SYSTEMATIC REVIEWS AND META-ANALYSES



Comparison of estimated treatment effects between randomized controlled trials, case-matched, and cohort studies on laparoscopic versus open distal gastrectomy for advanced gastric cancer: a systematic review and meta-analysis

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Abstract

Purpose In actual surgical research, case-matched studies are frequently conducted as an alternative to randomized controlled trials (RCTs). However, it is still unclear what differences there are between RCTs and case-matched studies in upper gastrointestinal surgery, and clarifying them is a very important clinical issue. Thus, the purpose of this study was to investigate estimated treatment effects between RCTs, case-matched studies, and cohort studies regarding laparoscopic distal gastrectomy (LDG) for advanced gastric cancer (AGC).

Methods We searched the PubMed, Cochrane Central Register of Controlled Trials, and Web of Science databases for studies that compared LDG versus open distal gastrectomy for AGC published from the inception of the databases until July 2021. A meta-analysis was performed using the Review Manager version 5.3 software program from the Cochrane Collaboration, and six short-term outcomes and three long-term outcomes were assessed.

Results Twenty-three studies with 13698 patients were included. There was no difference in estimated treatment effects between RCTs and case-matched studies for all outcomes except for the number of retrieved lymph nodes and postoperative complications. In terms of intraoperative blood loss, postoperative hospital stay, number of retrieved lymph nodes, and recurrence, observational studies tended to overestimate the treatment effects.

Conclusion The estimated treatment effects of LDG for AGC in the case-matched study were almost the same as in the RCTs. However, to assess the true magnitude of the treatment effect, the design and actual implementation of the analysis must be critically evaluated.

Keywords Case-matched study \cdot Randomized controlled trial \cdot Laparoscopic distal gastrectomy \cdot Open distal gastrectomy \cdot Advanced gastric cancer

Introduction

It is generally accepted that the gold standard for evaluating the efficacy of therapeutic interventions is randomized controlled trials (RCTs). In RCTs, random assignment of participants to treatment and control groups virtually eliminates distortion of results due to differences in patient characteristics between study groups. However, in most surgical studies, randomization is difficult for ethical and practical reasons [1]. In addition, RCTs are costly and inefficient because they require many resources, including subjects, time, and the cooperation of diverse experts, to estimate treatment effects with sufficient accuracy [2]. Therefore, as a practical alternative, many observational studies have been performed in actual clinical settings.

Observational studies are susceptible to biases such as confounding, selection, and differential ascertainment bias because they lack randomization and other elements of RCT design [3]. Some reports have suggested that both randomized and observational studies may produce very similar

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results [4, 5], while others have reported conflicting results [6]. However, the topics covered in these previous reports are very limited, and more empirical and quantitative evidence is needed to clarify the accuracy of and differences in each study design [7]. In recent years, case-matched studies have been frequently conducted in surgical research for appropriate confounder adjustment in observational studies, and the most common technique is propensity score matching [1]. The propensity score, proposed as a potential solution to the problem of confounding associations between treatment and outcome, represents the probability of being treated with an intervention based on variables measured during or before treatment [8]. Although there are methodological differences between case-matched studies and RCTs, such as patient selection and adjustment for confounders [9, 10], only one report, concerning rectal cancer, has investigated the similarities and differences between different study designs in the field of gastrointestinal surgery [2]. Therefore, it is still unclear what differences there are between RCTs, case-matched studies, and cohort studies in other gastrointestinal surgeries, and clarifying them is a very important clinical issue.

Thus, the purpose of this study was to investigate estimated treatment effects between RCTs, case-matched studies, and cohort studies regarding upper gastrointestinal surgery areas. As a clinical topic, we selected the comparison of laparoscopic distal gastrectomy (LDG) versus open distal gastrectomy (ODG) for advanced gastric cancer (AGC), which is one of the most discussed and interested issues among gastrointestinal surgeons. While there have been several meta-analysis studies that evaluated the efficacy of LDG in AGC [11–14], none of them focused on the differences in study design.

Therefore, in the present study, we evaluated the differences in study designs by addressing this clinical topic for which sufficient evidence has been accumulated.



Fig. 1 Flow diagram of study selection

Year	Country	/ Institu- tion	Type of study	Particij	ants, n	Gender, M:F		Mean age, years		Mean BMI, kg	/m ²	Clinical stage, I/II/II	NIV	Pathological stage,]	VIIIIIVIN	Operati	ve time, min	
				Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	ō	en
RCTs																		
Hu [31] 2016	China	Multi	Prospective	519	520	380:139	346:174	56.5 ± 10.4	55.8 ± 11.1	22.7 ± 3.2	22.7 ± 3.2	NR	NR	151/137/219/11	152/138/221/8	217.3±	60.3 18	6 ± 53.3
Park [33] 2018	Korea	Multi	Prospective	100	96	69:31	65:31	58.6	60.1	23.7 ± 3.0	23.3 ± 3.1	23/52/25/0	22/46/28/0	42/29/28/1	36/33/23/4	257.4±	86.7 18	3 ± 52.5
Wang [37] 2019	China	Multi	Prospective	222	220	144:78	133:87	59.4 ± 12.4	60.6 ± 10.2	23.1 ± 3.1	23.5 ± 3.3	NR	NR	75/63/80/4	68/63/83/6	242.5±	63.5 20	9.9 ± 53.6
Yu [38] 2019	China	Multi	Prospective	519	520	380:139	346:174	56.5 ± 10.4	55.8 ± 11.1	22.7 ± 3.2	22.7 ± 3.2	64/248/207/0	88/247/185/0	151/137/219/11	152/138/221/8	NR	N	~
Hyung 2020 [40]	Korea	Multi	Prospective	492	482	351:141	335:147	59.8 ± 11.0	59.4±11.5	23.5 ± 2.9	23.7 ± 3.3	134/159/199/0	116/169/197/0	178/148/166/0	165/167/150/0	227.0±	67.9 16	4.4±45.8
Case-matched studi	65																	
Scatizzi 2011 [24]	Italy	Single	Retrospective	30	30	16:14	14:16	70.0 ± 12.0	69.0 ± 10.8	22.0 ± 1.0	24.0 ± 6.5	NR	NR	0/12/18/0	0/10/20/0	240.0±	32.5 18	0.0 ± 30.0
Shuang 2011 [25]	China	Single	Retrospective	35	35	30:5	30:5	58.0 ± 10.5	59.0 ± 13.5	21.0 ± 3.0	23.0 ± 3.0	NR	NR	10/15/10/0	9/13/13/0	320.0±	77.5 21	0.0 ± 40.5
Zhang [30] 2015	China	Single	Retrospective	86	86	57:29	61:25	62.0 ± 4.8	61.0 ± 4.0	NR	NR	9/66/11/0	10/62/9/0	5/52/29/0	4/56/26/0	210.0±	15.0 18	0.0 ± 11.7
Yoshida 2018 [34]	Japan	Multi	Retrospective	3738	3738	2450:1288	2444:1294	71.0±2.7	70.0 ± 2.5	22.2 ± 3.4	22.2 ± 3.3	NR	NR	0/2318/1220/200	0/2320/1224/19	4 NR	IN	~
Kim [35] 2019	Korea	Single	Retrospective	60	60	38:22	41:19	62.5 ± 14.2	62.4 ± 10.4	24.3 ± 4.3	24.1 ± 3.5	22/29/9/0	17/33/10/0	0/37/23/0	0/38/22/0	234.8±	46.9 21	7.2±48.0
Garbarino 2020 [39]	Italy	Single	Retrospective	34	34	23:11	21:13	70.9 ± 10.7	71.1±9.1	24.2 ± 4.1	24.2 ± 3.2	NR	NR	2/18/14/0	2/10/22/0	257.2±	46.3 19	7.2±66.4
Wang [41] 2020	China	Single	Retrospective	190	190	134:56	131:59	57.7 ± 10.7	58.3 ± 10.2	21.6 ± 3.1	21.7 ± 2.8	12/87/91/0	14/71/105/0	44/44/102/0	35/37/118/0	195.0±	52.2 20	3.3 ± 63.8
Huang [42] 2021	China	Multi	Retrospective	461	461	135/326	137/324	NR	NR	21.7 ± 3.5	21.0 ± 3.4	NR	NR	NR	NR	169.0±	62.8 16	9.8±47.1
Cohort studies																		
Hur [20] 2008	Korea	Single	Retrospective	26	25	19:7	19:6	NR	NR	NR	NR	NR	NR	NR	NR	255.0±	42.5 18	3.8±31.3
Du [21] 2009	China	Single	Retrospective	78	90	55:23	62:28	56.0 ± 6.0	60.0 ± 8.0	NR	NR	NR	NR	8/27/37/5	9/30/40/11	245.0±	35.0 22	0.0 ± 20.0
Hwang 2009 [22]	Korea	Single	Retrospective	45	83	25:20	58:25	55.8±12.5	59.2±12.6	NR	NR	NR	NR	22/10/13/0	34/21/28/0	255.5±	58.1 20	8.3±36.6
Huang [23] 2010	China	Single	Retrospective	99	69	40:26	39:30	55.8 ± 9.2	56.4 ± 10.6	NR	NR	NR	NR	18/21/26/1	16/21/30/2	266.1±	55.1 22	3.8 ± 26.8
Zhao [26] 2011	China	Single	Retrospective	346	313	248:98	221:92	51.4 ± 11.5	52.6 ± 12.4	NR	NR	NR	NR	42/99/199/6	37/87/181/8	211.0±	56.0 20	4.0 ± 41.0
Chun [27] 2012	Korea	Single	Retrospective	52	67	30:22	48:19	61.1 ± 12.6	60.8 ± 11.1	22.8 ± 2.8	22.9 ± 3.0	NR	NR	NR	NR	$207.7 \pm$	40.6 15	9.9 ± 39.0
Gordon 2013 [28]	Japan	Single	Retrospective	66	135	48:18	93:39	64.0 ± 12.1	67.0±11.9	22.8 ± 3.5	22.1 ± 3.3	NR	NR	22/29/15/0	11/50/71/0	291.0±	47.8 23	5.0±55.8
Hosoda 2015 [29]	Japan	Single	Retrospective	32	4	21:11	33:11	60.6 ± 11.1	64.6 ± 9.3	23.2 ± 3.4	23.0 ± 3.0	NR	NR	22/5/4/1	31/7/4/2	297.0±	12.0 22	6.0 ± 10.0
Matsuda 2018 [32]	Japan	Single	Retrospective	61	67	48:13	36:31	69.5 ± 11.6	70.2 ± 11.1	23.8 ± 4.9	20.9 ± 4.0	27/20/14/0	8/33/26/0	12/34/15/0	9/29/29/0	321.0±	77.5 24	5.0 ± 50.8
Shibuya 2019 [36]	Japan	Single	Retrospective	87	27	61:26	15:12	67.5 ± 1.3	69.4±2.3	23.1 ± 0.3	22.5 ± 0.6	36/34/17/0	4/12/11/0	21/33/33/0	2/9/16/0	237.5±	50.4 19	7.6±44.9
Intraoperati	ve bloo	d loss, n	IC	Posto	perativ	e hospital	stay, days	Retrieved ly	/mph node	es, n	Postof plicati	perative comons, n	Recurrer	nce, n	3-year DF	s, %	3-year	0S, %
Lap		Open		Lap		Open		Lap	Ope	u	Lap	Open	Lap	Open	Lap	Open	Lap	Open
RCTs									-									
105.5 ± 88.0	2	117.3±	-84.5	10.8 ±	5.9	$11.3 \pm$	7.6	36.1 ± 16.7	36.9	9±16.1	79	67	NR	NR	NR	NR	NR	NR
NR		NR		9.8±	7.0	9.1 ± 5	5.5	37.0 ± 13.4	39.7	7 ± 13.3	17	18	NR	NR	80.1	81.9	NR	NR
91.4 ± 90.9		117.5 ±	= 103.5	$9.9 \pm$	3.7	$10.9 \pm$	5.2	29.5 ± 10.4	31.4	4 ± 12.3	29	39	NR	NR	NR	NR	NR	NR
NR		NR		NR		NR		36.1 ± 16.7	36.9)±16.1	NR	NR	95	85	76.5	77.8	83.1	85.2
152.4 ± 260	.5	225.0±	-211.5	8.0±	5.3	9.1 ± 6	6.3	46.8 ± 18.0	47.2	2 ± 16.2	LL	113	76	72	80.3	81.3	90.6	90.3

Table 1 Study characteristics

Table 1 (continue	(pç												
Intraoperative blc	od loss, ml	Postoperative	hospital stay, days	Retrieved lymp	h nodes, n	Postope plicatio	stative com- ns, n	Recurre	nce, n	3-year D	0FS, %	3-year O	S, %
Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open	Lap	Open
Case-matched stu	dies										-		
NR	NR	7.0 ± 11.0	9.0 ± 4.3	31.0 ± 11.0	37.0 ± 20.3	2	8	NR	NR	NR	NR	70.9	56.8
200.0 ± 125.0	300.0 ± 250.0	12.0 ± 7.8	17.0 ± 9.3	35.0 ± 14.0	38.0 ± 15.0	2	3	NR	NR	NR	NR	NR	NR
200.0 ± 40.0	260.0 ± 25.0	8.0 ± 1.7	12.0 ± 2.5	20.0 ± 1.2	21.0 ± 1.0	6	13	NR	NR	NR	NR	NR	NR
NR	NR	NR	NR	NR	NR	397	451	NR	NR	NR	NR	NR	NR
NR	NR	9.6 ± 4.3	11.5 ± 5.1	30.5 ± 15.5	32.8 ± 16.9	8	8	NR	NR	86.3	75.3	98	86.9
140.8 ± 170.9	180.3 ± 165.3	11.8 ± 8.3	15.8 ± 13.7	26.0 ± 10.6	26.1 ± 12.3	10	12	NR	NR	NR	NR	NR	NR
92.0 ± 79.1	117.0 ± 102.9	11.5 ± 4.5	13.1 ± 5.1	30.2 ± 10.8	28.1 ± 10.1	24	32	49	47	64	60.3	68.7	66.6
78.7 ± 98.9	121.3 ± 115.5	13.0 ± 8.3	14.1 ± 8.6	31.3 ± 10.8	30.5 ± 12.1	68	80	140	137	65.1	63.2	76.1	74.2
Cohort studies													
160.0 ± 87.5	241.3 ± 91.3	7.0 ± 4.0	10.3 ± 3.3	30.5 ± 16.5	41.3 ± 17.8	4	4	8	9	53.4	71.4	88.2	77.2
110.0 ± 25.0	196.0 ± 30.0	8.6 ± 1.2	12.1 ± 2.5	23.5 ± 6.0	21.0 ± 7.5	9	10	22	31	NR	NR	81.2	74.7
333.3 ± 89.2	440.6 ± 156.7	9.8 ± 6.9	11.1 ± 5.6	35.6 ± 14.2	38.3 ± 11.4	7	10	9	17	NR	NR	NR	NR
131.9 ± 88.7	342.3 ± 178.7	9.2 ± 3.4	11.4 ± 4.6	25.8 ± 12.5	24.5 ± 10.3	4	11	NR	NR	NR	NR	NR	NR
128.0 ± 85.0	301.0 ± 156.0	7.9 ± 3.6	10.7 ± 5.8	33.2 ± 12.5	32.8 ± 15.6	24	41	147	141	NR	NR	57.2	54.1
NR	NR	7.0 ± 16.1	7.0 ± 1.6	39.1 ± 15.2	39.3 ± 11.2	5	9	NR	NR	NR	NR	NR	NR
107.0 ± 97.3	495.0 ± 432.5	8.4 ± 4.1	18.1 ± 16.1	35.9 ± 12.6	36.6 ± 14.5	6	33	NR	NR	NR	NR	NR	NR
90.0 ± 27.0	314.0 ± 23.0	9.7 ± 0.5	10.3 ± 0.4	44.0 ± 2.0	39.0 ± 2.0	1	4	б	2	NR	NR	NR	NR
50.0 ± 142.5	333.0 ± 478.5	7.0 ± 13.3	9.0 ± 9.8	29.0 ± 12.5	33.0 ± 12.8	б	5	6	16	NR	NR	NR	NR
34.1 ± 56.4	157.1 ± 129.5	12.3 ± 5.7	14.5 ± 6.8	44.8 ± 14.3	41.7 ± 18.7	4	1	NR	NR	NR	NR	NR	NR
RCTs randomized	controlled trials, L_{t}	ap laparoscopy, e	CI confidence interv	al, HR hazard r	tio, DFS disease	-free survi	val, OS overa	ll survival	, NR not rep	oorted			

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Table 2Quality assessment ofthe included RCTs based on therevised Cochrane risk-of-boastool

Study	Randomiza- tion process	Intended interven- tions	Missing outcome data	Measurement of outcome	Reported result	Overall risk-of- bias judgement
Hu [<mark>31</mark>]	Low	Low	Low	Low	Low	Low
Park [33]	Low	Low	Low	Low	Low	Low
Wang [37]	Low	Low	Low	Low	Low	Low
Yu [<mark>38</mark>]	Low	Low	Low	Low	Low	Low
Hyung [40]	Low	Low	Low	Low	Low	Low

RCTs randomized controlled trials

Materials and methods

We performed a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15].

Literature search strategy

 Table 3
 Quality assessment of observational studies

We searched the PubMed, Cochrane Central Register of Controlled Trials, and Web of Science databases for studies in which LDG was compared with ODG for AGC published from inception until July 2021. The search terms used were "laparoscopy" OR "laparoscopic" AND "stomach neoplasms" OR "gastric cancer" OR "stomach cancer" AND "open gastrectomy" AND "distal gastrectomy" (Appendix S1). The reference lists of all relevant articles were evaluated to identify other related papers. The study title, study authors, year of publication, and study characteristics were checked, and duplicates were removed. Two authors (R.O. and Y.M.) independently reviewed the title and abstract of articles after eliminating duplicates. The same authors then evaluated the full text according to the study eligibility criteria described below. In cases of disagreement, the authors discussed or consulted a third author until agreement was reached.

Eligibility

The inclusion criteria were as follows: (1) RCTs, casematched studies, or cohort studies; (2) studies that compared LDG versus ODG for AGC; (3) studies that provided available outcome data; and (4) articles written in English.

The exclusion criteria were as follows: (1) studies without appropriate data; (2) laboratory or animal studies; and (3) papers identified as letters, comments, correspondence, editorials, or reviews.

Studies	Sele	ction			Comparability	Out	come		Total star
	1	2	3	4	5	6	7	8	
Scatizzi [24]	*	*	*	*	**	*		*	8
Shuang [25]	*	*	*	*	**	*	*	*	9
Zhang [30]	*	*	*	*	**	*	*	*	9
Yoshida [34]	*	*	*	*	**	*	*	*	9
Kim [35]	*	*	*	*	**	*	*	*	9
Garbarino [39]	*	*	*	*	**	*	*	*	9
Wang [41]	*	*	*	*	**	*	*	*	9
Huang [42]	*	*	*	*	**	*	*	*	9
Hur [20]	*	*	*	*	*	*	*	*	8
Du [21]	*	*	*	*	*	*	*	*	8
Hwang [22]	*	*	*	*	*	*	*	*	8
Huang [23]	*	*	*	*	*	*	*	*	8
Zhao [26]	*	*	*	*	*	*	*	*	8
Chun [27]	*	*	*	*	*	*	*	*	8
Gordon [28]	*	*	*	*	*	*	*	*	8
Hosoda [29]	*	*	*	*	*	*	*	*	8
Matsuda [32]	*	*	*	*	*	*	*	*	8
Shibuya [36]	*	*	*	*	*	*	*	*	8

Data extraction and outcome parameters

Two authors (R.O. and Y.M.) collected the data independently. The following data were extracted: population characteristics (year of publication, study design, country in which the study was performed, number of patients), short-term outcome parameters (operative time, intraoperative blood loss, postoperative hospital stay, retrieved lymph nodes, postoperative complications), and longterm outcome parameters (recurrence, 3-year diseasefree survival (DFS), 3-year overall survival (OS)). The collected data were double-checked by each author, and any discrepancies were resolved by rechecking and discussion.

Assessment of study quality and risk of bias

RCTs were assessed using the revised Cochrane risk-ofbias tool [16]. For observational studies, the Newcastle–Ottawa quality assessment scale (NOS) was used to assess the quality of the included studies [17]. The score ranged from 0 to 9 stars, and studies with a score of ≥ 6 were considered to be of a high quality. For each outcome, a funnel plot was used to examine the publication bias among the included studies.

Statistical analyses

All statistics analyses were carried out using Review Manager version 5.3 software (The Cochrane Collaboration, Oxford, UK). The random effects model were used. Heterogeneity was assessed using the I^2 statistic. Odds ratio (OR) with corresponding 95% confidence interval (CI) was evaluated for categorical variables. The mean difference (MD) with corresponding CI was assessed for continuous variables. The mean with standard deviation (SD) was estimated from the median, the range, and the size of a sample using the method of Hozo et al. [18]. Survival outcome was analyzed according to the pooled hazard ratio (HR) and 95% CI. If the HR was not provided directly, an estimated HR was calculated from Kaplan–Meier curves according to the method of Tierney et al. [19]. The *P* value of < 0.05 was defined statistically significant.

Results

Study characteristics

The comprehensive electronic literature search detected 1385 articles. In total, 392 articles were removed due to duplication. According to the eligible criteria, 849 were excluded by title/abstract screening. The remaining 144

articles were evaluated by full-text review. Ultimately, 23 studies with 13698 patients were included (Fig. 1) [20–42]. Although two RCTs were from the same trial (CLASS-01 trial, NCT01609309) [31, 38], one reported the short-term outcomes [31] and the other was a follow-up that reported the long-term outcomes [38], so both were included in this study to analyze the results of each. The included studies were 5 RCTs, 8 case-matched studies, and 10 cohort studies. The characteristics of the included studies are summarized in Table 1.

The study quality and risk of bias

The risk of bias assessed using the revised Cochrane risk-of-bias tool is shown in Table 2. For overall risk-of-bias judgement, all included RCTs were rated as low risk of bias. The quality of the included observational studies was assessed using the NOS, and all studies were graded as a high quality (Table 3). In addition, we conducted a funnel plot analysis to assess the possibility of a publication bias (Fig. 2). The spread of the distribution of the effect sizes of the studies in the funnel plot was more pronounced in observational studies than in others.

Short-term outcomes

Operative time

A total of 21 studies with 6222 patients (4 RCTs with 2651 patients, 7 case-matched studies with 1792 patients, and 10 cohort studies with 1779 patients) reported operative time (Table 4). The meta-analysis showed that the operative time of the LDG group was significantly longer than that in the ODG group in RCTs (MD: 49.2, 95% CI: 29.38 to 69.02, P < 0.00001), case-matched studies (MD: 32.25, 95% CI: 15.2 to 55.3, P = 0.0006), and cohort studies (MD: 47.85, 95% CI: 29.37 to 66.33, P < 0.00001) (Fig. 3).

Intraoperative blood loss

In total, 17 studies with 4831 patients (3 RCTs with 1562 patients, 5 case-matched studies with 1612 patients, and 9 cohort studies with 1657 patients) revealed intraoperative blood loss (Table 4). The LDG group showed significantly less intraoperative blood loss than the ODG group in RCTs (MD: – 35.91, 95% CI: – 67.54 to – 4.28, P=0.03), case-matched studies (MD: – 44.89, 95% CI: – 64.65 to – 25.12, P < 0.00001), and cohort studies (MD: – 179.3, 95% CI: – 235.81 to – 122.8, P < 0.00001) (Fig. 4).

Postoperative hospital stay

Twenty-one studies with 6222 patients (4 RCTs with 2651 patients, 7 case-matched studies with 1792 patients,



Fig. 2 Funnel plot of publication bias. a Operative time. b Intraoperative blood loss. c Postoperative hospital stay. d Retrieved lymph nodes. e Postoperative complications. f Recurrence. g The 3-year disease-free survival. h The 3-year overall survival

and 10 cohort studies with 1779 patients) showed postoperative hospital stay (Table 4). The LDG group had significantly less postoperative hospital stay than the ODG group in RCTs (MD: -0.73, 95% CI: -1.28 to -0.19, P = 0.009), case-matched studies (MD: -2.49, 95% CI: -3.84 to -1.13, P = 0.0003), and cohort studies (MD: -2.75, 95% CI: -4.1 to -1.41, P < 0.00001) (Fig. 5).

Table 4 Sum	mary of met	ta-analysis											
		Randomiz	zed controlle	d trials		Case-mat	tched studies			Cohort st	udies		
Outcomes	Measures	Study, n	Patients, n	Point esti- mation	95% CI	Study, n	Patients, n P	oint esti- nation	95% CI	Study, n	Patients, n	Point esti- mation	95% CI
Short-term													
Operative time	MD	4	2651	49.2	29.38, 69.02	7	1792	32.25	15.2, 55.3	10	1779	47.85	29.37, 66.33
Intraop- erative blood loss	MD	e	1562	- 35.91	-67.54, -4.28	Ś	- 1612	- 44.89	- 64.65, - 25.12	6	1657	- 179.3	- 235.81, - 122.81
Postop- erative hospital stay	MD	4	2651	- 0.73	-1.28, -0.19	٢	1792	- 2.49	- 3.84, - 1.13	10	1779	-2.75	-4.1, -1.41
Retrieved lymph nodes	MD	4	2651	-1.19	-2.23, -0.04	٢	1792	-0.14	-1.63, -1.35	10	1779	0.21	- 2.16, 2.58
Postop- erative compli- cations	OR	4	2651	0.82	0.56, 1.20	×	9268	0.84	0.74, 0.95	10	1779	0.6	0.44, 0.84
Long-term													
Recur- rence	OR	5	2013	1.1	0.87, 1.39	7	1302	1.04	0.82, 1.32	6	1210	0.85	0.66, 1.09
3-year DFS	HR	c,	2209	1.07	0.88, 1.31	3	1422	0.83	0.53, 1.30	NA	NA	NA	NA
3-year OS	HR	7	2013	1.11	0.87, 1.43	5	1552	0.68	0.38, 1.24	NA	NA	NA	NA
<i>CI</i> confidence	interval, M	'D mean di	fference, OH	e odds ratio, <i>H</i>	<i>HR</i> hazard ratio, <i>DH</i>	S disease	-free survival,	OS overall su	urvival, NA not app	licable			

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Test for subgroup differences: Chi² = 1.16, df = 2 (P = 0.56), l² = 0%

Fig. 3 Results of the meta-analysis of operative time stratified by study design

Number of retrieved lymph nodes

A total of 21 studies with 6222 patients (4 RCTs with 2651 patients, 7 case-matched studies with 1792 patients, and 10 cohort studies with 1779 patients) reported the number of retrieved lymph nodes (Table 4). The number of retrieved lymph nodes was significantly larger in the ODG group than in the LDG group in RCTs (MD: -1.19, 95% CI: -2.23 to -0.04, P = 0.04). In contrast, there were no significant differences between the groups in case-matched studies (MD: -0.14, 95% CI: -1.63 to 1.35, P = 0.85) and cohort studies (MD: 0.21, 95% CI: -2.16 to 2.58, P = 0.86) (Fig. 6).

Postoperative complications

Twenty-two studies with 13,698 patients (4 RCTs with 2651 patients, 8 case-matched studies with 9268 patients, and 10 cohort studies with 1779 patients) revealed the incidence of

postoperative complications (Table 4). There were no significant differences between the two groups in RCTs (OR: 0.82, 95% CI: 0.56 to 1.20, P = 0.30). Conversely, the LDG group had a significantly lower incidence of postoperative complications than the ODG group in case-matched studies (OR: 0.84, 95% CI: 0.74 to 0.95, P = 0.006) and cohort studies (OR: 0.60, 95% CI: 0.44 to 0.84, P = 0.002) (Fig. 7).

Results of long-term outcomes

Recurrence

In total, 10 studies with 4525 patients (2 RCTs with 2013 patients, 2 case-matched studies with 1302 patients, and 6 cohort studies with 1210 patients) showed the incidence of recurrence (Table 4). There were no significant differences between the two groups in RCTs (OR: 1.10, 95% CI: 0.87 to 1.39, P = 0.45), case-matched studies (OR: 1.04, 95% CI: 0.82 to 1.32, P = 0.76), and

	Lap	aroscop	by		Open			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.2.1 Randomized co	ntrolled	trial							
Hu 2016	105.5	88.6	79	117.3	84.5	67	6.3%	-11.80 [-39.93, 16.33]	
Wang 2019	91.4	90.9	222	117.5	103.5	220	6.4%	-26.10 [-44.27, -7.93]	
Hyung 2020	152.4	260.5	492	225	211.5	482	6.3%	-72.60 [-102.37, -42.83]	
Subtotal (95% CI)			793			769	19.0 %	-35.91 [-67.54, -4.28]	\bullet
Heterogeneity: Tau ² =	612.34;	Chi ² = !	9.53, d	f = 2 (P :	= 0.009)	; i ² = 79	3%		
Test for overall effect:	Z = 2.23	8 (P = 0.)	03)						
1.2.2 Case-matched	studv								
Shuang 2011	200	125	35	300	250	35	4.6%	-100 00 (-192 60 -7 40)	
Zhang 2015	200	40	86	260	25	86	6.5%	-60.00 [-69.97 -50.03]	•
Garbarino 2020	140.8	170.9	34	180.3	165.3	34	5.0%	-39.50 [-119.42, 40.42]	
Wang 2020	92	79.1	190	117	31.8	190	6.5%	-25.00 [-37.12, -12.88]	+
Huang 2021	78.7	98.9	461	121.3	115.5	461	6.5%	-42.60 [-56.48, -28.72]	+
Subtotal (95% CI)			806			806	29.0%	-44.89 [-64.65, -25.12]	◆
Heterogeneity: Tau ² =	298.27;	Chi ² = 3	20.63,	df = 4 (F	e = 0.00	04); l² =	81%		
Test for overall effect:	Z= 4.45	5 (P < 0.)	00001)						
123 Cobort study									
Lux 2000	160	37.5	26	241.2	01.2	25	6 1 04	01 20 (110 00 42 72)	_ _
Hui 2000	100	37.0	20	241.3	91.3	20	0.170	-01.30 [-119.00, -42.72]	
Du 2009 Hwana 2000	222.2	20	10	190	156.7	90	0.0% 6.0%	-00.00 [-94.32, -77.00]	
Hwang 2009	333.3	09.2	40	440.0	100.7	00 60	0.0% 5.0%	-107.30[-149.91,-04.09]	I
Huang 2010 7boo 2014	131.9	00.7	246	342.3	1/0./	242	0.970	172 00 [102 47 162 62]	+
Cordon 2012	120	07.2	340	301	100	125	0.4% 5.10/	-173.00 [-182.47, -103.03]	
Hoeodo 2015	007	37.3	22	430	432.3	135	6.6%	-224 00 [-225 56 -212 44]	.
Motoudo 2010	90 60	1425	52	214	470.6	44 67	2.0%	-224.00 [-235.50, -212.44]	
Shihuya 2010	24.1	142.U 66.A	07	167.1	470.0	24	5.0%	-203.00 [-403.03, -102.37]	
Subtotal (95% CI)	34.1	50.4	807	157.1	125.5	850	52.0%	-179.30 I-235.81122.801	•
Hotorogeneity: Tou ² -	6765 4	8. Chi≊ -	· //1 1	1 df - 9	(P < 0)	000	· IZ - 0.9%		•
Test for overall effect:	7 = 6.22	0,011 -)/P < 0 i	00001)	1, ui – 0	(i = 0.)	50001)	,1 = 30 %		
	- 0.22		,						
Total (95% CI)			2406			2425	100.0%	-114.31 [-150.71, -77.92]	◆
Heterogeneity: Tau² =	5277.4	9; Chi² =	952.0	1, df = 1	6 (P < 0	.00001); l² = 989	6	
Test for overall effect:	Z = 6.16	6 (P ≤ 0.0	00001)						Favours (Laparoscopy) Favours (Open)
Test for subgroup diff	erences	: Chi²=	20.96,	df = 2 (l	P < 0.00	01), I² =	= 90.5%		· · · · · · · · · · · · · · · · · · ·

Fig. 4 Results of the meta-analysis of intraoperative blood loss stratified by study design

cohort studies (OR: 0.85, 95% CI: 0.66 to 1.09, P = 0.21) (Fig. 8).

The 3-year DFS

Six studies with 3631 patients (3 RCTs with 2209 patients and 3 case-matched studies with 1422 patients) reported the 3-year DFS (Table 4). There were no significant differences between the two groups in RCTs (HR: 1.07, 95% CI: 0.88 to 1.31, P = 0.51) and case-matched studies (HR: 0.83, 95% CI: 0.53 to 1.3, P = 0.42) (Fig. 9). However, the LDG group tended to be correlated with favorable 3-year DFS in casematched studies compared to in RCTs.

The 3-year OS

A total of 7 studies with 3565 patients (2 RCTs with 2013 patients and 5 case-matched studies with 1552 patients) showed the 3-year OS (Table 4). There were no significant differences between the two groups in RCTs (HR: 1.11, 95% CI: 0.87 to 1.43, P = 0.40) and

case-matched studies (HR: 0.68, 95% CI: 0.38 to 1.24, P = 0.21) (Fig. 10). However, the LDG group tended to be associated to favorable 3-year OS in case-matched studies compared to in RCTs.

Discussion

In this study, we performed a meta-analysis including 23 studies for 5 short-term outcomes and 3 long-term outcomes. There was no difference in estimated treatment effects between RCTs and case-matched studies for all outcomes except for the number of retrieved lymph nodes and postoperative complications. For all analyzable items, the results of cohort studies were similar to those of case-matched studies. In terms of short-term outcomes, both RCTs and case-matched studies found significantly longer operative time, less intraoperative blood loss, and shorter postoperative complications were significantly less in case-matched studies but not in RCTs. However, given

	Lapa	rosco	ру	C)pen			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.3.1 Randomized co	ontrolled	trial							
Hu 2016	10.8	5.9	519	11.3	7.6	520	6.3%	-0.50 [-1.33, 0.33]	
Park 2018	9.8	7	100	9.1	5.5	96	5.0%	0.70 [-1.06, 2.46]	
Wang 2019	9.9	3.7	222	10.9	5.2	220	6.3%	-1.00 [-1.84, -0.16]	
Hyung 2020	8	6.3	492	9.1	6.3	482	6.4%	-1.10 [-1.89, -0.31]	
Subtotal (95% CI)			1333			1318	24.0%	-0.73 [-1.28, -0.19]	•
Heterogeneity: Tau ² =	: 0.08; Cl	ni² = 4.	05, df=	= 3 (P =	0.26);	I ² = 269	Хо		
Test for overall effect:	Z = 2.63	(P = 0	.009)						
1.3.2 Case-matched	study								
Scatizzi 2011	7	11	30	q	43	30	23%	-2.00 [-6.23, 2.23]	
Shuang 2011	12	7.8	35	17	9.3	35	2.4%	-5.00 (-9.02 -0.98)	
Zhang 2015	.2	1.7	86	12	2.5	86	6.5%	-4.00 [-4.64, -3.36]	-
Kim 2019	9.6	4.3	60	11.5	5.1	60	5.2%	-1.90 [-3.59, -0.21]	
Garbarino 2020	11.8	8.3	34	15.8	13.7	34	1.6%	-4.00 [-9.38, 1.38]	
Wang 2020	11.5	4.5	190	13.1	5.1	190	6.2%	-1.60 [-2.57, -0.63]	
Huang 2021	13	8.3	461	14.1	8.6	461	6.0%	-1.10 [-2.19, -0.01]	
Subtotal (95% CI)			896			896	30.1%	-2.49 [-3.84, -1.13]	•
Heterogeneity: Tau ² =	2.05; Cl	ni² = 31	1.36, dt	(= 6 (P <	< 0.00	01); I ^z =	81%		
Test for overall effect:	Z = 3.60	(P = 0	.0003)						
1.3.3 Cohort study									
Hur 2008	7	4	26	10.3	3.3	25	4.7%	-3.30 [-5.31, -1.29]	<u> </u>
Du 2009	8.6	1.2	78	12.1	2.5	90	6.6%	-3.50 [-4.08, -2.92]	+
Hwang 2009	9.8	6.9	45	11.1	5.6	83	4.2%	-1.30 [-3.65, 1.05]	
Huang 2010	9.2	3.4	66	11.4	4.6	69	5.6%	-2.20 [-3.56, -0.84]	
Zhao 2011	7.9	3.6	346	10.7	5.8	313	6.4%	-2.80 [-3.55, -2.05]	+
Chun 2012	7	16.1	52	7	1.6	67	2.1%	0.00 [-4.39, 4.39]	
Gordon 2013	8.4	4.1	66	18.1	16.1	135	3.5%	-9.70 [-12.59, -6.81]	<u> </u>
Hosoda 2015	9.7	0.5	32	10.3	0.4	44	6.8%	-0.60 [-0.81, -0.39]	•
Matsuda 2018	7	13.3	61	9	9.8	67	2.4%	-2.00 [-6.08, 2.08]	
Shibuya 2019	12.3	5.7	87	14.5	6.8	27	3.6%	-2.20 [-5.03, 0.63]	
Subtotal (95% CI)			859			920	45.9%	-2.75 [-4.10, -1.41]	•
Heterogeneity: Tau ² =	: 3.49; Cl	ni² = 1	49.29, (df = 9 (P	< 0.0	0001); I	²= 94%		
Test for overall effect:	Z= 4.00	(P < 0	.0001)						
Total (95% CI)			3088			3134	100.0%	-2.13 [-2.91, -1.35]	◆
Heterogeneity: Tau ² =	2.30; CI	ni² = 23	35.34, (df = 20 (P < 0.	00001);	I² = 92%		
Test for overall effect:	Z= 5.38	(P < 0	.00001)					-10 -5 0 5 10 Favours (Laparoscopy) Eavours (Open)
Test for subgroup diff	ferences	: Chi ^z :	= 11.39	, df = 2 i	(P = 0)	.003), I ^a	= 82.4%		ravous (Eaparoscopy) ravous (open)

Fig. 5 Results of the meta-analysis of postoperative hospital stay stratified by study design

the distribution of the 95% CIs for postoperative complications, we considered the estimated treatment effect in both studies to be comparable. Regarding long-term outcomes, although LDG had relatively better 3-year DFS and 3-year OS in case-matched studies, there was no significant difference between LDG and ODG in both RCTs and case-matched studies. Thus, the findings of RCTs and case-matched studies were similar for almost all outcomes.

The estimated treatment effects of LDG in casematched studies were intermediate between RCTs and cohort studies in terms of intraoperative blood loss, postoperative hospital stay, retrieved lymph nodes, and recurrence. RCTs can adjust for all confounders (including unknown ones), whereas propensity score matching, a typical case-matching method, has been shown to potentially miss some confounders [43]. Therefore, such differences in estimated treatment effects among study designs may be due to the different degree of adjustment for covariates in each study design. The amount of intraoperative blood loss, hospitalization period, number of retrieved lymph nodes, and recurrence are outcomes that can be objectively assessed from medical records, surgical records, pathology reports, and imaging findings. Hence, it is suggested that differences in research design may affect even objective endpoints. In addition, it has been reported that observational studies such as case-matched studies and cohort studies may overestimate treatment effects [44]. The nature of the overestimation of observational studies, which was also observed in this study regarding upper gastrointestinal surgery areas, is consistent with the results of a study

	Lapa	rosco	ру	(Open			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.4.1 Rantomized co	ntrolled	trial							
Hu 2016	36.1	16.7	519	36.9	16.1	520	6.3%	-0.80 [-2.79, 1.19]	
Park 2018	37	13.4	100	39.7	13.3	96	4.8%	-2.70 [-6.44, 1.04]	
Wang 2019	29.5	10.4	222	31.4	12.3	220	6.2%	-1.90 [-4.02, 0.22]	
Hyung 2020	46.8	18	492	47.2	16.2	482	6.2%	-0.40 [-2.55, 1.75]	
Subtotal (95% CI)			1333			1318	23.6%	-1.19 [-2.33, -0.04]	◆
Heterogeneity: Tau ² =	0.00; C	hi² = 1	.72, df=	= 3 (P =	0.63);	$l^{2} = 0\%$			
Test for overall effect:	Z = 2.03	8 (P = 0	0.04)						
1.4.2 Case-matched	study								
Scatizzi 2011	31	11	30	37	20.3	30	2.1%	-6.00 [-14.26, 2.26]	
Shuang 2011	35	14	35	38	15	35	2.7%	-3.00 [-9.80, 3.80]	
Zhang 2015	20	1.2	86	21	1	86	7.2%	-1.00 [-1.33, -0.67]	•
Kim 2019	30.5	15.5	60	32.8	16.9	60	3.2%	-2.30 [-8.10, 3.50]	
Garbarino 2020	26	10.6	34	26.1	12.3	34	3.5%	-0.10 [-5.56, 5.36]	
Wang 2020	30.2	10.8	190	28.1	10.1	190	6.2%	2.10 [-0.00, 4.20]	
Huang 2021	31.3	10.8	461	30.5	12.1	461	6.7%	0.80 [-0.68, 2.28]	
Subtotal (95% CI)			896			896	31.6%	-0.14 [-1.63, 1.35]	•
Heterogeneity: Tau ² =	: 1.64; C	hi² = 1	5.31, di	f= 6 (P =	= 0.02)); I^z = 61	1%		
Test for overall effect:	Z = 0.19	9 (P = 0).85)						
1.4.3 Cohort study									
Hur 2008	30.5	16.5	26	41.3	17.8	25	1.7%	-10.80 [-20.23, -1.37]	
Du 2009	23.5	6	78	21	7.5	90	6.3%	2.50 [0.46, 4.54]	
Hwang 2009	35.6	14.2	45	38.3	11.4	83	3.9%	-2.70 [-7.52, 2.12]	
Huang 2010	25.8	12.5	66	24.5	10.3	69	4.7%	1.30 [-2.57, 5.17]	
Zhao 2011	33.2	12.5	346	32.8	15.6	313	6.2%	0.40 [-1.77, 2.57]	
Chun 2012	39.1	15.2	52	39.3	11.2	67	3.8%	-0.20 [-5.13, 4.73]	
Gordon 2013	35.9	12.6	66	36.6	14.5	135	4.6%	-0.70 [-4.60, 3.20]	
Hosoda 2015	44	2	32	39	2	44	7.0%	5.00 [4.09, 5.91]	*
Matsuda 2018	29	12.5	61	33	12.8	67	4.2%	-4.00 [-8.39, 0.39]	
Shibuya 2019	44.8	14.3	87	41.7	18.7	27	2.3%	3.10 [-4.57, 10.77]	
Subtotal (95% CI)			859			920	44.8%	0.21 [-2.16, 2.58]	•
Heterogeneity: Tau ² =	: 9.96; C	hi² = 5	2.99, di	f= 9 (P	< 0.00	001); I ^z	= 83%		
Test for overall effect:	Z = 0.18	8 (P = 0).86)						
T-4-1 (05%) ON			0000				100.00	0.001 4 70 4 000	
Total (95% CI)		1.1 (1.5.1.) 	3088	10%-100 621/10%-10	(2000) • 37 · · · · ·	3134	100.0%	-0.32 [-1.73, 1.08]	· · · •
Heterogeneity: Tau ² =	: 7.04; C	hi² = 1	78.78,	df = 20 (P < 0.	00001)	l ² = 89%		-20 -10 0 10 20
Test for overall effect:	Z=0.45	5 (P = 0).65)						Favours (Open) Favours (Laparoscopy)
Test for subaroup diff	ferences	Chi ² :	= 1.79	df = 2/8	P = 0.4	1) $ \vec{r} = 1$	0%		······································

Fig. 6 Results of the meta-analysis of retrieved lymph nodes stratified by study design

conducted in the lower gastrointestinal surgery field [2], indicating that this review is significant in terms of accumulating evidence regarding differences in treatment effects among study designs in the gastrointestinal surgery field. Possible causes of overestimation in observational studies include missing data, possible crossover, publication bias, selective reporting of results, selection bias, outcome ascertainment bias, immortal-time bias, and residual confounding [43, 44]. Therefore, although observational studies are a very useful research tool in real clinical practice, the design and actual implementation of the analysis must be critically evaluated on a

case-by-case basis in order to assess the true magnitude of treatment effects.

The strengths of this study are its novelty in the absence of similar studies in the field of upper gastrointestinal surgery and the inclusion of a relatively large number of studies to assess the differences among RCTs, case-matched studies, and cohort studies. However, there are several limitations of the present study. First, cohort studies lacked the long-term outcome data for calculating the HR needed to conduct a meta-analysis. These would have allowed us to examine in more detail the differences in long-term outcomes between the study designs. Second, only published studies were _

	Laparos	сору	Oper	n		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.5.1 Randomized co	ntrolled tr	ial					
Hu 2016	79	519	67	520	10.0%	1.21 [0.85, 1.72]	- -
Park 2018	17	100	18	96	2.5%	0.89 [0.43, 1.84]	
Wang 2019	29	222	39	220	4.8%	0.70 [0.41, 1.17]	
Hyung 2020	77	492	113	482	11.6%	0.61 [0.44, 0.84]	
Subtotal (95% CI)		1333		1318	28.8%	0.82 [0.56, 1.20]	◆
Total events	202		237				
Heterogeneity: Tau ² =	0.09; Chi ²	²= 8.61,	df = 3 (P	= 0.03)	; l² = 65%		
Test for overall effect:	Z = 1.03 (F	P = 0.30)				
1.5.2 Case-matched	study						
Scatizzi 2011	2	30	8	30	0.5%	0.20 [0.04, 1.02]	
Shuang 2011	2	35	3	35	0.4%	0.65 [0.10, 4.13]	
Zhang 2015	9	86	13	86	1.6%	0.66 [0.26, 1.63]	
Yoshida 2018	397	3738	451	3738	39.5%	0.87 [0.75, 1.00]	=
Kim 2019	8	60	8	60	1.2%	1.00 [0.35, 2.87]	
Garbarino 2020	10	34	12	34	1.3%	0.76 [0.28, 2.12]	
Wang 2020	24	190	32	190	4.0%	0.71 [0.40, 1.27]	
Huang 2021	68	461	80	461	9.9%	0.82 [0.58, 1.17]	
Subtotal (95% CI)		4634		4634	58.4%	0.84 [0.74, 0.95]	◆
Total events	520		607				
Heterogeneity: Tau ² =	0.00; Chi ²	²= 3.99,	df = 7 (P	= 0.78)	; I² = 0%		
Test for overall effect:	Z = 2.73 (F	P = 0.00	6)				
153 Cohort study							
	4	26	4	26	200	0.05 (0.21 / 22)	
Du 2000	4	20	4	20	1 20%	0.80 [0.21, 4.32]	
Du 2009 Hwong 2000	7	10	10	90	1.270	0.07 [0.25, 1.95]	
Hwang 2009	<i>.</i>	40	10	00 60	1.270	1.34 [0.47, 3.01]	
Huang 2010	4	246	44	242	0.970	0.34 [0.10, 1.13]	
Zild0 2011	24	540	41	313	4.7 %	0.49 [0.29, 0.04]	
Condep 2012	о 0	52	22	107	0.9%		
Gordon 2013	9	00	33	135	2.1%	0.49 [0.22, 1.09]	
Motoudo 2015	1	32	4	44	0.3%	0.32 [0.03, 3.03]	
Matsuua 2018 Obibuwa 2018	3	01	о 4	07	0.0%	0.04 [0.10, 2.80]	
Shipuya 2019 Subtotal (95% CI)	4	8/	1	020	0.3% 12.7%	1.25 [0.13, 11.71]	
Total quanta	67	033	105	520	12.1 /0	0.00 [0.44, 0.04]	•
Hotorogonoity: Tou?-	0/ 0.00.05	2-601	0/D = 120	- 0.75	· 12 – 004		
Toot for everall effect:	7 - 2 06 /	- 0.91,	ui=9(P 2)	- 0.75)	, I ⁻ = 0%		
restior overall effect.	∠ = 3.00 (f	0.00	2)				
Total (95% CI)		6826		6872	100.0%	0.79 [0.71, 0.89]	•
Total events	789		969				
Heterogeneity: Tau ² =	0.00; Chi ²	²= 21.97	7, df = 21	(P = 0.4	40); l² = 49	%	
Test for overall effect:	Z = 3.90 (F	P < 0.00	01)	100	2.5		UUD U.Z 1 5 ZU Favoure (Lanaroscony) Favoure (Open)
Test for subgroup diff	erences: C	Chi² = 3.	47. df = 2	(P = 0.	18), l ² = 4	2.3%	ravous (Laparoscopy) ravous (Open)

Fig. 7 Results of the meta-analysis of postoperative complications stratified by study design

included in the present study, which made it difficult to eliminate potential publication bias. Finally, most of the articles included in this review were conducted in East Asia. Therefore, more extensive studies should be conducted in other countries and regions to improve the quality of the research and to find general trends in differences among study designs.

In recent years, observational data representative of clinical practice has become available from nationwide clinical databases, such as the National Clinical Database (NCD) and the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) [45, 46]. Given this background, case-matched studies using modern design methods such as propensity score matching will become more and more important in the future because it is an efficient way to evaluate the effects of interventions in typical clinical settings [1]. In addition, the results of

	Laparos	сору	Ope	n		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.6.1 Randomized co	ntrolled tri	al					
Yu 2019	95	519	85	520	18.9%	1.15 (0.83, 1.58)	
Hyung 2020	76	492	72	482	16.0%	1.04 [0.73, 1.48]	
Subtotal (95% CI)		1011		1002	34.9%	1.10 [0.87, 1.39]	+
Total events	171		157				
Heterogeneity: Tau ² =	0.00; Chi ²	= 0.16,	df = 1 (P	= 0.69)); I² = 0%		
Test for overall effect:	Z = 0.76 (F	P = 0.45)				
1.6.2 Case-matched	study				1.211 10 10 10		
Wang 2020	49	190	47	190	9.1%	1.06 [0.67, 1.68]	
Huang 2021	140	461	137	461	24.7%	1.03 [0.78, 1.37]	T
Subtotal (95% CI)		651		651	33.8%	1.04 [0.82, 1.32]	—
Total events	189		184				
Heterogeneity: Tau* =	0.00; Chi*	= 0.01,	df = 1 (P	= 0.93)); 1* = 0%		
l est for overall effect:	Z = 0.31 (F	' = 0.76)				
1.6.3 Cohort study							
Hur 2008	8	26	6	25	1.3%	1.41 [0.41, 4.86]	
Du 2009	22	78	31	90	4.5%	0.75 [0.39, 1.44]	
Hwang 2009	6	45	17	83	1.9%	0.60 [0.22, 1.64]	
Zhao 2011	147	346	141	313	20.6%	0.90 [0.66, 1.23]	
Hosoda 2015	3	32	2	44	0.6%	2.17 [0.34, 13.83]	
Matsuda 2018	9	61	16	67	2.4%	0.55 [0.22, 1.36]	
Subtotal (95% CI)		588		622	31.3%	0.85 [0.66, 1.09]	•
Total events	195		213				
Heterogeneity: Tau ² =	0.00; Chi²	= 3.25,	df = 5 (P	= 0.66)); I² = 0%		
Test for overall effect:	Z=1.25 (F	P = 0.21)				
Total (95% CI)		2250		2275	100.0%	0.99 [0.87, 1.14]	
Total events	555		554				
Heterogeneity: Tau ² =	0.00; Chi ²	= 5.66,	df = 9 (P	= 0.77)); I² = 0%	-	
Test for overall effect:	Z = 0.07 (F	P = 0.94)				Eavours (Lanaros conv) Eavours (Onen)
Test for subgroup diff	erences: C	hi² = 2.	24, df = 2	(P = 0.	.33), I ² = 1	0.6%	ravous [Eaparoscopy] ravous [open]

Fig. 8 Results of the meta-analysis of recurrence stratified by study design

Hazard Ratio Hazard Ratio IV, Random, 95% CI Study or Subgroup log[Hazard Ratio] SE Weight IV, Random, 95% CI 1.7.1 Randomized controlled trial Park 2018 0.094566 0.953817 1.0% 1.10 [0.17, 7.13] Yu 2019 0.091661 0.135721 46.9% 1.10 [0.84, 1.43] Hyung 2020 0.03447 0.156265 35.4% 1.04 [0.76, 1.41] Subtotal (95% CI) 1.07 [0.88, 1.31] 83.3% Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 2 (P = 0.96); l² = 0% Test for overall effect: Z = 0.66 (P = 0.51) 1.7.2 Case-matched study Kim 2019 0.492805 3.6% 0.57 [0.22, 1.51] -0.55626 Wang 2020 -0.08617 0.264947 12.3% 0.92 [0.55, 1.54] Huang 2021 -0.053 1.0268549 0.8% 0.95 [0.13, 7.10] Subtotal (95% CI) 16.7% 0.83 [0.53, 1.30] Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 2 (P = 0.70); l² = 0% Test for overall effect: Z = 0.81 (P = 0.42) Total (95% CI) 100.0% 1.03 [0.85, 1.23] Heterogeneity: Tau² = 0.00; Chi² = 1.82, df = 5 (P = 0.87); l² = 0% 0.2 0.5 5 2 Test for overall effect: Z = 0.27 (P = 0.79) Favours [Laparoscopy] Favours [Openl] Test for subgroup differences: Chi² = 1.02, df = 1 (P = 0.31), l² = 2.2%

Fig. 9 Results of the meta-analysis of the 3-year disease-free survival stratified by study design

				Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.8.1 Randomized co	ontrolled trial				
Yu 2019	0.177717	0.161724	36.8%	1.19 [0.87, 1.64]	
Hyung 2020	-0.01031	0.21083	28.2%	0.99 [0.65, 1.50]	- + -
Subtotal (95% CI)			65.0%	1.11 [0.87, 1.43]	◆
Heterogeneity: Tau² =	= 0.00; Chi ² = 0.50, df	f = 1 (P = 0.4	48); I ^z = 09	8	
Test for overall effect	Z = 0.84 (P = 0.40)				
1.8.2 Case-matched	study				
Scatizzi 2011	-0.45933	1	2.1%	0.63 [0.09, 4.48]	
Shuang 2011	-0.4217	0.5	7.8%	0.66 [0.25, 1.75]	
Kim 2019	-2.56413	1.080123	1.8%	0.08 [0.01, 0.64]	
Wang 2020	-0.08372	0.264947	21.2%	0.92 [0.55, 1.55]	
Huang 2021	-0.07647	1.038975	2.0%	0.93 [0.12, 7.10]	
Subtotal (95% CI)			35.0%	0.68 [0.38, 1.24]	
Heterogeneity: Tau ² =	= 0.11; Chi ² = 5.17, dt	f = 4 (P = 0.2	27); I ² = 23	3%	
Test for overall effect	Z = 1.25 (P = 0.21)				
Total (95% CI)			100.0%	0.95 [0.71, 1.28]	•
Heterogeneity: Tau ² =	= 0.03; Chi ² = 7.86, dt	f = 6 (P = 0.2	25); I ² = 24	1%	
Test for overall effect	Z = 0.31 (P = 0.75)				Eavours (Lanaroscony) Eavours (Open)
Test for subgroup dif	ferences: Chi ² = 2.19), df = 1 (P =	0.14), l ² =	= 54.4%	ravous (Caparoscopy) ravous (Open)

Fig. 10 Results of the meta-analysis of the 3-year overall survival stratified by study design

properly conducted and analyzed observational studies are expected to help prioritize research needs that should be addressed in more resource-intensive RCTs. Therefore, this study, which compares the estimated treatment effects of RCTs and observational studies, has important implications for clinical practice and future research.

Conclusion

Our analysis indicated that the estimated treatment effects of LDG for AGC in the case-matched study were almost the same as in the RCTs. However, to assess the true magnitude of the treatment effect, the design and actual implementation of the analysis must be critically evaluated.

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Authors' contributions Ryota Otsuka conceived and designed the study. Yasunori Matsumoto and Ryota Otsuka performed the literature search and data acquisition. Takashi Toyozumi, Hiroshi Suito, Tetsuro Isozaki, Yoshihiro Kurata, and Ryota Otsuka contributed to the data analysis and interpretation. The manuscript was prepared by Ryota Otsuka under the supervision of Hideki Hayashi, Masaya Uesato, Koichi Hayano, Kentaro Murakami, Masayuki Kano, and Hisahiro Matsubara. All authors read and approved the final manuscript.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki.

Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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