

Similarities and differences between study designs in short- and long-term outcomes of laparoscopic versus open low anterior resection for rectal cancer: A systematic review and meta-analysis of randomized, case-matched, and cohort studies

Nobuaki Hoshino  | Yudai Fukui | Koya Hida | Kazutaka Obama

Department of Surgery, Kyoto University
Graduate School of Medicine, Kyoto, Japan

Correspondence

Nobuaki Hoshino, Department of Surgery,
Kyoto University Graduate School of
Medicine, 54 Shogoin-Kawahara-cho,
Sakyo-ku, Kyoto 606-8507, Japan
Email: hoshinob@kuhp.kyoto-u.ac.jp

Funding information

Kondou Kinen Medical Foundation

Abstract

Aim: Randomized controlled trials (RCT) are the gold standard in surgical research, and case-matched studies, such as studies with propensity score matching, are expected to serve as an alternative to RCT. Both study designs have been used to investigate the potential superiority of laparoscopic surgery to open surgery for rectal cancer, but it remains unclear whether there are any differences in the findings obtained using these study designs. We aimed to examine similarities and differences between findings from different study designs regarding laparoscopic surgery for rectal cancer.

Methods: Systematic review and meta-analyses. A comprehensive literature search was conducted using PubMed, Scopus, and Cochrane. RCT, case-matched studies, and cohort studies comparing laparoscopic low anterior resection and open low anterior resection for rectal cancer were included. In total, 8 short-term outcomes and 3 long-term outcomes were assessed. Meta-analysis was conducted stratified by study design using a random-effects model.

Results: Thirty-five studies were included in this review. Findings did not differ between RCT and case-matched studies for most outcomes. However, the estimated treatment effect was largest in cohort studies, intermediate in case-matched studies, and smallest in RCT for overall postoperative complications and 3-year local recurrence.

Conclusion: Findings from case-matched studies were similar to those from RCT in laparoscopic low anterior resection for rectal cancer. However, findings from case-matched studies were sometimes intermediate between those of RCT and unadjusted cohort studies, and case-matched studies and cohort studies have a potential to overestimate the treatment effect compared with RCT.

KEYWORDS

case-matched study, low anterior resection, randomized controlled trial, rectal cancer

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1 | INTRODUCTION

Observational studies inherently include confounding factors that can affect their results, and several differences have been noted between the findings of randomized controlled trials (RCT) and those of observational studies¹. For adequate comparison of interventions in observational studies, matching methods are frequently used in surgical research and the most common method is propensity score matching². First introduced by Rosenbaum et al, propensity score matching is expected to be an alternative to RCT^{3,4}, which are currently considered the gold standard in surgical research investigating the treatment effect of an intervention. Although it may be favorable to conduct RCT, this is often difficult to do for practical and ethical reasons in surgical research². In addition, RCT generally require substantial resources including time, money, and collaboration among diverse specialists in order to ensure patient safety, data correctness, and standardization of interventions.

Recently, nationwide databases such as the National Clinical Database (NCD) and the National Database (NDB) have become available, despite several restrictions on their use^{5,6}. If findings from case-matched studies are similar to those from RCT, case-matched studies using a nationwide database may supersede RCT. There are methodological differences between RCT and case-matched studies such as patient selection and adjustment for confounding factors^{7,8}. However, it remains unclear whether there are differences in findings between RCT and case-matched studies.

We aimed to investigate similarities and differences in findings between RCT, case-matched studies, and cohort studies regarding laparoscopic low anterior resection (LAR) for rectal cancer. LAR is defined as a procedure representing the performance of surgery in NCD⁵. These study designs have been used to investigate the potential superiority of laparoscopic LAR to open LAR for rectal cancer, which is of major interest to surgeons.

2 | METHODS

We conducted a systematic review and meta-analyses.

2.1 | Eligibility

Studies in which laparoscopic LAR was compared with open LAR for rectal cancer were eligible. When multiple surgical procedures were included in a study, studies in which over 70% of patients underwent LAR were included. Small studies that included less than 50 patients for each intervention group were excluded. Study design was restricted to RCT, case-matched study, or cohort study. Both prospective and retrospective studies were included, and the method of randomization or matching was not restricted. The language was restricted to English.

2.2 | Outcome measures

Short-term outcomes were the incidence of postoperative overall complications, the incidence of anastomotic leakage, mortality, re-operation rate, length of stay, operative time, estimated blood loss, and rate of positive circumferential resection margins. Long-term outcomes were 3-year overall survival (OS), 3-year disease-free survival (DFS), and 3-year local recurrence rate (LRR).

2.3 | Literature search and study selection

A comprehensive literature search was conducted on June 12, 2019, using PubMed, Scopus, and Cochrane Central Register of Controlled Trials. The search terms used were "rectal cancer", "anterior resection", "laparoscopy", "open", and related terms (Appendix S1). Duplications were excluded by checking the names of study authors, publication year, and study characteristics such as study design, setting, and period. Two review authors (NH and YF) independently screened the titles and abstracts of studies identified by literature search, and then assessed the full texts of potential eligible articles. Disagreement was resolved by discussion.

2.4 | Data extraction

The same authors (NH and YF) also independently extracted data from the included studies; the data included study design and setting, number and characteristics of patients, surgical procedure, and short- and long-term outcomes. Each double-checked the extracted data for the other, and any discordance between them was resolved by discussion. For cohort studies, unadjusted data were extracted to assess the results without adjusting for confounding factors.

2.5 | Statistical analysis

Data synthesis was carried out using Review Manager 5.3 (Cochrane Collaboration Software, Nordic Cochrane Centre). A random-effects model was used for all meta-analyses because of presumed heterogeneity in the surgical quality of LAR across the included studies. The Mantel-Haenszel method was used for dichotomous variables and inverse-variance weighting was applied for continuous variables. Risk ratio (RR) with 95% confidence interval (CI) was used for dichotomous variables in a meta-analysis. Risk difference (RD) was applied instead of RR when a rare outcome was assessed. Mean difference (MD) with 95% CI was used for continuous variables when a single measure was included in a meta-analysis. The median with range was converted to mean with standard difference (SD) by the method of Hozo et al.⁹ A two-sided *P*-value <.05 was considered statistically significant.



3 | RESULTS

3.1 | Characteristics of included studies

The comprehensive literature search identified 3229 articles. Of these, 1368 duplications were removed. Screening was conducted for 1861 articles by checking the titles and abstracts for the potential to be included in this review. After screening, the full text of 106 articles was checked to assess whether they met the inclusion criteria. Finally, 35 studies (40 articles) were included in this review (Figure 1)¹⁰⁻⁴⁹. Nine articles were reported from 4 RCT and were treated as 4 studies¹⁰⁻¹⁸. Included studies comprised 5 RCT, 10 case-matched studies, and 20

cohort studies. Four studies were conducted internationally and the remaining 31 were reported from 11 countries. One case-matched study was prospective and the remaining 9 were retrospective. Among cohort studies, 1 was prospective and 19 studies were retrospective (Table 1).

3.2 | Short-term outcomes

3.2.1 | Incidence of overall postoperative complications

Twenty-four studies with 9881 patients including 4 RCT with 2012 patients, 6 case-matched studies with 2939 patients, and 14 cohort

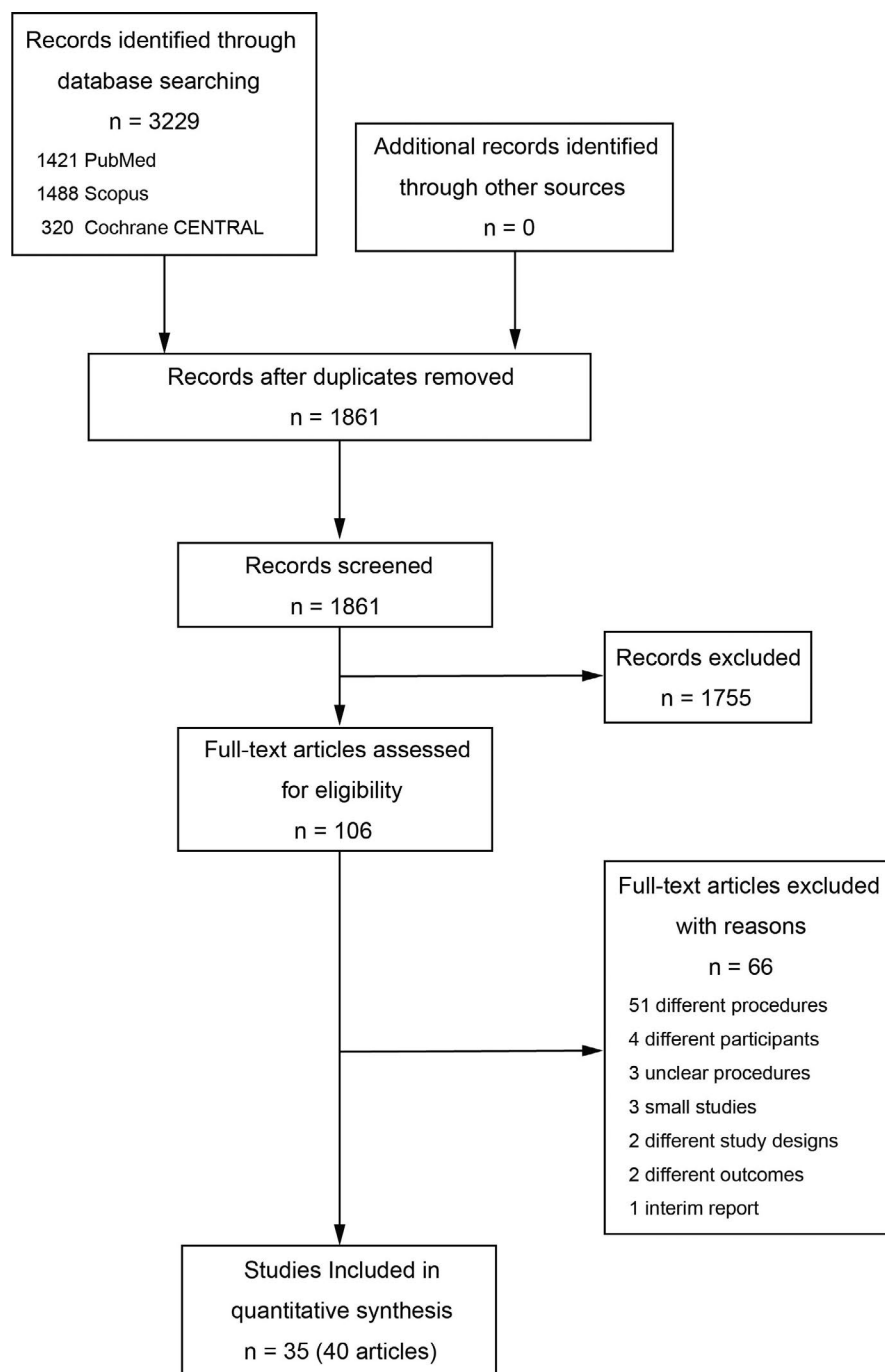


FIGURE 1 Flow diagram of study selection Central Register of Controlled Trials (CENTRAL)

TABLE 1 Patient characteristics

	Setting		Prospective/ Retrospective	Study period		Surgical procedures	Patients, n	
Study	Country	Institution		Start	End		Laparoscopy	Open
Randomized controlled trials								
ACOSOG ^{10,11}	International	Multi	Prospective	2008/10	2013/9	LAR, APR, HP, TC	240	222
ALaCaRT ^{12,13}	International	Multi	Prospective	2010/3	2014/11	LAR, APR	238	235
COLAR II ¹⁴⁻¹⁶	International	Multi	Prospective	2004/1	2010/5	AR, APR, HP	699	345
COREAN ^{17,18}	Korea	Multi	Prospective	2006/4	2009/8	LAR, APR	170	170
Braga 2007 ¹⁹	Italy	Single	Prospective	NR	NR	LAR, APR	83	85
Case-matched studies								
da Luz Moreira 2011 ²⁰	USA	Single	Retrospective	1992	2008	LAR, APR	91	91
de'Angelis 2017 ²¹	International	Multi	Retrospective	2005/1	2015/12	LAR, APR	52	52
Guo 2015 ²²	China	Single	Retrospective	2007/4	2013/12	LAR, APR	191	191
Katsuno 2016 ²³	Japan	Multi	Prospective	2010/6	2013/2	LAR	209	209
Koulas 2009 ²⁴	Greece	Single	Retrospective	1998/10	2006/12	AR, ISR, APR	57	60
Manchon-Walsh 2019 ²⁵	Spain	Multi	Retrospective	2011	2012	AR,APR, HP	842	517
Milone 2017 ²⁶	Italy	Multi	Retrospective	2009/1	2015/12	AR, APR	242	235
Nussbaum 2015 ²⁷	USA	Multi	Retrospective	2010	2011	LAR	6430	6430
Park 2013 ²⁸	Korea	Single	Retrospective	2003/1	2008/11	AR, ISR, APR	406	406
Tayar 2018 ²⁹	Brazil	Single	Retrospective	2008	2012	LAR	50	50
Cohort studies								
Allaix 2016 ³⁰	Italy	Single	Retrospective	1994/4	2005/8	AR, APR	153	154
Anthuber 2003 ³¹	Germany	Single	Retrospective	1996/1	2002/3	AR, APR, HP	101	334
Du 2017 ³²	China	Single	Retrospective	2015/1	2017/1	AR	80	70
Kellokumpu 2012 ³³	Finland	Single	Retrospective	1999/1	2006/12	HAR, LAR, APR	100	91
Kim 2015 ³⁴	Korea	Single	Retrospective	2002/1	2011/12	AR	131	176
Laurent 2009 ³⁵	France	Single	Retrospective	1994/1	2006/12	AR, APR, HP	238	233
Law 2009 ³⁶	China	Single	Retrospective	2000/6	2006/12	AR, APR, HP	111	310
Lee 2013 ³⁷	Korea	Single	Retrospective	2001/6	2008/12	LAR	80	80
Li 2010 ³⁸	China	Multi	Prospective	2005/6	2007/6	AR, APR	65	70
Li 2011 ³⁹	China	Single	Retrospective	2000/1	2005/6	AR, APR	113	123
Li 2015 ⁴⁰	China	Single	Retrospective	2003/1	2008/12	AR, APR	129	152
Liu 2016 ⁴¹	China	Single	Retrospective	2011	2013	AR, APR	84	65
Mohamed 2014 ⁴²	China	Single	Retrospective	2000/1	2011/12	AR, APR, HP	470	593
Pan 2016 ⁴³	China	Single	Retrospective	2009/1	2012/12	AR, APR	85	102
Staudacher 2007 ⁴⁴	Italy	Single	Retrospective	1998/1	2005/9	AR	108	79
Strouch 2013 ⁴⁵	USA	Single	Retrospective	2005/1	2011/6	LAR	75	75
Wu 2018 ⁴⁶	China	Single	Retrospective	2009/1	2013/12	LAR, APR, HP	277	614
Yang 2013 ⁴⁷	China	Single	Retrospective	2010/5	2012/5	LAR, APR	87	90
Zhang 2019 ⁴⁸	China	Single	Retrospective	2008/1	2011/12	AR, CAA	112	116
Zhou 2014 ⁴⁹	China	Single	Retrospective	2005/1	2008/1	LAR, APR	57	65

Abbreviations: APR, abdominoperineal resection; AR, anterior resection; CAA, colo-anal anastomosis; HAR, high anterior resection; HP, Hartmann's procedure; ISR, intersphincteric resection; LAR, low anterior resection; NR, not reported; TC, total colectomy.

studies with 4930 patients reported on the incidence of overall complications and were included in a meta-analysis stratified by study design.

There were no significant differences between laparoscopic LAR and open LAR in RCT (RR 1.00, 95% CI 0.89-1.12, $P = .95$) and

case-matched studies (RR 0.91, 95% CI 0.83-1.01, $P = .07$). However, laparoscopic LAR had a significantly lower incidence of overall post-operative complications than open LAR in cohort studies (RR 0.76, 95% CI 0.67-0.87, $P < .001$) (Table 2, Figure 2).

3.2.2 | Incidence of anastomotic leakage

In total, 27 studies with 9256 patients including 5 RCT with 2144 patients, 6 case-matched studies with 1986 patients, and 16 cohort studies with 5126 patients reported on the incidence of anastomotic leakage and were included in a meta-analysis stratified by study design.

There were no significant differences between laparoscopic LAR and open LAR in all three types of study design; RCT (RR 1.11, 95% CI 0.78-1.57, $P = .57$), case-matched studies (RR 1.05, 95% CI 0.79-1.39, $P = .74$), and cohort studies (RR 0.98, 95% CI 0.77-1.24, $P = .88$) (Table 2, Figure S1).

3.2.3 | Mortality

Twenty-four studies with 22 931 patients including 5 RCT with 2487 patients, 7 case-matched studies with 15 799 patients, and 12 cohort studies with 4645 patients reported on mortality and were included in a meta-analysis stratified by study design.

There were no significant differences between laparoscopic LAR and open LAR in RCT (RD -0.00, 95% CI -0.01 to 0.00, $P = .53$). In contrast, laparoscopic LAR showed significantly lower mortality than open LAR in case-matched studies (RD -0.00, 95% CI -0.01 to -0.00, $P = .03$), and cohort studies (RD -0.01, 95% CI -0.01 to -0.00, $P = .04$) (Table 2, Figure S2).

3.2.4 | Reoperation rate

A total of 16 studies with 7048 patients including 4 RCT with 2012 patients, 4 case-matched studies with 1745 patients, and 8 cohort studies with 3291 patients reported on reoperation rate and were included in a meta-analysis stratified by study design.

No significant differences were noted between laparoscopic LAR and open LAR in all three types of study design: RCT (RR 1.07, 95% CI 0.71-1.61, $P = .76$), case-matched studies (RR 1.21, 95% CI 0.67-2.19, $P = .53$), and cohort studies (RR 0.82, 95% CI 0.60-1.13, $P = .22$) (Table 2, Figure S3).

3.2.5 | Length of stay

Seventeen studies with 5745 patients including 2 RCT with 630 patients, 7 case-matched studies with 3056 patients, and 8 cohort studies with 2059 patients reported on length of stay and were included in a meta-analysis stratified by study design.

There were no significant differences between laparoscopic LAR and open LAR in RCT (MD -1.83, 95% CI -5.74 to 2.07, $P = .36$). Conversely, laparoscopic LAR had significantly shorter length of stay than open LAR in case-matched studies (MD -2.96, 95% CI -4.50 to -1.42, $P < .001$), and cohort studies (MD -2.15, 95% CI -3.38 to -0.91, $P < .001$) (Table 2, Figure S4).

3.2.6 | Operative time

In total, 16 studies with 4748 patients including 3 RCT with 970 patients, 3 case-matched studies with 1298 patients, and 10 cohort studies with 2480 patients reported on operative time and were included in a meta-analysis stratified by study design.

Laparoscopic LAR had longer operative time than open LAR in RCT (MD 48.13, 95% CI 38.11 to 58.14, $P < .001$). In contrast, there were no significant differences between laparoscopic LAR and open LAR in case-matched studies (MD -6.32, 95% CI -60.17 to 47.53, $P = .82$) and cohort studies (MD 13.88, 95% CI -1.16 to 28.92, $P = .07$) (Table 2, Figure S5).

3.2.7 | Estimated blood loss

Fourteen studies with 3608 patients including 2 RCT with 630 patients, 3 case-matched studies with 1298 patients, and 9 cohort studies with 1680 patients reported on estimated blood loss and were included in a meta-analysis stratified by study design.

There were no significant differences between laparoscopic LAR and open LAR in RCT (MD -116.84, 95% CI -234.90 to 1.22, $P = .05$). However, laparoscopic LAR had significantly less estimated blood loss than open LAR in case-matched studies (MD -64.79, 95% CI -93.98 to -35.60, $P < .001$) and cohort studies (MD -79.71, 95% CI -108.05 to -51.37, $P < .001$) (Table 2, Figure S6).

3.2.8 | Rate of positive circumferential resection margins

Fourteen studies with 18 486 patients including 4 RCTs with 2163 patients, 4 case-matched studies with 14 644 patients, and 6 cohort studies with 1679 patients reported on the rate of positive circumferential resection margins and were included in a meta-analysis stratified by study design.

There were no significant differences between laparoscopic LAR and open LAR in RCT (RR 1.25, 95% CI 0.81-1.92, $P = .31$) and cohort studies (RR 1.28, 95% CI 0.80-2.04, $P = .30$). However, laparoscopic LAR had a significantly lower rate of positive circumferential resection margins than open LAR in case-matched studies (RR 0.75, 95% CI 0.65-0.85, $P < .001$) (Table 2, Figure S7).

3.3 | Long-term outcomes

3.3.1 | Three-year OS

A total of 20 studies with 9157 patients including 3 RCT with 1834 patients, 6 case-matched studies with 2956 patients, and 11 cohort studies with 4367 patients reported on the 3-year OS and were included in a meta-analysis stratified by study design.



TABLE 2 Summary of meta-analyses based on study designs

Outcomes	Randomized controlled trials				Case-matched studies				Cohort studies							
	Measures	Study		Patients	Point estimation	95% CI	Study		Patients	Point estimation	95% CI	Study		Patients	Point estimation	95% CI
		n	n				n	n				n	n			
Short-term																
Postoperative overall complications	RR	4	2012	1.00	0.89, 1.12	6	2939	0.91	0.83, 1.01	14	4930	0.76	0.67, 0.87			
Anastomotic leakage	RR	5	2144	1.11	0.78, 1.57	6	1986	1.05	0.79, 1.39	16	5126	0.98	0.77, 1.24			
Mortality	RD	5	2487	-0.00	-0.01, 0.00	7	15 799	-0.00	-0.01, 0.00	12	4645	-0.00	-0.01, -0.00			
Reoperation	RR	4	2012	1.07	0.71, 1.61	4	1745	1.21	0.67, 2.19	8	3291	0.82	0.60, 1.13			
Length of stay	MD	2	630	-1.83	-5.74, 2.07	7	3056	-2.96	-4.50, -1.42	8	2059	-2.15	-3.38, -0.91			
Operative time	MD	3	970	48.13	38.11, 58.14	3	1298	-6.32	-60.17, 47.53	10	2480	13.88	-1.16, 28.92			
Estimated blood loss	MD	2	630	-116.84	-234.90, 1.22	3	1298	-64.79	-93.98, -35.60	9	1680	-79.71	-108.05, -51.37			
Positive CRMs	RR	4	2163	1.25	0.81, 1.92	4	14 644	0.75	0.65, 0.85	6	1679	1.28	0.80, 2.04			
Long-term																
3-year OS	RR	3	1834	1.02	0.98, 1.06	6	2956	1.05	0.99, 1.10	11	4367	1.06	1.00, 1.12			
3-year DFS	RR	4	2296	1.03	0.97, 1.09	4	1480	0.99	0.94, 1.05	6	1858	0.98	0.95, 1.01			
3-year LRR	RR	4	2002	1.05	0.66, 1.68	2	994	0.70	0.39, 1.25	7	3243	0.64	0.47, 0.88			

Abbreviations: CI, confidence interval; CRM, circumferential resection margin; DFS, disease-free survival; LRR, local recurrence rate; MD, mean difference; OS, overall survival; RD, risk difference; RR, risk ratio.

There were no significant differences between laparoscopic LAR and open LAR in RCT (RR 1.02, 95% CI 0.98-1.06, $P = .28$) and case-matched studies (RR 1.05, 95% CI 0.99-1.10, $P = .09$). In contrast, laparoscopic LAR had a significantly higher 3-year OS rate than open LAR in cohort studies (RR 1.06, 95% CI 1.00-1.12, $P = .04$) (Table 2, Figure S8).

3.3.2 | Three-year DFS

Fourteen studies with 5634 patients including 4 RCT with 2296 patients, 4 case-matched studies with 1480 patients, and 6 cohort studies with 1858 patients reported on the 3-year DFS rate and were included in a meta-analysis stratified by study design.

There were no significant differences between laparoscopic LAR and open LAR in all three types of study design: RCT (RR 1.03, 95% CI 0.97-1.09, $P = .28$), case-matched studies (RR 0.99, 95% CI 0.94-1.05, $P = .76$), and cohort studies (RR 0.98, 95% CI 0.95-1.01, $P = .24$) (Table 2, Figure S9).

3.3.3 | Three-year LRR

In total, 13 studies with 6239 patients including 4 RCT with 2002 patients, 2 case-matched studies with 994 patients, and 7 cohort studies with 3243 patients reported on the 3-year LRR and were included in a meta-analysis stratified by study design.

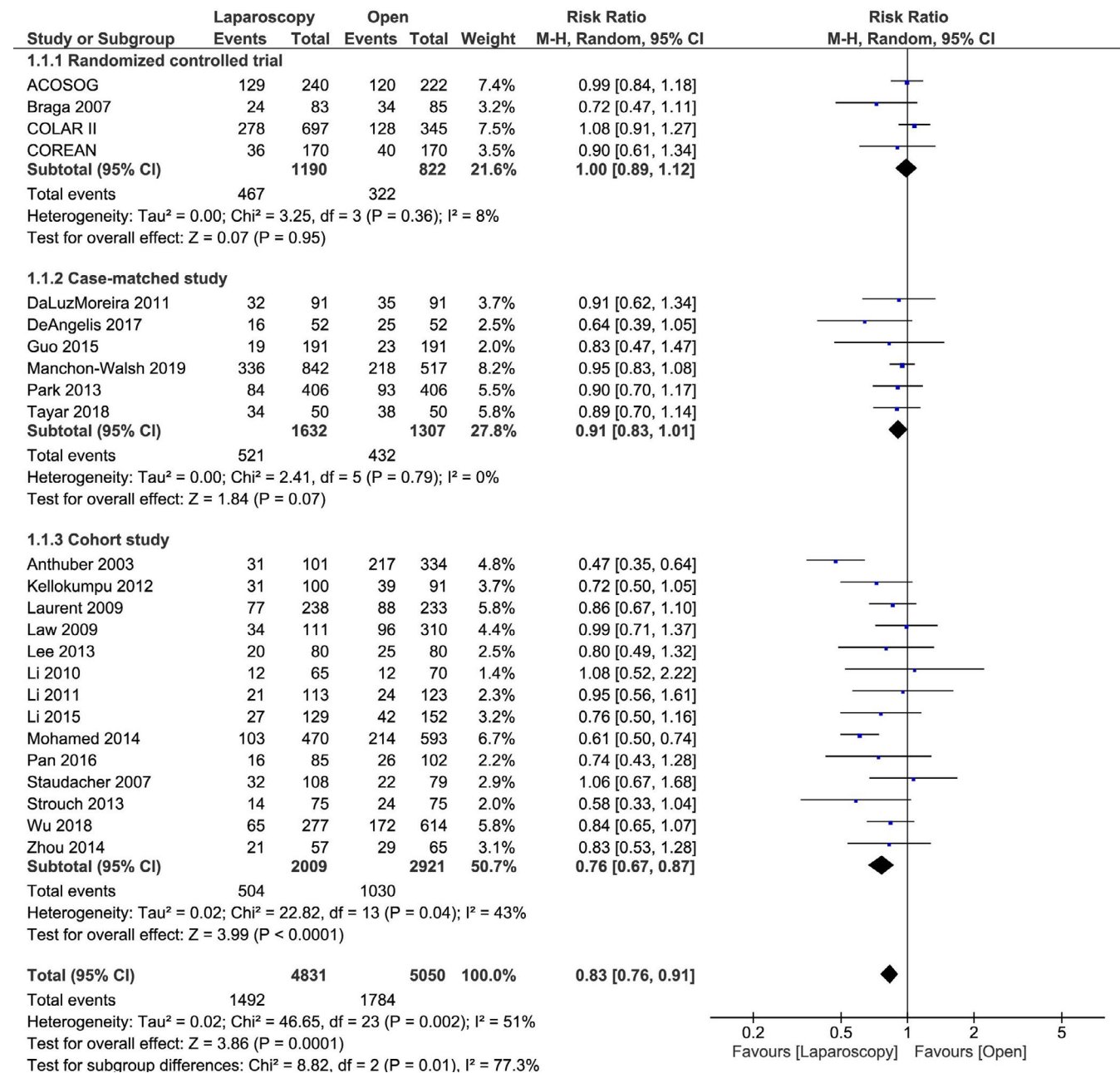


FIGURE 2 Results of meta-analysis stratified by study design: Incidence of postoperative overall complications

There were no significant differences between laparoscopic LAR and open LAR in RCT (RR 1.05, 95% CI 0.66-1.68, $P = .82$) and case-matched studies (RR 0.70, 95% CI 0.39-1.25, $P = .23$). By contrast, laparoscopic LAR had a significantly lower 3-year LRR than open LAR in cohort studies (RR 0.64, 95% CI 0.47-0.88, $P = .007$) (Table 2, Figure 3).

4 | DISCUSSION

This systematic review and meta-analysis including 35 studies that compared laparoscopic LAR with open LAR for rectal cancer showed some similarities and differences in findings from the different study designs, particularly RCT and case-matched studies. Results from cohort studies were used as a reference for unadjusted results potentially affected by confounding factors. We conducted a meta-analysis for 11 outcomes and found similarities for all outcomes other than operative time and the rate of positive circumferential resection margins between RCT and case-matched studies. Cohort studies without covariate adjustment tended to overestimate the treatment effect of laparoscopic LAR in the incidence of postoperative overall complications, 3-year OS, and 3-year LRR.

Short-term outcomes were not significantly different between laparoscopic LAR and open LAR in both RCT and case-matched studies for the incidence of postoperative overall complications, the incidence of anastomotic leakage, and reoperation rate. Meanwhile, significant differences were noted in case-matched studies but not in RCT regarding mortality, length of stay, and estimated blood loss. However, we deemed these three outcomes similar between RCT and case-matched studies based on the distribution of 95% CI in forest plots. Thus, the findings of RCT were similar to those of case-matched studies in terms of 9 short-term outcomes. However, the number of patients was smaller in RCT than in case-matched studies and the 95% CI of RCT were wider than those of case-matched studies in length of stay and estimated blood loss. In addition, the two outcomes can be influenced by the retrospective nature of case-matched studies. There remains potential difference between RCT and case-matched studies in these outcomes. Operative time of laparoscopic LAR was significantly longer in RCT but not in case-matched studies and the rate of positive circumferential resection margins was significantly lower in case-matched studies but not in RCT. Case-matched studies might overestimate the treatment effect of laparoscopic LAR in terms of operative time and the rate

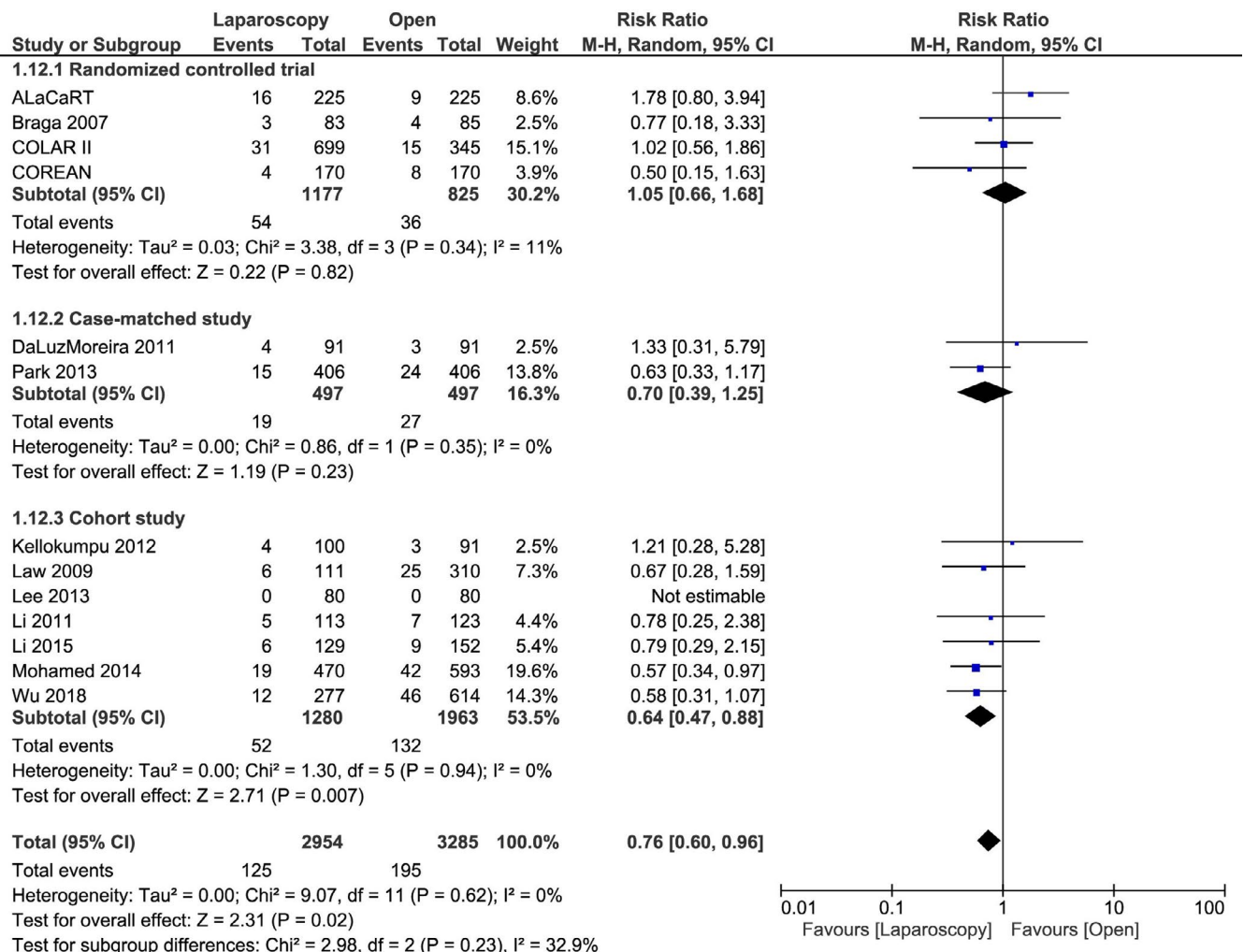


FIGURE 3 Results of meta-analysis stratified by study design: 3-year local recurrence rate

of positive circumferential resection margins. No significant differences in any long-term outcomes were noted between laparoscopic LAR and open LAR in both RCT and case-matched studies. Thus, RCT were similar to case-matched studies in terms of the majority of outcomes.

We deemed there to be no difference between RCT and case-matched studies in terms of all outcomes other than operative time and the rate of positive circumferential resection margins. However, we found that the estimated treatment effect of laparoscopic LAR tended to be larger in case-matched studies compared with RCT but smaller in case-matched studies compared with cohort studies in the incidence of overall complications and 3-year LRR according to the distribution of 95% CI in forest plots. RCT can adjust for all confounding factors, and case-matched studies can adjust for measurable confounding factors only. In this review, cohort studies were not adjusted for any confounding factors because we extracted unadjusted data from cohort studies. Therefore, the difference in the 95% CI between study designs might be due to the difference in adjustments for confounding factors.

Propensity score matching is a representative matching method that was first reported in 1983³. Propensity score matching is now widely used, but has several attendant problems such as insufficient reporting of the details of covariant selection, rate of missing covariates, and matching methods^{50,51}. Although there are methodological differences between RCT and case-matched studies such as patient selection and residual confounding, it remains unclear whether findings of RCT differ from those of case-matched studies^{7,8}. Kuss et al reported that outcomes of RCT were similar to those of case-matched studies in cardiac surgery⁵². According to Dahabreh et al, case-matched studies potentially overestimate treatment effects in acute coronary syndrome⁵³. In addition, there are currently no reports on the similarities and differences between RCT and case-matched studies in gastrointestinal surgery. In this study, we dealt with LAR for rectal cancer and showed there to be differences between study designs in some outcomes. It remains unclear whether similar results are found in other gastrointestinal surgeries. Further studies are needed to elucidate the similarities and differences in outcomes between study designs in other gastrointestinal surgeries.

This review highlights two outcomes, the incidence of overall postoperative complications and 3-year LRR, that could be influenced by the adjustment for covariates. The incidence of overall postoperative complications often comprises multiple complications, some of which are sometimes evaluated subjectively, especially in retrospective cohort studies. The subjective assessment of postoperative complications could explain the difference between study designs in terms of outcomes. Nevertheless, local recurrence is usually evaluated objectively by using imaging modalities such as computed tomography and magnetic resonance imaging. Thus, study design can influence both short- and long-term study outcomes, whether the evaluation is subjective or objective. Case-matched studies and cohort studies are useful in surgical research because it is often difficult to conduct RCT. However, it is necessary to carefully consider the impact of study design on study outcomes.

The strength of the present review is the large number of studies analyzed to comparatively investigate similarities and differences in findings between RCT and case-matched studies. This review included 35 studies and investigated numerous outcomes including both short- and long-term outcomes for a single comparison. However, this study has some limitations. The number of studies and patients differed between study designs, with a tendency to be lower in RCT and higher in cohort studies. Also, this review included published data only and did not assess study quality. In this review, we showed the similarities and differences in terms of outcomes among RCT, case-matched studies, and cohort studies on laparoscopic LAR for rectal cancer. Although further study is required in order for the results of this review to be generalizable, we hope these results help clinicians to better interpret the results of surgical research.

In conclusion, findings from case-matched studies were similar to those of RCT in laparoscopic LAR for rectal cancer. However, findings of case-matched studies were sometimes intermediate between those of RCT and unadjusted cohort studies, and case-matched studies and cohort studies had a potential to overestimate the treatment effect compared with RCT.

ACKNOWLEDGEMENTS

This review was supported by a grant from Kondou Kinen Medical Foundation.

DISCLOSURE

Funding: This review was supported by a grant from Kondou Kinen Medical Foundation.

Conflicts of interest: The authors declare no conflicts of interest for this study.

Author Contributions: All authors contributed to the study concept and design. Literature search and data collection were performed by NH and YF. Statistical analysis was conducted by NH and checked by the other authors. The first draft of manuscript was written by NH and all authors commented on previous version of the manuscript. All authors read and approved the final.

ORCID

Nobuaki Hoshino  <https://orcid.org/0000-0002-7171-8971>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Hoshino N, Fukui Y, Hida K, Obama K. Similarities and differences between study designs in short- and long-term outcomes of laparoscopic versus open low anterior resection for rectal cancer: A systematic review and meta-analysis of randomized, case-matched, and cohort studies. *Ann Gastroenterol Surg*. 2021;5:183–193. <https://doi.org/10.1002/ags3.12409>