful resection according to the definition was achieved in 81.7% of laparoscopic specimens (95% CI 76.4–86.9%) and 86.9% of specimens after conventional surgery (95% CI 76.8–86.6%). The difference did not meet noninferiority criteria (difference –5.3%, 95% CI –10.8 to ∞, p = 0.41 for noninferiority). Additionally, the operative time was significantly longer in the laparoscopic group (266.2 vs. 220.6 min; difference 45.5 min, 95% CI 27.7–63.4, p < 0.01; Table 2). The length of hospital stay and the rate of severe postoperative complications and readmissions within 30 days after surgery did not differ significantly. The authors (many of them with big and significant names in colorectal cancer surgery) claimed that the findings do not support the use of laparoscopic techniques in patients with stages II and III rectal cancer. Analyzing the results of the ACOSOG Z6051, we agreed with the authors’ opinion; however, the authors recognized the noninferiority margin (delta) at the quite low level of 6.0%.

The results of the third multicenter study came from 24 sites in Australia and New Zealand [Australian Laparoscopic Cancer of the Rectum (ALaCaRT) study] and included 475 patients with T1 to T3 rectal cancer [19]. Patients were operated on by 24 accredited surgeons. Similar to Z6051, this study was designed in the “noninferiority” model with the boundary set at the 8.0% level. The differences between the rates of CRM involvement, clearance of distal resection margins, and completeness of TME were not statistically significant. Successful resection criteria, similar to the previously mentioned study, were achieved at 82.0% in the laparoscopic group and 89% in the open-surgery group (difference –7.0%, 95% CI 12.4% to ∞, p = 0.39 for noninferiority). These findings did not reach the criteria for noninferiority.

In conclusion, the authors wrote that there was no sufficient evidence for routine use of laparoscopic approach in patients with T1 to T3 rectal cancer. They claimed that one of the reasons for these results was the fact that for the resection of the rectum the deep and narrow pelvic space is a challenging area for rigid and straight laparoscopic tools. They also noted that access to this difficult anatomical area might be better with the use of open techniques. The authors established the “noninferiority” margin at the level of about 2.0% more than in the ACOSOG Z6051; likewise, their results did not reach noninferiority criteria. It allowed us to confirm that laparoscopic approaches should not be recommended to a very wide group of patients with rectal cancer. In the same issue of JAMA in the editorial, Strong and Soper wrote, “The studies do not signal a moratorium on these approaches, but surgeons must proceed in a judicious manner to ensure that patients are informed about the benefits and risks associated with minimally invasive and open operations” [21].

Chand et al. recognized no clear scientific and medical evidence to offer laparoscopic approaches to all patients with rectal cancer. All recently published trials have not shown that laparoscopy is a better option for patients with rectal cancer. They did not find any confirmed advantages of this modality compared to open procedures. They also noted that laparoscopy suffers from the rigidity of its straight tools, which enables to achieve some angles and to perform complicated maneuvers in the deep and narrow pelvis [22].

In our opinion, laparoscopic approaches in rectal cancer are challenging. These three multicenter trials published last year are well designed and included only specialized colorectal surgeons; nevertheless, their results did not meet the criteria of noninferiority (Z6051 and ALaCaRT studies). Based on these results and the opinions of the experts, we would not offer laparoscopic techniques to patients with tumor located in the low rectum. It might be oncologically safe mainly in upper rectal tumors and safe only in experienced surgical hands. Further multicenter randomized trials have to be planned to compare these two approaches. Some further technological studies should be conducted to invent improvements in laparoscopic instruments to make the laparoscopic approach easier, especially in patients with low rectal cancer.

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Author Contributions
Design of the study: Adam Dziki; Data retraction: Łukasz Dziki, Michal Mik; Data analysis: Łukasz Dziki, Michal Mik; Writing of the manuscript: Michal Mik; Revision of the manuscript: Adam Dziki; Approval of the manuscript: Adam Dziki, Łukasz Dziki, Michal Mik.
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