

Long-term outcomes of laparoscopy vs. open surgery for colorectal cancer in elderly patients: A meta-analysis

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Abstract. The long-term outcome of laparoscopic surgery for geriatric patients with colorectal cancer remains unclear due to decreased functional reserves and increased medical comorbidities. A meta-analysis was performed in the present study to compare the long-term outcome between laparoscopy and laparotomy. Randomized controlled trials and comparative studies regarding laparoscopy vs. open surgery for colorectal cancer in elderly patients were searched in Pubmed, Embase, and Cochrane library between inception and April 20, 2017. The methodological quality of the cohort studies was evaluated using the Newcastle-Ottawa Scale. The meta-analysis was performed using Stata v12.0 software. Eight cohort studies were enrolled in the meta-analysis. Laparoscopic surgery was associated with a higher 3-year survival rate compared with open surgery [risk ratio (RR), 0.74; 95% confidence interval (CI), 0.61-0.90; P=0.003]. No significant difference was identified between laparoscopy and laparotomy regarding the 5-year survival rate (RR, 0.93; 95% CI, 0.78-1.11, P=0.424). The results of the meta-analysis indicated that the use of laparoscopic surgery on geriatric patients with colorectal cancer should be increased due to more improved long-term outcomes. All the studies included in the meta-analysis were case-control studies with selection bias and other confounding factors. Thus, larger sample sizes and multicenter randomized controlled trials are required to further validate the use of laparoscopic surgery as the preferred therapeutic option for elderly patients with colorectal cancer.

Introduction

Colorectal cancer is a common malignancy worldwide with approximately 1400,000 newly diagnosed cases and 694,000 cancer-related death cases (1). Due to the increasing life expectancy, earlier diagnosis and improved surgery, pre- and postoperative oncological treatment and regular checkups, the proportion of elderly colorectal cancer patients has been on the increase (2), reaching up to 75% as reported by Hermans *et al* (3). Elderly patients of colorectal cancer frequently experience decreased functional reserve and increased comorbidities such as cardiovascular and pulmonary diseases, which make them under-represented in clinical trials (2). In general colorectal cancer patients, laparoscopy can achieve shorter hospital stay, faster postoperative recovery, equal local recurrence rate, as well as disease-free and overall survival (4,5).

In elderly colorectal cancer patients, comparative clinical trials concerning laparoscopic vs. open surgery are limited. Several meta-analyses compared the short-term outcomes between laparoscopy and laparotomy for elderly colorectal cancer patients and concluded that laparoscopic surgery achieved less intraoperative blood loss (6), longer operating time (6), shorter length of hospital stay (6-8), lower postoperative morbidity and rapid bowel function recovery (6-8). To the best of our knowledge, no meta-analysis of laparoscopy vs. laparotomy has been performed with regard to long-term outcomes for elderly colorectal cancer patients.

In the present meta-analysis, we collected data from previous studies to perform a meta-analysis of laparoscopy vs. laparotomy concerning long-term outcomes for elderly colorectal cancer patients with the aim of selecting improved surgical techniques in this age subgroup.

Data collection methods

Search strategy. Studies were searched with regard to the comparison of long-term outcomes between laparoscopy and open surgery for elderly colorectal cancer patients from inception to April 20, 2017. The search strategy for Medline and other databases involved the following key words: (((('Colorectal Neoplasms' [MeSH] OR 'Rectal Neoplasms'[MeSH] OR 'Colonic Neoplasms'[MeSH] OR colectomy[Title] OR sigmoidectomy[Title] OR 'Colorectal

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Abbreviations: CI, confidence interval; RR, risk ratio; R, rectal cancer; C, colon cancer; CRC, colorectal cancer; CS, cohort study; lap, laparoscopy; Open, open surgery; NM, not mentioned

Key words: colorectal neoplasms, laparoscopic, open surgery, elderly

resection'[Title])) AND (laparoscopically[Title/Abstract] OR laparoscopic[Title/Abstract] OR laparoscopy[Title/Abstract]) AND (open[Title/Abstract] OR laparotomy[Title/Abstract]) AND (elder[Title/Abstract] OR elderly[Title/Abstract] OR old[Title/Abstract] OR aged[Title/Abstract] OR octogenarian[Title/Abstract] OR nonagenarian[Title/Abstract] OR octogenarians[Title/Abstract] OR nonagenarians[Title/Abstract] OR older[Title/Abstract]). Randomized control trials (RCTs), two-arm prospective studies, retrospective studies, and cohort studies were included. The reference list of potential studies was searched manually for eligibility by two independent reviewers, and if there was disagreement regarding inclusion, a third reviewer was consulted.

Inclusion criteria. Inclusion criteria for the study were: i) Research population was colorectal cancer patients who were ≥ 65 . ii) The intervention of the experimental and control groups was laparoscopy and open surgery, respectively. iii) The endpoints included a 3- or 5-year survival rate. iv) The study design was RCT or other comparative study.

Exclusion criteria. Exclusion criteria for the study were: i) Non-elderly colorectal cancer patients. ii) Any study without a control group. iii) The patients were limited to tumor stage I or II. iv) No long-term outcomes were described. v) Non-English articles were excluded.

Data extraction. Data extraction was crosschecked synchronously between two authors to rule out any discrepancy. The third author made a final decision for the discrepancy. The following data were independently extracted for each included study: first author's surname, publication year, age of patients, tumor location, 3- and 5-year survival rate. If no 3- and 5-year survival rates were given, it was read from the results of the Kaplan-Meier curve using Engauge Digitizer version 4.1 (<http://sourceforge.net/>). If data sets overlapped or were duplicated, only the most recent data were included. If it was necessary, the authors were contacted for additional information.

Evaluation of methodological quality. The methodological quality of the included cohort studies was evaluated according to the Newcastle-Ottawa Scale (NOS). The concrete content was as follows: selection of patients, comparability, and evaluation of results. The cohort study was evaluated as low quality when the score was ≤ 5 and excluded from our meta-analysis. By contrast, the study was evaluated as high quality when the score was ≥ 6 and included in our meta-analysis.

Endpoint. The primary endpoint included the 3- and 5-year survival rates.

Statistical analysis. Statistical analysis was carried out using Stata12.0 software (Chicago, IL, USA). Risk ratio (RR) was calculated to express the effect size of categorical variables such as the 3- and 5-year survival rate. I^2 statistic was used to show the heterogeneity between studies. The random effects model was used when there was obvious heterogeneity between studies ($I^2 \geq 50\%$). The fixed effect model was used when there was no obvious heterogeneity between studies ($I^2 < 50\%$).

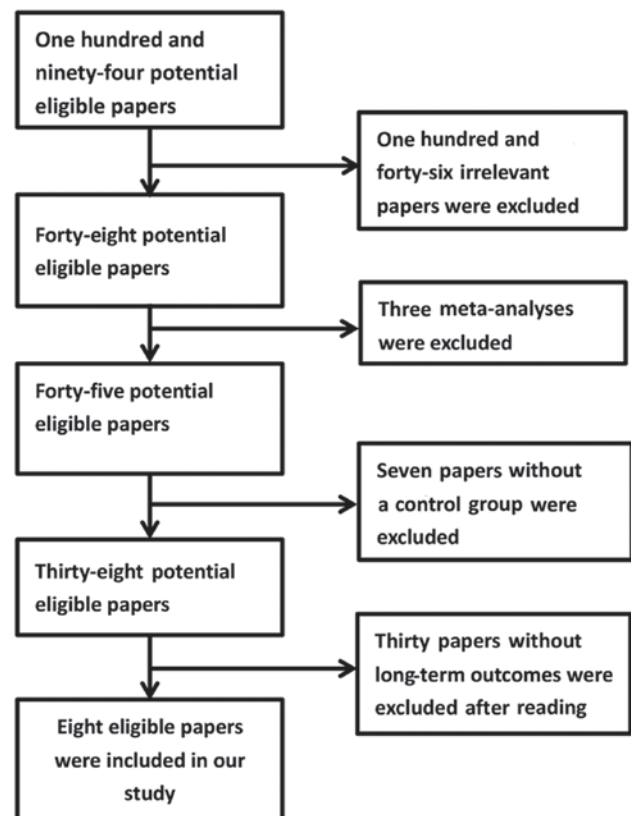


Figure 1. Flowchart of procedure selection.

The study was approved by Ethics Committee of Beijing Tiantan Hospital (Beijing, China). Publication consent is not applicable, since our paper does not contain any individual persons data. All data supporting the results are available.

Results

Eight cohort studies (9-16) were included in our meta-analysis. The selection procedure is shown in the flowchart of Fig. 1. No missing studies were found by reviewing the reference list of included articles. In total, 29,663 patients were incorporated in the 8 studies, in which 1,410 patients were in the laparoscopic group and the remaining 28,253 patients were in the open surgery group. Two studies limited the patient age to ≥ 65 (10,13). Other studies limited the patient age to ≥ 70 (9,11,12,14-16). Basic characteristics and methodological quality of included studies are shown in Table I.

Three-year survival rate. Eight cohort studies reported the 3-year survival rate in our meta-analysis (Table II) (9-16). One study showed the 3-year survival rate directly (12). Other studies showed the survival curve, by which the 3-year survival rate can be calculated (9-11,13-16). The I^2 value was 54.8%; thus, the random effects model was used to pool the 8 studies. The result indicated that laparoscopic surgery had a higher 3-year survival rate than open surgery (RR=0.74, 95% CI: 0.61-0.90, P=0.003) (Fig. 2).

Five-year survival rate. Six cohort studies reported a 5-year survival rate in our meta-analysis (Table II). Two

Table I. Basic characteristics and methodological quality of included studies.

Authors	Year	Age, years	Location	Study design	Total	Sample size			(Refs.)
						Lap	Open	Score	
Zeng <i>et al</i>	2015	≥70	R	CS	294	112	182	7	(16)
She <i>et al</i>	2013	≥75	C	CS	434	189	245	6	(14)
Altuntas <i>et al</i>	2012	≥70	R	CS	90	56	34	7	(9)
Robinson <i>et al</i>	2011	≥65	CRC	CS	242	47	195	6	(13)
Cummings <i>et al</i>	2012	≥65	C	CS	27,436	424	27,012	7	(10)
Hinoi <i>et al</i>	2015	≥80	CRC	CS	918	459	459	6	(11)
Moon <i>et al</i>	2016	≥80	CRC	CS	142	71	71	6	(12)
Shigeta <i>et al</i>	2016	≥80	CRC	CS	107	52	55	5	(15)

Location, tumor location; R, rectal cancer; C, colon cancer; CRC, colorectal cancer; CS, cohort study; Lap, laparoscopic surgery; Open, open surgery.

Table II. Long-term outcomes of 8 cohort studies.

Authors	3-year survival rate				5-year survival rate				(Refs.)
	LAP		OPEN		LAP		OPEN		
	Dead	Alive	Dead	Alive	Dead	Alive	Dead	Alive	
Zeng <i>et al</i>	11	101	38	144	NM	NM	NM	NM	(16)
She <i>et al</i>	60	129	93	152	81	108	127	118	(14)
Altuntas <i>et al</i>	13	43	20	14	24	32	25	9	(9)
Robinson <i>et al</i>	13	34	57	138	23	24	76	119	(13)
Cummings <i>et al</i>	155	269	10,751	16,261	212	212	13,803	13,209	(10)
Hinoi <i>et al</i>	70	389	93	366	123	336	105	354	(11)
Moon <i>et al</i>	14	57	18	53	21	50	26	45	(12)
Shigeta <i>et al</i>	5	47	13	42	NM	NM	NM	NM	(15)

LAP, laparoscopic surgery; OPEN, open surgery.

studies showed the 5-year survival rate directly (10,14). Other studies showed the survival curve, by which the 5-year survival rate can be calculated (9,11-13). The I^2 value was 67.5%; thus, the random effects model was used to pool the 6 studies. No statistical difference was found between laparoscopic surgery and open surgery with regard to the 5-year survival rate for the elderly colorectal cancer patients (RR=0.93, 95% CI: 0.78-1.11, P=0.424) (Fig. 3).

Publication bias. Funnel plot and Begg's test was used to evaluate the publication bias of the included studies. The shape of the funnel plot for the meta-analysis of studies on 3-year survival rate demonstrated symmetry (Pr >|z|=0.108) (Fig. 4).

Discussion

Colorectal cancer has become a disease of older age (2), which may be explained by the increased life expectancy of recent years (17). The decreasing functional reserve and

comorbidities in elderly patients highlight the significance of operation style selection. In general, laparoscopic surgery can achieve decreased surgical trauma, faster postoperative recovery (18,19) and equal long-term outcomes (4,5,20) for colorectal cancer patients. Current studies comparing laparoscopy and open surgery in elderly colorectal cancer patients are limited and retrospective, making the short- and long-term outcomes unclear.

To the best of our knowledge, there are 3 meta-analyses comparing the short-term outcomes following laparoscopic and open colorectal resections in elderly populations. Grailey *et al* pooled 11 studies and concluded the reduction in length of hospital stay, intraoperative blood loss, incidence of postoperative pneumonia, time to return of normal bowel function, incidence of postoperative cardiac complications, and wound infections in the elderly population (≥70) receiving laparoscopic colorectal resection (6). Li *et al* pooled 10 studies and concluded that laparoscopy can reduce the length of hospital stay, intraoperative blood loss, time to return of normal bowel

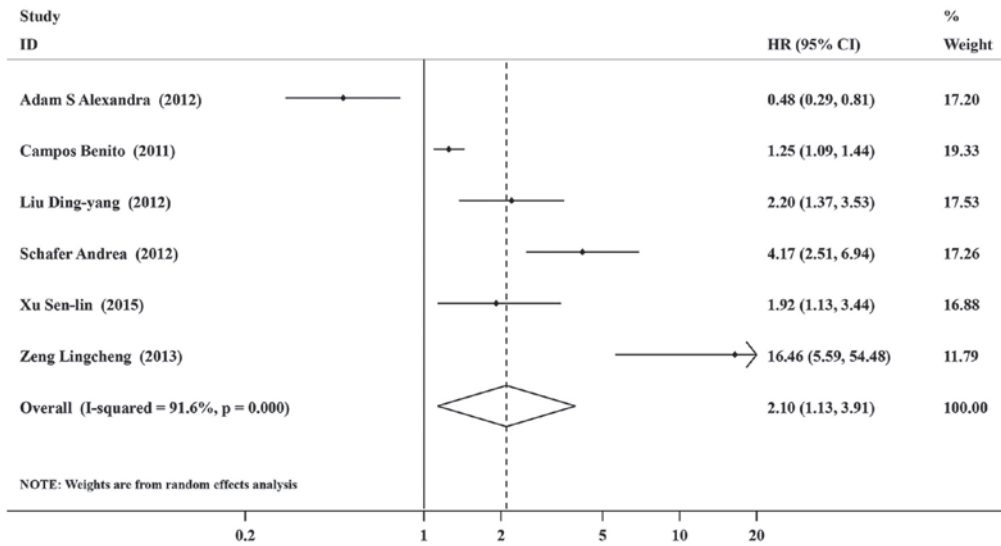


Figure 2. Meta-analysis of 3-year survival rate. RR, risk ratio; CI, confidence interval.

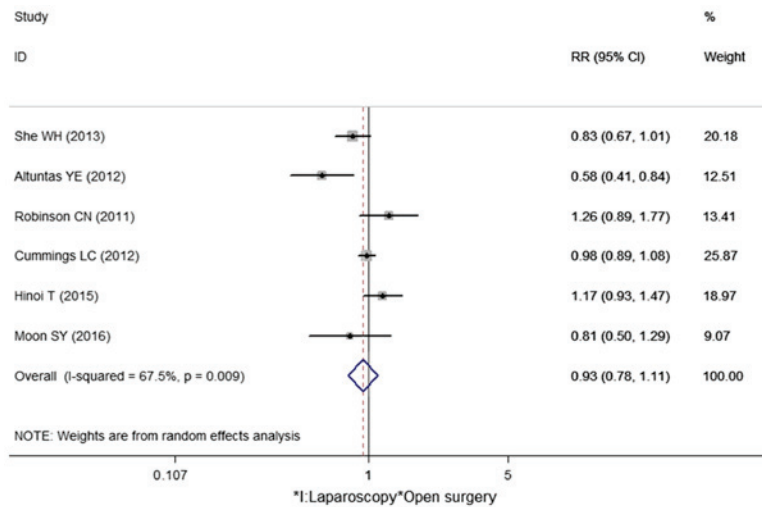


Figure 3. Meta-analysis of 5-year survival rate. RR, risk ratio; CI, confidence interval.

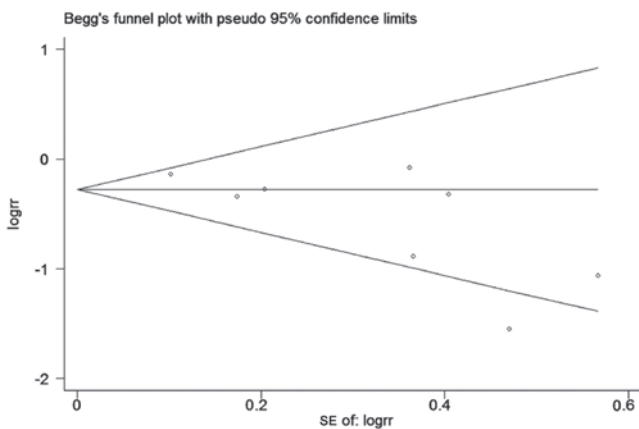


Figure 4. Funnel graph of included studies. SE, standard error; logrr, log risk ratio.

function, incidence of postoperative pneumonia, wound infection and postoperative ileus in the elderly population (≥ 80)

receiving laparoscopic colorectal resection (7). Xie *et al* performed a similar meta-analysis including 7 studies in octogenarian patients and concluded that the laparoscopic approach was associated with a lower rate of mortality, and prolonged ileus, quicker bowel function return, and shorter length of hospital stay (8). It is noteworthy that Xie *et al* found a lower rate of mortality in the laparoscopic group ($P=0.03$) (8), which is different from that identified by Grailey ($P=0.82$) (6) and Li *et al* ($P=0.05$) (7) in their respective meta-analyses. Thus, laparoscopic colorectal resection is associated with improved short-term outcomes, and the evidence was reinforced by several recent cohort studies (12,15,21). However, the above-mentioned meta-analyses did not report long-term outcomes.

We collected the previous comparative studies and performed a meta-analysis in long-term outcomes for elderly colorectal cancer patients. Our meta-analysis showed that, compared with open surgery, the laparoscopic surgery had a higher 3-year survival rate and an equivalent 5-year survival in elderly colorectal cancer patients. Koh *et al* performed a matched case-control study in octogenarian patients, and concluded that

patients who have undergone laparoscopic surgery were associated with a better 1-year survival rate (94.4 vs. 75.0%, $P=0.09$) compared with those who underwent open surgery (22). Of note is that the deaths in the open group were due to causes unrelated to surgery, the author explained the longer lasting effect of open surgery on physiological reserve may play an important role (22). In general population, no statistical significance was found in long-term outcomes between laparoscopic and open surgery (4,5,20,23). Jiang *et al* pooled 12 studies and found disease-free survival ($OR=1.80$, $P=0.18$) and overall survival ($OR=1.44$, $P=0.33$) were similar between laparoscopic and open surgery for low rectal cancer (24). Feinberg *et al* performed a similar meta-analysis for pT4 colon cancer patients and concluded there was no significant difference in overall survival (HR , 1.28; 95% CI, 0.94-1.72), and disease-free survival (HR , 1.20; 95% CI, 0.90-1.61) between laparoscopic and open surgery (25). Thus, the issue raised is why long-term outcomes are different between the general and elderly populations. One reason may be that the poorer function reserve and more serious comorbidities after larger trauma of open surgery may impair the anti-tumor ability of immunologic function, which may cause earlier tumor recurrence and cancer-related death. By contrast, elderly colorectal cancer patients with advanced disease (11,26,27), larger tumor size (15,27,28) and emergency events (10) are often advised to undergo open surgery, which may lead to the open surgery group having inferior outcomes.

There are limitations to our meta-analysis that should be considered. First, all our eligible studies are non-RCTs, which may have selection bias. Second, obvious heterogeneity has been found between studies on the 3- and 5-year survival, which may be explained by confounding factors such as tumor location, adjuvant chemotherapy, level of hospital stay and surgeon. Third, only 8 studies were included in our meta-analysis; thus a larger cohort is required to confirm the results. Fourth, the age was limited to individuals aged ≥ 65 in 2 studies (10,13), ≥ 70 in 2 studies (9,16), ≥ 75 in 1 study (14), and ≥ 80 in 3 studies (11,12,15). Varying age may play an important role on reliability. Fourth, the majority of the eligible studies did not show a 3- and 5-year survival rate directly, and this had to be estimated by survival curve, which may lead to errors. Finally, the difference of tumor location between eligible studies may also influence the reliability [colorectal cancer in 4 studies (11-13,15), colon cancer in 2 studies (10,14), and rectal cancer in 2 studies (9,16)]. However, we performed funnel plot and Begg's test to evaluate the publication bias of the included studies and no obvious publication bias was found, which demonstrated our meta-analysis was reliable.

Improved long-term outcomes have been found for the laparoscopic surgery group for elderly colorectal cancer patients in our meta-analysis. However, most of the previous studies are non-RCTs exhibiting selection bias. Consequently, large sample and multicenter RCTs are needed to identify the optimal operation style for elderly colorectal cancer patients.

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