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ORIGINAL ARTICLE

Comparison of recurrence patterns of colorectal cancer in laparoscopic and open surgery groups of patients: A meta-analysis

Aleksandar Karanikolic[1,2], Ilija Golubovic[1,2], Milan Radojkovic[1,2], Milorad Pavlovic[2,3], Dusan Sokolovic[2,4], Predrag Kovacevic[2,5]

[1]General Surgery Clinic, Clinical Center Nis, Nis, Serbia; [2]Faculty of Medicine, University of Nis, Nis, Serbia; [3]Department of Thoracic Surgery, Clinical Center Nis, Nis, Serbia; [4]Institute of Biochemistry, Faculty of Medicine, University of Nis, Nis, Serbia; [5]Plastic and Reconstructive Surgery Clinic, Clinical Center Nis, Nis, Serbia

Summary

Purpose: *The purpose of this meta-analysis was to evaluate differences between laparoscopic and open surgery and also the development of local and distant colorectal cancer (CRC) recurrences in treated patients.*

Methods: *2,058 cases treated with laparoscopic surgery and 2,365 cases with open surgery from 20 included studies were analyzed, using the random-effects model. The mean difference and odds ratio (OR) with 95% confidence interval (95%CI) were calculated. An overall and a subgroup analysis was performed according to the type of cancer – colon or rectal, and we registered the operating time, number of dissected lymph nodes and need for intraoperative blood transfusion in the laparoscopic and open surgery group of patients.*

Results: *The operating time in the laparoscopic surgery group was significantly longer than in the open surgery group (mean difference 38.23 min). There was no significant differences in the number of dissected lymph nodes between the two groups when we pooled data for treatment of CRC (p=0.16). The OR of overall and local recurrences was significantly decreased in patients in the laparoscopic surgery group compared to those in the open surgery group (OR 0.83; 95%CI 0.70-0.98; p=0.03) and (OR 0.70; 95%CI 0.50-0.97; p=0.03), respectively. No significant differences were found between patients who underwent laparoscopic surgery and those that had open surgery for distant recurrences after CRC treatment.*

Conclusions: *There was statistically significant difference between laparoscopic or open surgery and development of local and overall CRC recurrences.*

Key words: *colorectal cancer, laparoscopic surgery, meta-analysis, open surgery, recurrences*

Introduction

Colorectal cancer (CRC) is the third most common malignancy in the world with nearly 1.4 million new cases diagnosed in 2012 [1]. Despite the growing development of cancer treatments, surgery is still the only curative treatment for patients with potentially curable CRC [2,3]. However, in almost half of all CRC patients after some time following CRC operations, the disease recurs with both local (4.9-23.5%) and distant metastases (6.4-48%), with increasing disease stage [4-6]. Although no definitive cause of these recurrences is described in the relevant literature, surgical trauma is considered as one of the risk factors among others, which is associated with the occurrence of the metastatic spread [7-9].

Lately, more focus is placed on minimally invasive surgical techniques. Since its starting in the 1991 [10], laparoscopic surgery (LS) of co-

Correspondence to: Aleksandar Karanikolic, MD, MSc, PhD. Bul. dr Zorana Djindjica 48t, 18000 Nis, Serbia.
Tel: +381 691495156, E-mail: pean@ptt.rs, aleksandarkaranikolic@gmail.com
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lon has become widely accepted for resection of colorectal malignancies. Advantageous over open surgery (OS), LS is associated with less postoperative pain, faster return of bowel function, and shorter hospital stay [11-13]. Despite long clinical success, it still remains unclear whether there is a difference between LS and OS in terms of the likelihood of recurrences. Some trials have shown LS is more effective with reduced disease recurrences than OC [14,15], whereas others have reported no difference between LS and OS [16,17]. Previous meta-analyses of literature data that addressed the issue of recurrences of CRC after LS and OS included small number of studies and detected no statistically significant differences [18-20].

The primary objective of this meta-analysis was to extend the current knowledge of recurrences of CRC, and to evaluate differences between the outcomes of LS or OS and the development of local and distant recurrences in treated patients. Additionally, secondary objective was the assessment of the risk of local and distant recurrences after LS or OS according to type of cancer – colon or rectal. Furthermore, operating time, number of dissected lymph nodes and need for intraoperative blood transfusion in the LS and OS group of patients were evaluated.

Methods

Study selection

During February 2016, we searched PubMed using the following key words: colorectal cancer, recurrences, laparoscopic surgery, open surgery, meta-analysis. No language restriction was imposed. The search was enriched by manual searches of the reference list of each article. Both randomized and nonrandomized prospective and retrospective studies were included in the meta-analysis. Abstracts of articles, narrative studies, letters to the Editors and cross-sectional studies were not included in this meta-analysis.

An article was relevant if it contained data reporting to patients with colon, rectal and colorectal cancer treated with LS or OS, and local recurrences and distant metastases. We identified a total of 132 articles of which 112 were excluded because these articles did not neet the criteria for inclusion in the present meta-analysis. At the end of the search 20 studies [13-17,21-35] remained for analysis of differences between LS or OS based on cancer recurrence patterns (Figure 1).

Data analysis

The following data were registered: authors' last name; year of publication; study design; type of cancer (colon, rectal and colorectal); number of patients in LS or OS group; tumor stage; length of follow-up; therapy received; mean and standard deviation (SD) of operating time (min±SD), number of dissected lymph nodes (number±SD) for patients in LS and OS group; positive and total events for overall, local recurrences and distant metastases, as well as need for intraoperative blood transfusion in patients in the LS and OS group. Recurrences were classified as local recurrences (tumor restricted to the anastomosis or the region of primary operation). However, wound recurrences and port/extraction site recurrences were not included in local recurrences. Some studies had the principle that patients converted from the LS group to the OS group remained in the laparoscopic group for analysis. Some of relevant articles included only data on CRC. These data was used in the overall but not in the subgroup analysis.

Statistics

The summary mean difference (MD) with 95% CI for operating time and the number of dissected lymph nodes, and OR with 95% CI for overall, local and distant recurrences, as well as need for intraoperative blood transfusion in patient in LS and OS group were calculated for colon, rectal, and for colorectal cancer. If an article included data on more than one type of cancer, separate data was used whenever possible. For studies that included data in the form of median and range, we calculated mean and standard deviation as described by Hozo et al. [36].

DerSimonian-Laird method for the random-effects model was used to compute the outcome of study-specific MD and OR [37]. To assess statistical heterogeneity among studies, we used the Q and I^2 statistics [38].

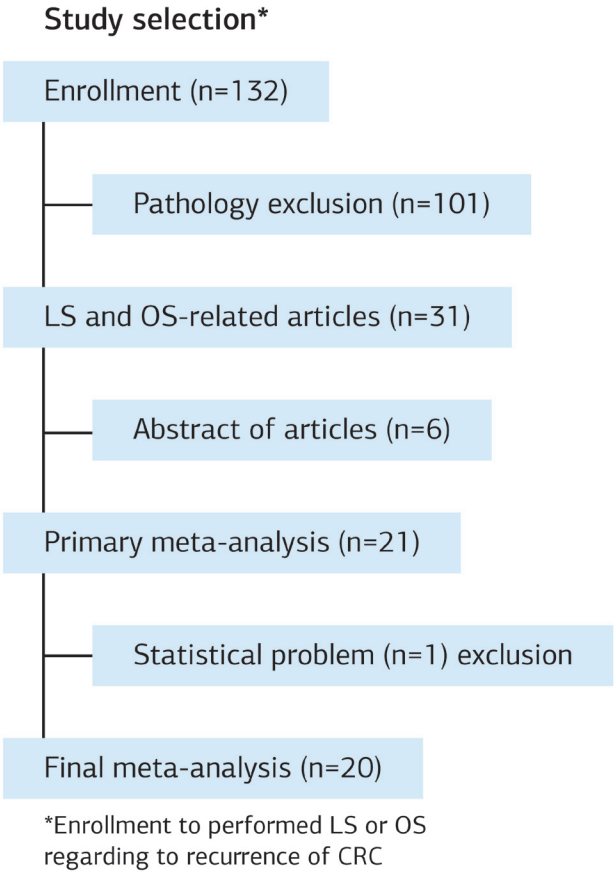

Figure 1. Study selection process with number of included studies in this meta-analysis.

Table 1. Characteristics of included studies

Study	*Study design*	*Type of cancer*	*No. of patients**		*Tumor stage*	*Follow-up*	*Therapy received***
			LS	*OS*			
Milsom [13] (1998)	Prospective randomized trial	Colorectal	55	54	I-IV (TNM)	Median, 1.5 years (LS); 1.7 years (OS)	NR
Curet [21] (2000)	Prospective randomized trial	Colon	18	18	A-D (Dukes)	Mean, 4.9 years	NR
Hartley [22] (2000)	Prospective comparative trial	Colorectal	57	52	A-D (Dukes)	Median, 42 months	Adjuvant chemotherapy and postoperative radiotherapy
Lacy [14] (2002)	Randomized trial	Colon	111	108	I-IV (TNM)	Median, 44 months (LS); 43 months (OS)	Adjuvant chemotherapy
Patankar [16] (2003)	Prospective, non-randomized, longitudinal cohort study	Colorectal	172	172	I-IV (TNM)	Mean, 52 months (LS); 59 months (OS)	Neoadjuvant and adjuvant chemotherapy and radiotherapy
Araujo [17] (2003)	Prospective randomized trial	Rectal	13	13	A-D (Astler-Coller)	Mean, 47.2 months	All patients underwent chemoradiation before surgery
Feliciotti [23] (2003)	Prospective, non-randomized comparative trial	Rectal	48	33	A-C A-D (Dukes)	Mean, 43.8 months	All patients underwent chemoradiation before surgery
Kojima [24] (2004)	Retrospective, non-randomized clinical trial	Colorectal	58	130	II-III (TNM)	Median, 56 months (LS); 56.5 (OS)	NR
Nelson [25] (2004)	Multicentre randomised controlled noninferiority trial	Colon	435	428	0-IV (TNM)	Median, 4.4 years	Adjuvant postoperative chemotherapy
Braga [26] (2005)	Randomized trial	Colorectal	190	201	I-IV (TNM)	60 months	Adjuvant chemotherapy
Liang [27] (2006)	Randomized controlled trial	Colon	135	134	II-III (TNM)	Median, 40 months	Adjuvant chemotherapy
Lacy [15] (2008)	Randomized clinical trial	Colon	106	102	I-III (TNM)	Median, 95 months (LS); 91 months (OS)	Adjuvant therapy
Ströhlein [28] (2008)	Prospective non-randomized analysis	Rectal	89	275	I-IV (UICC)	Mean, 31.1 months (LS); 32.6 months (OS)	Neoadjuvant radiochemotherapy; Postoperative chemotherapy
Ng [29] (2008)	Prospective randomized trial	Rectal	51	48	I-IV (AJCC)	Median, 87.2 months (LS); 90.1 months (OS)	Without preoperative therapy; Postoperative therapy - NR
Park [30] (2009)	Comparative prospective analysis	Rectal	107	72	I-III (TNM)	Mean, 36 months	Neoadjuvant and adjuvant chemoradiation therapy
Sambasivan [31] (2010)	Retrospective study	Rectal	24	66	I-IV (TNM)	Mean, 19 months (LS); 26 months (OS)	Neoadjuvant and adjuvant chemoradiation therapy
Lee [32] (2013)	Retrospective study	Rectal	80	80	I (TNM)	Median, 34 months (LS); 70 months (OS)	No patient received chemoradiotherapy preoperatively or postoperatively
Jeong [33] (2014)	Randomised controlled trial	Rectal	170	170	I-IV (TNM)	Median, 48 months (LS); 46 months (OS)	Neoadjuvant chemoradiotherapy and adjuvant chemotherapy; adjuvant radiotherapy – NR
Desiderio [34] (2014)	Prospective cohort study	Colon	28	27	I-III (TNM)	Mean, 67.9 months	NR
Zeng [35] (2014)	Prospective non-randomized trial	Rectal	112	182	I-IV (TNM)	Median, 29 months (LS); 29 months (OS)	Neoadjuvant therapy; Adjuvant therapy – NR

NR: not reported, AJCC: American Joint Committee on Cancer, UICC: International Union Against Cancer Tumor Classification, TNM: tumor/node/metastasis, LS : laparoscopic surgery , OS : open surgery; *lost to follow-up after surgery; ** not all patient received therapy

Heterogeneity was defined as mild (I^2 25%), as moderate (I^2 50%) and as severe (I^2 75%). Publication bias was identified by observation of funnel plots and was assessed by using Egger's test [39]. Statistical significance was defined for p value <0.05. All statistical analyses and graphs were performed using Comprehensive Meta-Analysis (Version 3; Biostat Inc, Englewood, NJ).

Results

A total of 20 studies were analyzed, that included 2,058 patients treated with LS and 2,365 patients treated with OS. The articles were published between 1998 and 2014. Details and characteristics are summarized in Table 1.

Operating time

The operating time in the LS group was significantly longer than in the OS group (MD 38.23 min, 95%CI 25.48-52.16, p=0.00). The operative time duration for LS was significantly longer than for OS for both treatment of the colon (MD 40.5 min, 95%CI 26.15-54.84, p=0.00) and rectal cancer (MD 28.09 min, 95%CI 8.21-64.4, p=0.13). There was statistically significant heterogeneity among studies (p<0.01) without evidence of publication bias assessed by Egger's test and based on the observation of funnel plot (Table 2).

Dissected lymph nodes

There was no significant differences in the number of dissected lymph nodes between the two groups when we pooled CRC data (MD -0.60, 95% CI -1.45-0.24, p=0.16). The number of dissected lymph nodes was significantly higher for patients in the OS group than for those in the LS group for rectal cancer (MD -0.58, 95% CI -3.91-2.75, p=0.73), but not for colon cancer (MD 0.73, 95% CI -0.55-2.02, p=0.26). There was statistically significant heterogeneity among studies (p<0.01). There was no evidence of publication bias assessed by Egger's test and based on the observation of funnel plot (Table 2).

Intraoperative blood transfusion

Patients in the OS group had significantly increased risk for intraoperative blood transfusion during treatment for rectal cancer (OR 0.45, 95% CI 0.24-0.85, p=0.01), as well as for CRC (OR 0.44, 95% CI 0.23-0.81, p=0.01). There was no statistically significant heterogeneity among studies and no evidence of publication bias assessed by Egger's test and based on the observation of funnel plot (Table 2).

Overall recurrences

The OR of overall recurrences was significantly decreased for patients in the LS group than for those in the OS group for both colon and rectal cancer treatment (OR 0.83, 95% CI 0.70-0.98, p=0.03). The OR of overall recurrences was significantly decreased for patients in the LS group than for those in the OS group for colon cancer treatment (OR 0.74, 95% CI 0.58-0.95, p=0.02), but not for rectal cancer treatment (OR 0.88, 95% CI 0.67-1.15, p=0.35). There was no statistically significant heterogeneity among studies and no evidence of publication bias assessed by Egger's test and based on the observation of funnel plot (Figure 2).

Table 2. Operating time, dissected lymph nodes and need for intraoperative blood transfusion in LS vs. OS

	Studies (No.)	*Effect size (95% CI)*	*p value*	*Heterogeneity*		*Egger's test (p value)*
				p value	*I^2 (%)*	
Operating time						
Colon cancer	4	40.5 (26.15-54.84)*	<0.01	<0.01	80.34	0.68
Rectal cancer	3	28.09 (-8.21-64.4)*	0.13	<0.01	92.85	0.35
Overall	7	38.23 (25.4-52.16)*	<0.01	<0.01	92.85	0.72
Dissected lymph nodes						
Colon cancer	5	0.73 (-0.55-2.02)*	0.26	0.12	44.55	0.05
Rectal cancer	5	-1.75 (-2.94- -0.56)*	<0.01	0.02	64.59	0.98
Colorectal cancer	3	-0.58 (-3.91-2.75)*	0.73	0.04	68.97	0.22
Overall	13	-0.60 (-1.45-0.24)*	0.16	<0.01	77.44	0.02
Need for intraoperative blood transfusion						
Rectal cancer	3	0.45 (0.24-0.85)**	0.01	0.59	0.00	0.65
Overall	4	0.44 (0.23-0.81)**	0.01	0.73	0.00	0.36

*Mean difference with corresponding 95% confidence interval (CI); **Odds ratio with corresponding 95% CI

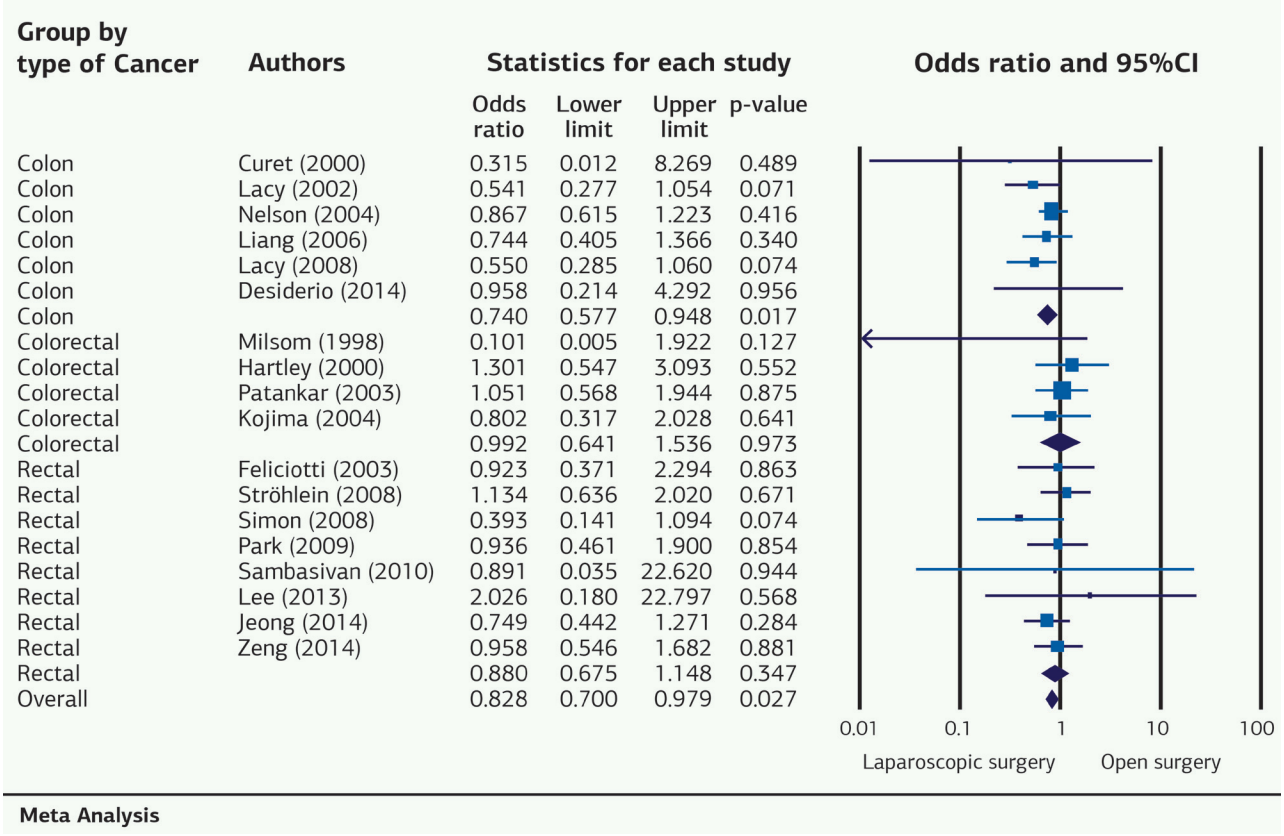

Figure 2. Comparison of overall recurrence patterns of colorectal cancer in laparoscopic and open surgery group of patients. Heterogeneity for overall: Q=11.46, p=0.83, I^2=0%.

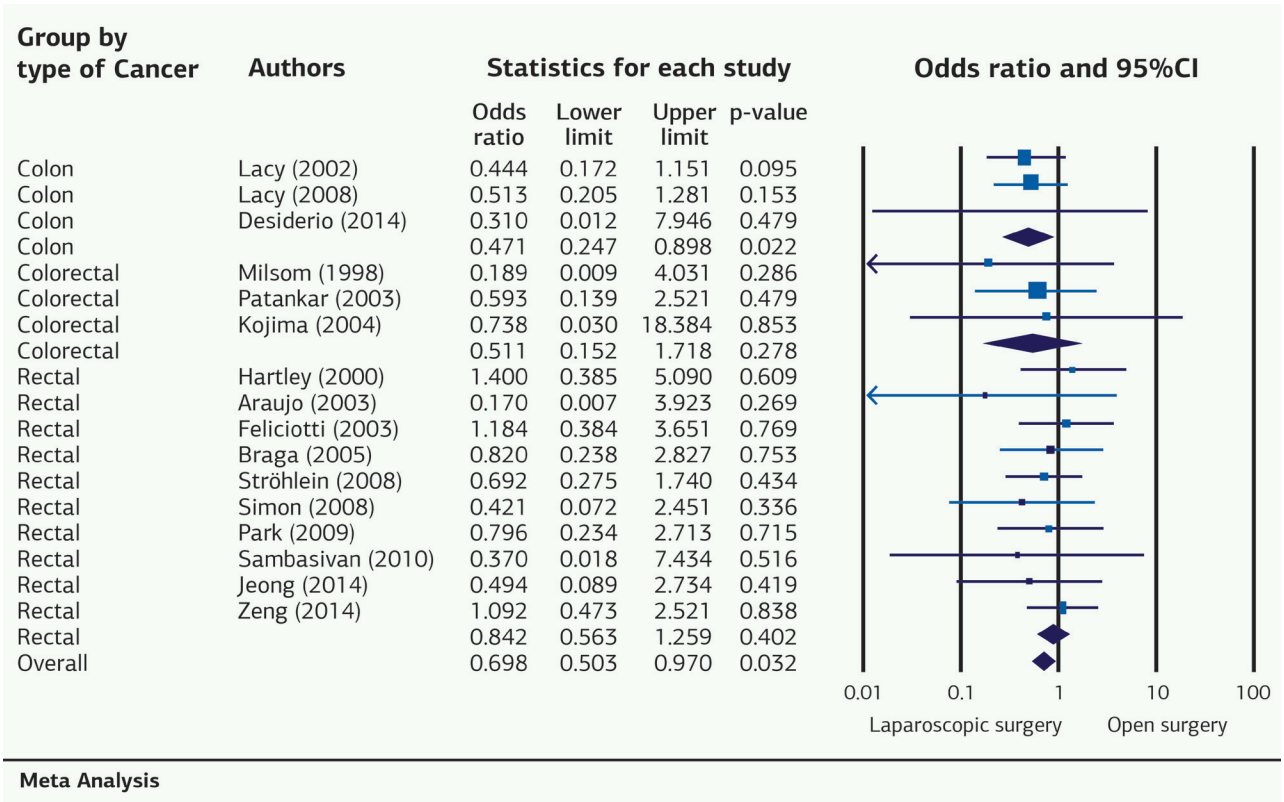

Figure 3. Comparison of local recurrence patterns of colorectal cancer in laparoscopic and open surgery group of patients. Heterogeneity for overall: Q=6.88, p=0.96, I^2=0%.

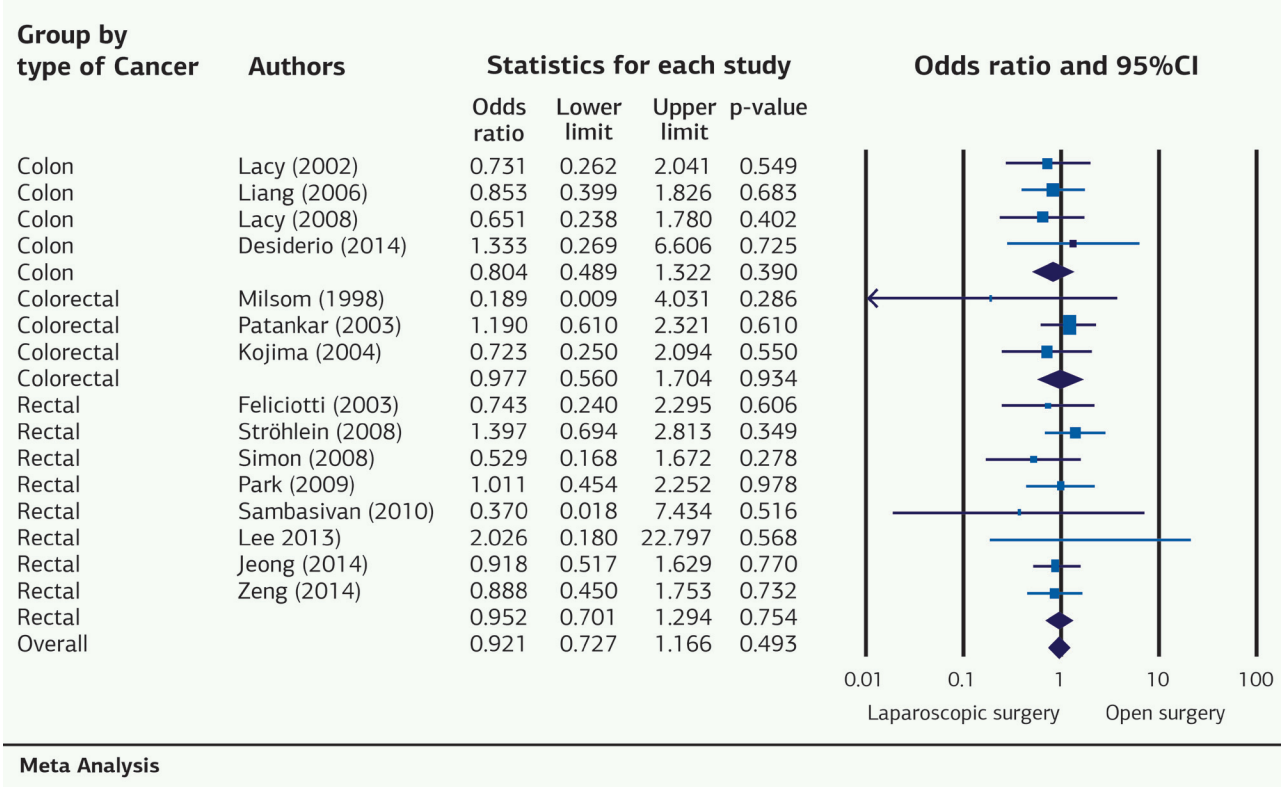

Figure 4. Comparison of distant recurrence patterns of colorectal cancer in laparoscopic and open surgery group of patients. Heterogeneity for overall: Q=5.91, p=0.97, I^2=0%.

Local recurrences

For patients in the LS group the OR of local recurrences was significantly decreased compared with those in the OS group for both colon and rectal cancer treatment (OR 0.70, 95% CI 0.50-0.97, p=0.03). The OR of local recurrences was significantly decreased for patients in the LS group than for those in the OS group for colon cancer treatment (OR 0.47, 95% CI 0.25-0.90, p=0.02), but not for rectal cancer treatment (OR 0.84, 95% CI 0.56-1.30, p=0.40). There was no statistically significant heterogeneity among studies and no evidence of publication bias assessed by Egger's test and based on the observation of funnel plot Figure 3).

Distant metastases

We found no significant differences between patients who underwent LS and those that had OS for distant metastases after both colon and rectal cancer treatment (OR 0.92, 95% CI 0.73-1.17, p=0.49). We also found no significant differences in distant metastases between the two groups when we pooled data for both treatments of the colon (OR 0.80, 95% CI 0.49-1.32, p=0.39) and rectal cancer (OR 0.95, 95% CI 0.70-1.29, p=0.75). There was no statistically significant heterogeneity among studies and no evidence of publication bias assessed by Egger's test and based on the observation of funnel plot (Figure 4).

Discussion

Previous studies investigating the effectiveness of LS and OS in the treatment of CRC, have undoubtedly shown numerous advantages for LS. The advantages are mainly related to shorter duration of hospital stay, less postoperative pain, shorter time required for resumption of oral intake, and reduction of intraoperative blood loss [40-42]. By the early 1990s, LS is experiencing steady growth [10,43]. Furthermore, advances in surgical techniques and improvements in laparoscopic instruments have allowed many colorectal operations to be performed using the laparoscopic technique. Today, LS is standard therapeutic protocol in many countries, because its implementation offers many benefits, and as importantly, causes a small surgical trauma. In recent years, surgical trauma is cited as one of the essential factors that can accelerate the rapid growth of cancer and lead to enhanced formation of metastases [44-46]. A possible explanation for this might be that cancer development and progress is based on the weakening of the immune response [47]. Therefore,

contribution to the field of risk for cancer recurrences, especially after open surgical procedures, would be important in problem solving i.e. whether there is any higher risk for recurrences after OS compared to LS, and if there is, how OS affects the cancer risk.

Due to the particularities of laparoscopic technique, instruments for laparoscopic surgery and videoscopic magnification, the operation time is significantly lengthened compared to the OS [48]. In order to approximate the operation time of LS to the operating time of OS, a good knowledge of the procedure and a significant experience of the surgeon is necessary. We have found that the operating time in the LS group was significantly longer than in the OS group for CRC treatment, but not for rectal cancer treatment. Our findings correlate with the previous reports of the differences in laparoscopic vs. open CRC resection [27,34,49,50].

The number of lymph nodes for staging colon and rectal cancer is a prognostic variable for outcome [51-53]. The literature [32,35,50,54] points out that the lack of differences in the number of harvested lymph nodes between the two groups may suggest that the quality of the operative method is the same for treatment of colon and/or rectal cancer. This finding corresponds to our results in overall analysis, which did not show statistically significant differences in terms of the number of harvested lymph nodes in LS and OS. However, the number of harvested lymph nodes in patients with rectal cancer who underwent LS was significantly less than in patients who underwent OS.

In this meta-analysis we summarized the data on development of cancer recurrences in patients that underwent either LS or OS. The most remarkable finding is the OR of overall recurrences for patients in the LS group that was significantly decreased compared with those in the OS group for both colon and rectal cancer treatment. According to subgroup analysis, it is crucial to note that, only for colon-related recurrences, statistically significant risk of overall recurrences was noted in the form of inverse association. Much research has been done on evaluating the safety and efficacy of laparoscopic compared to conventional approach for the surgical treatment of patients with CRC [13-17,21-35,55], and the literature shows a variety of results. The majority of the previous investigations have demonstrated that laparoscopically-assisted colon and/or rectal resection for malignant disease can be performed safely, but there was no difference in the recurrence patterns, patient survival and in terms of the number of the lymph nodes harvested compared to OS, and, in addition, longer follow-up is needed to fully assess oncologic outcomes [19,20,41]. The findings of the current study do not support these previous reports. A possible explanation for differences in relation to our analysis may be the lack of adequate number of studies included in meta-analyses.

The meta-analysis presented in 2008 by Liang et al., has shown that laparoscopic resection did not increase overall disease recurrence rates, local recurrence rates, distant metastasis rates and port or wounds recurrence rates following surgery for CRC resection when comparing open to laparoscopic surgery [19]. Furthermore, in 2011 Huang et al. suggested that there were no differences between laparoscopic-assisted and open surgery in terms of the number of lymph nodes harvested and local recurrence [20]. Unlike them, we have shown that OR of local as well as overall recurrences for patients in the LS group was significantly decreased than for those in the OS group for colon and rectal cancer treatment. However, the differences between these two surgical techniques were not statistically significant for distant metastases. It is difficult to explain this result, but it might be related to increased manual manipulation of tissues and organs during the performance of the OS. To our knowledge, this is the only meta-analysis which demonstrated the significant differences between LS and OS in terms of recurrences after CRC surgical treatment.

Despite numerous investigations with the aim of shedding light on the causes of frequent appearance of metastases in larger surgical trauma, the exact pathogenetic mechanism is still not known. In 2012 Lejeune described possible mechanisms involved in metastasis facilitation [7]. The trauma affects the immunological defense system, which play a key role in controlling tumor changes [7]. Furthermore, recent studies have focused on surgically-mediated decrease in natural killer cell activity as the major contributing factor associated with an increase in metastasis rates [47]. In addition, transfusion may have contributed to the increase in recurrence of various cancers. Blood transfusion promotes cancer progression affecting the immune response [56]. This study has been able to demonstrate that need for intraoperative blood transfusion was statistically significantly higher in the OS group, which was associated with increased risk of overall and local recurrences of CRC. These data must be interpreted with caution because of the small number of included studies with data on need for intraoperative transfusion.

The present study should be viewed with caution due to some limitations. First, some studies included in this meta-analysis had the principle

that patients converted from the LS group to the OS group remained in the laparoscopic group for analysis. A note of caution is due here since high conversion rate may lead to overestimation of the recurrence rate in the LS group. Second, not all patients received preoperative or postoperative therapy. Thus, preoperative chemoradiotherapy may decrease local recurrence rates in resectable rectal cancer compared with surgery alone [57]. Third, subgroup analyses could have been affected by small sample size. These results therefore need to be interpreted with caution. A fourth limitation of our analyses is that there was heterogeneity among the results for operating time and dissected lymph nodes from individual studies in the overall analysis. This heterogeneity may be due to variation in the different stages of tumor and the skills of the surgeons.

In conclusion, it is evident that this meta-analysis has shown the existence of statistically significant differences between performed LS or OS and the development of local and overall recurrences in colorectal as well as in colon cancer treated patients. Although this research has shown that OS had the benefits of reducing operating time, LS can be performed safely and the need for intraoperative blood transfusion was lower than for patients in the OS group in the overall analysis. We believe that our research will serve as a base for future studies on this issue. It is recommended that further research should be undertaken with more data on LS and OS and risk of tumor recurrence because more information on recurrence patterns would help us establish a greater degree of accuracy on this matter.

Ethical standards statement

For this type of study formal consent is not required (All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008).

Conflict of interests

The authors declare no conflict of interests.

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