Original Article

Laparoscopic versus open surgery in treating patients with gallbladder cancer: a systematic review and meta-analysis

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Background: Concerns over the security of laparoscopic radical operation for gallbladder cancer (GBC) persist. This systematic review and meta-analysis attempted to compare the safety and efficacy of laparoscopic surgery (LS) versus open surgery (OS) in the treatment of GBC.

Methods: The PubMed, EMBASE, and Web of Science were searched from inception to July 18, 2022. Literature search, quality assessment, and data extraction were completed independently and in duplicate. Effect-size estimates expressed as weighted mean difference (WMD) or odds ratio (OR) with 95% confidence interval (CI) were derived under the random-effects model.

Results: A total of 27 independent studies including 2,868 participants were meta-analyzed. Significance was noted for intraoperative blood loss (WMD: −117.194, 95% CI: −170.188 to 64.201, P<0.001), harvested lymph nodes (WMD: −1.023, 95% CI: −1.776 to −0.269, P=0.008), postoperative hospital stay (WMD: −3.555, 95% CI: −4.509 to −2.601, P<0.001), postoperative morbidity (OR: 0.596, 95% CI: 0.407 to 0.871, P=0.008), overall survival rate at 2-year (OR: 1.524, 95% CI: 1.143 to 2.031, P=0.004), T2 survival at 1-year (OR: 1.799, 95% CI: 1.777 to 2.749, P<0.01) and 2-year (OR: 2.026, 95% CI: 1.392 to 2.949, P<0.001), as well as T3 survival at 1-year (OR: 2.669, 95% CI: 1.564 to 4.555, P<0.001) and 2-year (OR: 2.300, 95% CI: 1.308 to 4.046, P=0.004). Subgroup analyses revealed that ethnicity, incidental GBC, sample size, and follow-up period were possible sources of heterogeneity. There was a low probability of publication bias for all outcomes except postoperative morbidity.

Conclusions: Our findings indicated that LS statistically had better 2-year survival rates, less intraoperative bleeding, shorter hospitalization times, and lower rates of complications than OS. However, the superiority and even the safety of LS still remain an open question due to the impact of incidental GBC, unaccounted heterogeneity, publication bias, lymph node dissection, and port-site metastasis.

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Introduction

Gallbladder cancer (GBC) is rare, as it accounts for 1.2% of all cancer cases and 1.7% of all cancer deaths (1). The majority of GBC patients are diagnosed at advanced stages, and the prognosis is unsatisfactory, with a 5-year survival rate less than 20% worldwide (2). Factors that benefit the prognosis of GBC patients include early diagnosis and proper treatment.

With the advancement of surgical techniques and instruments, minimally invasive surgeries such as laparoscopic surgery (LS) to treat gastrointestinal malignancies have gained widespread popularity (3-5), and can greatly reduce morbidity by reducing blood loss and shortening length of hospital stay (6-8). However, the security of LS in the management of GBC has aroused special concerns. Some clinical studies have compared the safety and efficacy of LS with open surgery (OS), yet no consensus was reached thus far. For example, a meta-analysis of 18 studies conducted by Lv *et al.* (9) supported the superiority of LS in postoperative rehabilitation. Similarly, another meta-analysis of 14 studies by Nakanishi *et al.* (10) showed a trend favoring LS as a possible alternative treatment option *vis-à-vis* OS in the management of GBC, and importantly they found that survival outcomes were improved in patients at T2 and T3 stages who received LS, differing from the nonsignificant observations by Lv *et al.* (9). Therefore, whether LS can be recommended as a routine surgical option for GBC still remains an open question, calling for further evaluation in a comprehensive manner.

To yield more information and provide evidence basis for future investigations, this systematic review and meta-analysis aimed to comprehensively compare the safety and efficacy of LS versus OS in the management of GBC patients. The research has been reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-22-597/rc) and AMSTAR (Assessing the Methodological Quality of Systematic Reviews) guidelines (available at https://cdn.amegroups.cn/static/public/hbsn-22-597-1.pdf) (11).

Highlight box

Key findings

- The key finding of this systematic review and meta-analysis revealed that laparoscopic surgery (LS) had better 2-year survival rates, less intraoperative bleeding, shorter hospitalization times, and lower rates of complications than open surgery (OS) from statistical aspects. However, the superiority and safety of LS still remain uncertain due to the impact of incidental gallbladder cancer, unaccounted heterogeneity, publication bias, lymph node dissection, and port-site metastasis.

What is known and what is new?

- Some, but not all, studies have reported that LS had advantages over OS in terms of survival, intraoperative, and postoperative outcomes for gallbladder cancer.
- This is thus far the largest systematic review and meta-analysis that has comprehensively compared the efficacy and safety of LS versus OS in the management of gallbladder cancer.

What is the implication, and what should change now?

- Despite LS had better 2-year survival rates, less intraoperative bleeding, shorter hospitalization times, and lower rates of complications than OS, the superiority and even the safety of LS still remain an open question, and we agree that further validations are essential before convincing clinical conclusions can be reached at this point.

Methods

Search strategy

The PubMed, EMBASE (Excerpt Medica Database), and Web of Science were searched from inception until July 18, 2022. Search terms are shown in the supplementary materials (Appendix 1). Two authors (D.L. and L.X.) independently completed literature search, and all retrieved articles were combined with manual removal of duplicates.

Eligibility criteria

Studies eligible for inclusion in this systematic review and meta-analysis should simultaneously fulfill the following criteria: (I) comparative studies evaluating LS *vis-à-vis* OS in the treatment of GBC; (II) studies involving human beings and written in the English language; (III) outcomes focusing on survival or intraoperative or postoperative outcomes.

Studies were excluded for the following reasons: (I) non-comparative studies such as abstracts, letters, reviews, case reports, and laboratory studies; (II) studies involving robotic surgeries.

Study identification

Initially, titles and abstracts were reviewed for selection, and in the case of uncertainty full texts and supplementary files (Appendix 1) if available were reviewed. The identification process was performed by two authors (D.L. and L.X.) independently, and disagreement was resolved by discussion or consulting with a third author (Z.Y.).

Data extraction and quality assessment

Data were extracted from each eligible study independently by two authors (D.L. and L.X.) using a standardized data form, and discrepancies were adjudicated by a third author (Z.Y.). Extracted data included first author's name, year of publication, country where study was conducted, ethnicity, study design, surgery procedure type, sample number of incidental GBC diagnoses, sources of patients, sample size in LS and OS, 1-, 2-, 3-, and 5-year disease-free rates, 1-, 2-, 3-, and 5-year survival rates for each tumor stage, operation time, intraoperative blood loss, transfusion rate, number of harvested lymph nodes (LNs), R0 resection rate, days of postoperative hospital stay, postoperative morbidity rate, recurrence rate, and port-site metastasis rate. The 1-, 2-, 3-, and 5-year survival rates for each tumor stage were extracted and calculated from either reported literature values or raw data. When survival rates could not be directly obtained from the context, the Kaplan-Meier (KM) curves were digitized using the Engauge Digitizer software (version 4.1) and literately computed to generate individual patient data and survival rates.

The quality of each study was independently evaluated by two authors (D.L. and L.X.) using the Newcastle-Ottawa Scale. Quality assessment scores are shown in Table S1.

Statistical analyses

The STATA software version 14.1 (StataCorp, College Station, TX, USA) was used for this systematic review and meta-analysis.

Odds ratio (OR) and 95% confidence interval (CI) were calculated to assess discrete outcomes. Weighted mean difference (WMD) and 95% CI were calculated to assess continuous outcomes.

The inconsistency index (I^2) was employed to quantify the magnitude of statistical heterogeneity, and it represents the percentage of observed variability between studies that is due to heterogeneity instead of chance. It is widely accepted that heterogeneity is deemed statistical significance if the I^2 exceeds 50%, and higher I^2 denotes stronger evidence of heterogeneity (12). In this systematic review and meta-analysis, effect-size estimates were derived under the random-effects model because of the assumption of clinical and methodological heterogeneity across studies, which can often lead to statistical heterogeneity. What's more, in case of no statistical heterogeneity, fixed-effects and random-effects models yield nearly identical estimates, and in the presence of statistical heterogeneity, random-effects model is preferred (13). Clinical and methodological heterogeneity across studies was assessed by means of subgroup analyses.

Cumulative analyses were conducted to assess the impact of the first publication on subsequent publications and the evolution of the accumulating estimates over time. Sensitivity analyses were conducted to assess the impact of any individual publications on overall effect-size estimates by omitting one study at a time.

Publication bias refers to the reduced likelihood of studies' results being published when they are near the null, lacking of statistical significance, or otherwise of little interest (14). To appraise the presence of publication bias, Begg's funnel plots were displayed for visual inspection of symmetry. In addition, Begg's tests and Egger's tests were used to statistically assess funnel asymmetry and quantify the probability of publication bias, with significance set at a level of 10%. In addition, the Duval and Tweedie nonparametric "trim and fill" method was used to take theoretically missing studies into consideration and generate theoretically "unbiased" effect-size estimates.

Results

Qualified studies

Initially, a total of 7,972 potentially eligible articles

published in the English language were retrieved after scanning predefined public databases, and of them, 27 independent studies involving 2,868 participants were synthesized in this systematic review and meta-analysis. The selection process annexed with concrete reasons for article exclusion is shown in Figure S1.

Study characteristics

All qualified studies were retrospective in design. Of 27 studies analyzed, 4 studies enrolled patients from multicenters (15-18), and 23 studies are single center studies (7,19-40). Twenty-two studies reported overall survival, 10 T1-staged survival, 12 T2-staged survival, 7 T3-staged survival, and 9 disease-free survival. Intraoperative and postoperative data were extracted, including operative time, intraoperative blood loss, postoperative hospital stay, postoperative morbidity, R0 resection rate, transfusion rate, number of harvested LNs, overall recurrence, and port-site metastasis.

Baseline characteristics

Table 1 shows the baseline characteristics of qualified studies in this systematic review and meta-analysis. All studies were published from the year 2000 to 2022. The total sample size ranged from 16 to 834. Of 2,868 patients, 1,442 and 1,426 patients underwent LS and OS, respectively.

Survival outcomes

As for disease-free survival, no significant difference existed at 1-year (OR: 1.310), 2-year (OR: 1.266), 3-year (OR: 1.377), and 5-year (OR: 1.393) (all P>0.01) between patients undergoing LS and OS.

Regarding overall survival, a higher survival rate was noted in patients undergoing LS than with OS at 2-year (OR: 1.524, P<0.01). Contrastingly, 1-year (OR: 1.193), 3-year (OR: 1.352), and 5-year (OR: 1.284) (all P>0.01) survival rates were similar between patients undergoing LS and OS.

At T1 tumor stage, pooled survival rate showed no statistical significance at 1-year (OR: 0.783), 2-year (OR: 0.785), 3-year (OR: 0.747), and 5-year (OR: 0.689) (all P>0.01). At T2 tumor stage, pooled survival rate was higher in patients undergoing LS than with OS in 1-year (OR: 1.799), and 2-year (OR: 2.026) (both P<0.01). By contrast, 3-year (OR: 1.013), and 5-year (OR: 1.070) (both P>0.01) survival rates were comparable between patients undergoing LS and OS at T2 tumor stage.

Likewise, at T3 tumor stage, 1-year (OR: 2.669) and 2-year (OR: 2.300) (both P<0.001) survival rates were higher in patients undergoing LS than OS. However, 3-year (OR: 2.116) and 5-year (OR: 2.517) (both P>0.01) survival rates were similar between the two groups (*Table 2*). Forest plots of survival outcomes are shown in online figure (Fig. S2; available at https://cdn.amegroups.cn/static/public/hbsn-22-597-2.doc).

Intraoperative outcomes

Comparisons of intraoperative outcomes between patients undergoing LS and OS are shown in *Table 2* and forest plots are shown in online figure (Fig. S2; available at https://cdn.amegroups.cn/static/public/hbsn-22-597-2.doc).

There were no significant differences between patients undergoing LS and OS in operation time (WMD: 5.160), R0 resection rate (OR: 1.862), and transfusion rate (OR: 1.390) (all P>0.01). Patients undergoing LS had less intraoperative lower blood loss (WMD: –117.194) and a smaller number of harvested LNs (WMD: –1.023) than those undergoing OS (both P<0.01).

Postoperative outcomes

Comparisons of postoperative outcomes between patients undergoing LS and OS are presented in *Table 2* and forest plots are shown in online figure (Fig. S2; available at https://cdn.amegroups.cn/static/public/hbsn-22-597-2.doc).

Patients undergoing LS had shorter postoperative hospital stay (WMD: –3.555) and lower postoperative morbidity (OR: 0.596) than those undergoing OS (both P<0.01). No significance was observed between patients undergoing LS and OS in recurrence (OR: 1.042) and port-site metastasis (PSM) (OR: 1.597) (both P>0.01).

Subgroup analyses

Considering significant heterogeneity in overall comparisons, there is a need to explore possible causes. Subgroup analyses were conducted according to ethnicity, proportion of incidental GBC, proportion of Tis & T1 & T2, sample size, publication year, and follow-up period to compare differences in survival, intraoperative, and postoperative outcomes between patients undergoing LS and OS (*Tables 3-6*). The corresponding forest plots are

Table 1 The baseline characteristics of qualified studies in this meta-analysis

First author	Year	Country	Design	Procedure type	Multi-centre	Patients (n)		Age (years), mean ± SD or mean/median (range)		Follow-up (months), mean ± SD or mean/median (range)		Male (n/n)		IGBC (n/n)	TisT1T2 (n/n)		N1N2 (n)	
						L	O	L	O	L	O	L	O		L	O	L	O
Regmi	2021	China	RCS	EC	No	20	30	59.3±10.3	58.4±9.7	21.3 (12.0–29.0)	20.4 (12.3–29.5)	7/20	11/30	50/50	20/20	30/30	NR	NR
Nag	2021	India	RCS	EC	No	30	38	49.6±12.8	49.0±10.1	24.0	36.0	3/30	15/38	17/68	20/30	23/38	10	13
Maharjan	2021	Nepal	RCS	EC	No	10	10	51.0±9.4	49.6±8.4	12.0 (2.0–12.0)		4/10	3/10	16/20	10/10	10/10	1	1
Lee	2022	Korea	RCS	EC	No	60	135	62.2±13.6	61.6±14.6	NR	NR	98/195		57/195	60/60	135/135	10	32
Kim	2021	Korea	RCS	EC	No	17	17	72.0 (59.0–79.0)	68.0 (61.0–77.0)	16.4±5.7	20.9±10.4	4/17	4/17	NR	15/17	16/17	3	6
D'Silva	2022	Korea	RCS	EC	No	23	33	68.6±9.4	63.4±11.2	21.5 (9.0–80.0)		11/23	14/33	17/56	16/23	25/33	5	8
Cao	2021	China	RCS	EC	No	53	61	61.0 (48.0–77.0)	64.0 (39.0–79.0)	NR	NR	18/53	14/61	NR	53/53	61/61	NR	NR
Wang	2020	China	RCS	EC	No	45	61	62.6 (45.0–76.0)	65.2 (51.0–82.0)	38.0 (3.0–84.0)	33.0 (6.0–72.0)	29/45	37/61	106/106	45/45	59/61	NR	NR
Vega	2019	USA	RCS	EC	Yes	65	190	64.0 (32.0–83.0)	60.0 (32.0–81.0)	70.8 (53.6–87.3)	111.8 (57.5–153.3)	11/65	49/190	255/255	57/65	151/190	14	61
Navarro	2020	Korea	RCS	SC & EC	No	43	43	66.7±10.3	65.4±7.6	32.0 (2.0–125.0)		25/43	28/43	17/86	43/43	43/43	NR	NR
Dou	2020	China	RCS	EC	No	32	31	NR	NR	NR	NR	7/32	7/31	NR	16/32	9/31	NR	NR
Jang	2019	Korea	RCS	SC & EC	No	55	44	70.1±8.1	65.5±10.5	35.2 (3.0–139.0)	38.6 (4.0–160.0)	19/55	23/44	NR	55/55	44/44	10	20
Feng	2019	China	RCS	SC & EC	No	41	61	64.0±14.0	66.0±10.0	12.0 (2.0–93.0)		24/41	39/61	NR	33/41	45/61	7	26
Losada	2018	Chile	RCS	SC	No	16	12	55.0±13.0	6.0±12.0	30.0±17.0		4/28		NR	16/16	12/12	NR	NR
Jang	2016	Korea	RCS	SC & EC	Yes	94	103	63.8±10.9	63.1±10.4	57.9±44.9	72.4±44.5	31/94	54/103	NR	94/94	103/103	0	4
Zhang	2015	China	RCS	SC & EC	No	20	8	65.7 (37.0–81.0)	63.5 (43.0–88.0)	60.0 (6.0–129.0)		4/20	6/8	28/28	14/20	7/8	NR	NR
Itano	2015	Japan	RCS	EC	Yes	16	14	68.1±19.9	71.5±13.2	37.0	48.0	9/16	5/14	NR	16/16	14/14	NR	NR
Ha	2015	Korea	RCS	SC & EC	No	53	150	NR	62.3±9.6	59.2±44.5		20/53	72/150	NR	53/53	150/150	5	31
Agarwal	2015	India	RCS	SC & EC	No	24	46	44.0 (21.0–61.0)	49.0 (23.0–70.0)	18.0 (6.0–34.0)		7/24	12/46	4/70	NR	NR	NR	NR
Cavallaro	2014	Italy	RCS	SC & EC	No	12	18	67.3±7.6	70.8±9.3	NR	NR	6/12	8/18	16/30	10/12	10/18	1	10
Hu	2013	China	RCS	SC & EC	No	10	28	61.2 (37.0–87.0)		NR	NR	7/38		0/38	26/38		NR	NR
Goetze	2013	Germany	RCS	SC & EC	Yes	634	200	NR	NR	NR	NR	NR	NR	834/834	472/634	120/200	NR	NR
Chan	2006	China	RCS	SC & EC	No	17	23	63.7±3.1	52.6±3.5	59.7±6.9		7/17	7/23	NR	17/17	23/23	NR	NR
Cucinotta	2005	Italy	RCS	SC & EC	No	8	8	63.0±9.0	63.0±9.6	21.1 (6.0–51.0)		2/8	1/8	16/16	8/8	8/8	NR	NR
de Aretxabala	2004	Chile	RCS	NR	No	24	40	56.8±10.3	NR	NR	NR	NR	NR	NR	18/24	28/40	NR	NR
Yoshida	2000	Japan	RCS	SC & EC	No	11	11	70.8±11.0	67.5±9.2	NR	NR	3/11	2/11	NR	9/11		NR	NR
Sarli	2000	Italy	RCS	NR	No	9	11	62.3±12.7	65.3±10.9	NR	NR	3/9	2/11	4/20	11/20		NR	NR

L, laparoscopic; O, open; SD, standard deviation; IGBC, incidental gallbladder cancer; RCS, retrospective comparative study; EC, extended cholecystectomy; NR, not reported; SC, simple cholecystectomy.

shown in online figure (Fig. S3; https://cdn.amegroups.cn/static/public/hbsn-22-597-2.doc). Considering the limited number of studies in some subgroups, analyses were conducted only on items involving 10 or more independent studies.

By ethnicity, survival outcomes (T2 survival and overall survival) were significantly improved in patients of European origin who underwent LS relative to OS, and contrastingly improvement in intraoperative and postoperative outcomes was seen in patients of Asian origin, except for recurrence rate and PSM rate. By proportion of incidental GBC, there was significant improvement in survival outcomes in studies exclusively involving incidental GBC, as well as in postoperative hospital stay, and in studies involving both incidental and non-incidental GBC, significance was observed for intraoperative blood loss and number of harvested LNs. By total sample size, improvement in survival outcomes was seen in studies with total sample sizes ≥60, as well as in intraoperative and postoperative outcomes, indicating the robustness of our observations.

By publication year, statistical significance was seen for survival outcomes in studies published before 2019, yet the magnitude of effect-sizes was comparable with that of studies published after 2019. For intraoperative and postoperative outcomes, effect-sizes were statistically significant in studies published both before and after 2019. By follow-up period, only significance was seen for intraoperative and postoperative outcomes in studies irrespective of periods, and effect-size magnitude was stronger in studies with follow-up period ≥36 months.

Cumulative analyses

In cumulative analyses, there was no hint of significant impact from the first publication on subsequent publications for survival, intraoperative and postoperative outcomes (Fig. S4; available at https://cdn.amegroups.cn/static/public/hbsn-22-597-2.doc).

Sensitivity analyses

Sensitive analyses were conducted by removing each individual study to evaluate whether any single study had a significant impact on pooled estimates, and no significance was detected for most outcomes except intraoperative blood loss, postoperative hospital stay, and operation time (Fig. S5; available at https://cdn.amegroups.cn/static/public/hbsn-22-597-2.doc).

It is worth noting that as for T2 survival outcomes, exclusion of the study by Goetze and colleagues (18) involving merely incidental GBC patients exerted a large impact on pooled estimates, and considering the overlapping CIs this impact was not significant.

Publication bias

The Begg's tests and Egger's tests were used to evaluate potential publication (*Table 2*). Postoperative morbidity (Egger's test P=0.035) and survival of T2 stage at 1-year (Egger's test P=0.026) had a significantly high probability of publication bias. The effect-size estimates for survival of T2 stage at 1st year still remained statistically significant (P<0.001) after taking 5 theoretically missing studies into consideration. By contrast, the effect-size estimates for postoperative morbidity were nonsignificant (P=0.061) after additionally adding 3 theoretically missing studies (Fig. S6; available at https://cdn.amegroups.cn/static/public/hbsn-22-597-2.doc).

Discussion

The aim of this systematic review and meta-analysis was to comprehensively compare the safety and efficacy of LS versus OS in the treatment of GBC patients. Our major findings indicated that LS was generally superior to OS for GBC in terms of overall 2-year survival, 1- and 2-year survival at T2 and T3 stages. Moreover, LS was found to be associated with less intraoperative blood loss, less postoperative morbidity, higher R0 resection rate, and shorter postoperative hospital stay than OS. To the best of our knowledge, this is thus far the largest systematic review and meta-analysis that has comprehensively compared LS with OS from safety and efficacy aspects in treating GBC in the medical literature.

In routine clinical practice, LS is not generally accepted as a priority option for GBC. With the development of laparoscopic technique, a growing number of studies have adopted LS in the management of GBC. Of all patients diagnosed with GBC, about 60–80% were incidental (41), and patients with incidental GBC had a good prognosis relative to non-incidental GBC cases (42-44). It is widely accepted that for incidental GBC, radical surgery involving resection of gallbladder liver beds and regional lymph nodes was the most popular choice to achieve R0 margins and proper staging (45). Vega *et al.* reported that prior

Table 2 Meta-analyses of survival outcomes, intraoperative outcomes, and postoperative outcomes and publication bias

Outcome	Studies, n	OR/WMD	95% CI	P	I^2 (%) (P)	Begg's test		Egger's test
						P	P (continuity corrected)	P
DFS								
1-year	9	1.310	0.615 to 2.786	0.484	53.4 (0.028)	0.211	0.251	0.416
2-year	9	1.266	0.693 to 2.316	0.443	53.2 (0.029)	0.835	0.917	0.656
3-year	9	1.377	0.847 to 2.238	0.120	37.4 (0.120)	0.677	0.754	0.469
5-year	9	1.393	0.958 to 2.026	0.082	8.3 (0.367)	0.404	0.466	0.361
OS								
1-year	22	1.193	0.775 to 1.837	0.423	41.1 (0.024)	0.632	0.652	0.383
2-year	22	1.524	1.143 to 2.031	0.004	21.3 (0.182)	0.933	0.955	0.419
3-year	22	1.352	0.973 to 1.877	0.072	43.7 (0.016)	0.672	0.693	0.893
5-year	22	1.284	0.908 to 1.816	0.157	50.1 (0.005)	0.432	0.450	0.690
T1 survival								
1-year	10	0.783	0.370 to 1.657	0.522	0.0 (1.000)	0.106	0.127	0.695
2-year	10	0.785	0.439 to 1.405	0.415	0.0 (0.977)	0.151	0.178	0.265
3-year	10	0.747	0.436 to 1.278	0.286	0.0 (0.833)	0.472	0.530	0.964
5-year	10	0.689	0.408 to 1.163	0.163	0.0 (0.706)	0.281	0.323	0.526
T2 survival								
1-year	12	1.799	1.177 to 2.749	0.007	0.0 (0.967)	0.273	0.304	0.035
2-year	12	2.026	1.392 to 2.949	<0.001	0.0 (0.520)	0.891	0.945	0.212
3-year	12	1.013	0.589 to 1.740	0.963	39.4 (0.078)	1.000	1.000	0.402
5-year	12	1.070	0.766 to 1.494	0.692	0.0 (0.505)	0.891	0.945	0.582
T3 survival								
1-year	7	2.669	1.564 to 4.555	<0.001	0.0 (0.892)	0.652	0.764	0.877
2-year	7	2.300	1.308 to 4.046	0.004	0.0 (0.701)	0.293	0.368	0.478
3-year	7	2.116	0.804 to 5.571	0.129	31.5 (0.187)	0.881	1.000	0.797
5-year	7	2.517	0.859 to 7.373	0.092	32.2 (0.182)	0.453	0.548	0.413
Transfusion rate	5	1.390	0.364 to 5.305	0.630	65.7 (0.020)	0.624	0.806	0.569
R0 resection rate	7	1.862	1.153 to 3.009	0.011	0.0 (0.536)	0.881	1.000	0.444
Postoperative morbidity	15	0.596	0.407 to 0.871	0.008	20.1 (0.230)	0.067	0.075	0.026
Recurrence rate	20	1.042	0.599 to 1.814	0.883	78.8 (<0.001)	0.948	0.974	0.710
Port-site metastasis rate	16	1.597	0.937 to 2.721	0.085	0.0 (0.993)	0.019	0.022	0.800
Operation time	16	5.160	–21.897 to 32.217	0.709	96.3 (<0.001)	0.589	0.620	0.558
Intraoperative blood loss	15	–117.194	–170.188 to –64.201	<0.001	91.2 (<0.001)	0.805	0.843	0.858
The number of harvested LNs	15	–1.023	–1.776 to –0.269	0.008	73.6 (<0.001)	0.729	0.767	0.565
Postoperative hospital stay	16	–3.555	–4.509 to –2.601	<0.001	87.0 (<0.001)	0.653	0.685	0.556

OR, odds ratio; WMD, weighted mean difference; CI, confidence interval; I^2, inconsistency index; DFS, disease-free survival; OS, overall survival; LN, lymph node.

Table 3 Subgroup analyses comparing laparoscopic surgery with open surgery in terms of T2 survival at 1-, 2-, 3- and 5-year for the management of gallbladder cancer

Subgroups	Studies†, n	T2 1-year survival				T2 2-year survival				T2 3-year survival				T2 5-year survival			
		OR	95% CI	P	I^2 (%) (P)	OR	95% CI	P	I^2 (%) (P)	OR	95% CI	P	I^2 (%) (P)	OR	95% CI	P	I^2 (%) (P)
By ethnicity																	
Asia	7/7/7/7	1.636	0.665 to 4.027	0.284	0.0 (0.933)	1.820	0.963 to 3.442	0.065	0.0 (0.574)	0.845	0.422 to 1.690	0.633	36.8 (0.148)	0.827	0.483 to 1.417	0.490	20.8 (0.271)
America	1/1/1/1	0.717	0.104 to 4.933	0.736	–	0.711	0.176 to 2.865	0.632	–	0.545	0.117 to 1.763	0.254	–	1.169	0.306 to 4.462	0.819	–
Europe	4/4/4/4	1.968	1.198 to 3.232	0.007	0.0 (0.752)	2.462	1.504 to 4.032	0.001	0.0 (0.476)	2.064	1.237 to 3.446	0.006	0.0 (0.970)	1.473	0.867 to 2.501	0.152	0.0 (0.979)
By proportion of IGBC																	
All	3/3/3/3	2.101	1.272 to 3.468	0.004	0.0 (0.911)	2.663	1.614 to 4.394	0.001	0.0 (0.834)	2.077	1.233 to 3.499	0.006	0.0 (0.934)	1.429	0.833 to 2.452	0.195	0.0 (0.954)
Mix	4/4/4/4	0.931	0.227 to 3.825	0.921	0.0 (0.966)	1.195	0.433 to 3.300	0.731	0.0 (0.679)	0.855	0.253 to 2.897	0.802	38.1 (0.183)	1.183	0.358 to 3.905	0.783	40.7 (0.168)
NA	5/5/5/5	1.381	0.529 to 3.608	0.509	0.0 (0.705)	1.561	0.672 to 3.627	0.300	27.2 (0.241)	0.813	0.403 to 1.640	0.564	28.7 (0.230)	0.876	0.532 to 1.443	0.604	0.0 (0.499)
By proportion of Tis & T1 & T2																	
All	5/5/5/5	1.862	0.674 to 5.147	0.231	0.0 (0.941)	1.774	0.858 to 3.666	0.122	8.9 (0.356)	0.796	0.334 to 1.901	0.608	52.7 (0.076)	0.960	0.514 to 1.794	0.898	28.4 (0.232)
Mix	7/7/7/7	1.786	1.120 to 2.847	0.015	0.0 (0.769)	2.150	1.371 to 3.371	0.001	0.0 (0.478)	1.638	1.041 to 2.578	0.033	0.0 (0.481)	1.188	0.757 to 1.865	0.454	0.0 (0.641)
NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
By total sample size																	
<60	5/5/5/5	1.027	0.233 to 4.535	0.972	0.0 (0.957)	1.147	0.261 to 5.037	0.856	0.0 (0.763)	1.231	0.324 to 4.675	0.760	0.0 (0.900)	0.886	0.232 to 3.380	0.859	0.0 (0.739)
≥60	7/7/7/7	1.891	1.215 to 2.943	0.005	0.0 (0.828)	1.907	1.144 to 3.179	0.013	21.7 (0.264)	0.954	0.479 to 1.900	0.894	64.9 (0.009)	1.035	0.673 to 1.591	0.876	27.1 (0.222)
By published year																	
≥2019	4/4/4/4	1.410	0.401 to 4.961	0.593	0.0 (0.685)	2.410	1.067 to 5.447	0.034	0.0 (0.413)	1.040	0.377 to 2.869	0.940	56.5 (0.075)	0.936	0.412 to 2.125	0.874	50.5 (0.109)
<2019	8/8/8/8	1.856	1.183 to 2.912	0.007	0.0 (0.931)	1.915	1.245 to 2.946	0.003	0.5 (0.425)	0.992	0.487 to 2.201	0.982	36.6 (0.137)	1.152	0.759 to 1.749	0.506	0.0 (0.790)

Table 3 (*continued*)

Table 3 (*continued*)

Subgroups	Studies†, n	T2 1-year survival				T2 2-year survival				T2 3-year survival				T2 5-year survival			
		OR	95% CI	P	I^2 (%) (P)	OR	95% CI	P	I^2 (%) (P)	OR	95% CI	P	I^2 (%) (P)	OR	95% CI	P	I^2 (%) (P)
By follow-up period																	
<36 months	3/3/3/3	0.723	0.122 to 4.285	0.721	0.0 (0.906)	1.210	0.340 to 4.313	0.768	0.0 (0.907)	0.525	0.164 to 1.675	0.276	18.7 (0.292)	0.476	0.211 to 1.071	0.073	0.0 (0.899)
≥36 months	3/3/3/3	2.594	0.772 to 8.712	0.123	0.0 (0.885)	2.530	0.666 to 9.618	0.173	48.8 (1.142)	1.033	0.343 to 3.113	0.954	54.4 (0.112)	1.001	0.553 to 1.812	0.997	0.0 (0.590)
NA	6/6/6/6	1.814	1.136 to 2.897	0.013	0.0 (0.803)	1.938	1.140 to 3.295	0.015	6.1 (0.377)	1.527	0.875 to 2.665	0.136	8.5 (0.362)	1.455	0.914 to 2.317	0.114	0.0 (0.630)

†, studies reporting T2 1-year/2-year/3-year/5-year survival. OR, odds ratio; CI, confidence interval; I^2, inconsistency index; IGBC, incidental gallbladder cancer; NA, not available.

Table 4 Subgroup analyses comparing laparoscopic surgery with open surgery in terms of overall survival at 1-year, 2-year, 3-year and 5-year for the management of gallbladder cancer

Subgroups	Studies†, n	1-year overall survival				2-year overall survival				3-year overall survival				5-year overall survival			
		OR	95% CI	P	I^2 (%) (P)	OR	95% CI	P	I^2 (%) (P)	OR	95% CI	P	I^2 (%) (P)	OR	95% CI	P	I^2 (%) (P)
By ethnicity																	
Asia	15/15/15/15	1.343	0.719 to 2.511	0.355	40.6 (0.052)	1.524	1.021 to 2.276	0.039	24.7 (0.181)	1.166	0.768 to 1.771	0.471	41.7 (0.046)	1.151	0.702 to 1.887	0.577	58.6 (0.003)
America	3/3/3/3	0.524	0.263 to 1.044	0.066	0.0 (0.908)	1.071	0.605 to 1.895	0.815	0.0 (0.537)	1.523	0.653 to 3.551	0.330	36.6 (0.206)	1.476	0.881 to 2.474	0.140	0.0 (0.721)
Europe	4/4/4/4	1.791	1.309 to 2.451	0.001	0.0 (0.625)	2.119	1.544 to 2.907	0.001	0.0 (0.628)	1.929	1.388 to 2.681	0.001	0.0 (0.463)	1.710	1.127 to 2.594	0.012	2.7 (0.379)
By proportion of IGBC																	
All	5/5/5/5	1.218	0.664 to 2.232	0.524	34.4 (0.192)	1.920	1.448 to 2.545	0.001	0.0 (0.531)	1.908	1.429 to 2.546	0.001	0.0 (0.843)	1.619	1.193 to 2.196	0.002	2.0 (0.395)
Mix	6/6/6/6	1.007	0.319 to 3.177	0.990	54.5 (0.052)	1.211	0.669 to 2.194	0.527	0.0 (0.691)	1.292	0.545 to 3.062	0.561	52.2 (0.063)	1.548	0.679 to 3.529	0.298	53.1 (0.059)
NA	11/11/11/11	1.368	0.658 to 2.843	0.401	42.5 (0.066)	1.539	0.877 to 2.703	0.133	43.9 (0.058)	1.161	0.708 to 1.905	0.554	42.9 (0.064)	1.010	0.576 to 1.773	0.971	53.5 (0.022)
By proportion of Tis & T1 & T2																	
All	10/10/10/10	1.011	0.531 to 1.922	0.974	0.0 (0.509)	1.469	0.807 to 2.671	0.208	30.7 (0.163)	1.105	0.590 to 2.068	0.755	51.1 (0.031)	1.214	0.635 to 2.321	0.558	60.2 (0.007)
Mix	12/1212/12	1.251	0.702 to 2.228	0.447	57.9 (0.006)	1.671	1.245 to 2.243	0.001	10.9 (0.339)	1.734	1.361 to 2.208	0.001	0.0 (0.512)	1.420	0.985 to 2.048	0.060	30.8 (0.153)
NA	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Table 4 (*continued*)

Table 4 (*continued*)

Subgroups	Studies†, n	1-year overall survival				2-year overall survival				3-year overall survival				5-year overall survival			
		OR	95% CI	P	I^2 (%) (P)	OR	95% CI	P	I^2 (%) (P)	OR	95% CI	P	I^2 (%) (P)	OR	95% CI	P	I^2 (%) (P)
By total sample size																	
<60	10/10/10/10	1.705	0.905 to 3.214	0.099	0.0 (0.902)	1.516	0.843 to 2.724	0.164	4.7 (0.397)	2.009	1.156 to 3.490	0.013	0.4 (0.434)	2.124	0.878 to 5.137	0.095	58.8 (0.009)
≥60	12/12/12/12	0.995	0.528 to 1.875	0.987	64.8 (0.001)	1.508	1.064 to 2.138	0.021	35.8 (0.104)	1.149	0.769 to 1.718	0.498	58.6 (0.005)	1.110	0.803 to 1.535	0.527	39.7 (0.084)
By publication year																	
≥2019	9/9/9/9	1.067	0.444 to 2.566	0.885	66.1 (0.003)	1.480	0.964 to 2.274	0.073	31.0 (0.170)	1.280	0.833 to 1.967	0.259	42.7 (0.083)	1.160	0.819 to 1.644	0.403	19.7 (0.273)
<2019	13/13/13/13	1.619	1.221 to 2.146	0.001	0.0 (0.697)	1.600	1.073 to 2.384	0.021	13.9 (0.305)	1.490	0.862 to 2.574	0.153	47.7 (0.028)	1.504	0.810 to 2.794	0.196	60.9 (0.002)
By follow-up period																	
<36 months	6/6/6/6	0.940	0.286 to 3.096	0.919	55.0 (0.049)	1.218	0.709 to 2.094	0.475	0.0 (0.886)	1.035	0.592 to 1.809	0.904	18.9 (0.291)	1.021	0.615 to 1.693	0.937	14.4 (0.322)
≥36 months	6/6/6/6	1.281	0.559 to 1.895	0.926	0.0 (0.442)	1.727	0.861 to 3.464	0.124	37.8 (0.117)	1.536	0.709 to 3.331	0.277	61.3 (0.017)	1.257	0.580 to 2.726	0.562	67.7 (0.005)
NA	9/9/9/9	1.029	0.675 to 2.431	0.449	50.2 (0.041)	1.614	0.996 to 2.616	0.052	40.6 (0.121)	1.523	0.943 to 2.460	0.085	38.8 (0.110)	1.591	0.900 to 2.813	0.110	46.3 (0.071)

†, studies reporting 1-year/2-year/3-year/5-year overall survival. OR, odds ratio; CI, confidence interval; I^2, inconsistency index; IGBC, incidental gallbladder cancer; NA, not available.

Table 5 Subgroup analyses comparing laparoscopic surgery with open surgery in terms of intraoperative blood loss, number of harvested LNs, postoperative hospital stay and operation time for the management of gallbladder cancer

Subgroups	Studies†, n	Intraoperative blood loss				Number of harvested LNs				Postoperative hospital stay				Operation time			
		WMD	95% CI	P	I^2 (%) (P)	WMD	95% CI	P	I^2 (%) (P)	WMD	95% CI	P	I^2 (%) (P)	WMD	95% CI	P	I^2 (%) (P)
By ethnicity																	
Asia	14/14/16/15	−130.156	−183.685 to −76.627	0.001	91.3 (0.001)	−1.109	−1.916 to 0.303	0.007	74.9 (0.001)	−3.659	−4.653 to −2.664	0.001	87.7 (0.001)	5.700	−25.645 to 37.045	0.722	96.6 (0.001)
America	1/1/1/1	100.001	−38.347 to 238.347	0.157	–	0	−1.502 to 1.502	1.000	–	−2.000	−4.057 to 0.057	0.057	–	0	−10.913 to 10.913	1.000	–
Europe	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

Table 5 (*continued*)

Table 5 (*continued*)

Subgroups	Studies†, n	Intraoperative blood loss				Number of harvested LNs				Postoperative hospital stay				Operation time			
		WMD	95% CI	P	I^2 (%) (P)	WMD	95% CI	P	I^2 (%) (P)	WMD	95% CI	P	I^2 (%) (P)	WMD	95% CI	P	I^2 (%) (P)
By proportion of IGBC																	
All	3/3/3/3	−79.023	−165.852 to 7.799	0.074	90.3 (0.001)	0.354	−1.042 to 1.749	0.619	39.3 (0.192)	−5.033	−6.740 to −3.326	0.001	89.7 (0.001)	10.131	−3.906 to 24.168	0.157	60.6 (0.079)
Mix	5/6/6/6	−70.839	−103.039 to −38.638	0.001	0.0 (0.629)	−2.362	−3.600 to −1.124	0.001	59.1 (0.032)	−2.593	−3.990 to −1.196	0.001	73.8 (0.002)	35.539	−17.437 to 88.515	0.189	94.3 (0.001)
NA	7/6/7/7	−176.395	−279.842 to −72.949	0.001	81.9 (0.004)	−0.565	−1.484 to 0.355	0.229	58.3 (0.035)	−2.169	−2.859 to −1.479	0.001	0.0 (0.921)	−24.338	−67.198 to 18.522	0.266	95.8 (0.001)
By proportion of Tis & T1 & T2																	
All	7/7/8/7	−173.636	−278.230 to −69.042	0.001	93.1 (0.001)	−1.967	−3.646 to −0.289	0.189	61.8 (0.015)	−4.360	−4.507 to −2.334	0.001	76.7 (0.001)	10.763	−64.173 to 85.698	0.778	98.0 (0.001_
Mix	7/7/7/8	−74.256	−149.724 to 1.212	0.054	90.1 (0.001)	−0.496	−1.237 to 0.245	0.022	76.4 (0.001)	−3.420	−6.116 to −2.604	0.001	90.5 (0.001)	−3.458	−21.880 to 14.963	0.713	86.8 (0.001)
NA	1/1/1/1	−75.000	−165.469 to 15.469	0.104	–	−0.400	−3.065 to 2.265	0.769	–	0	−1.647 to 1.647	1.000	–	30.000	9.380 to 50.620	0.004	–
By total sample size																	
<60	5/5/5/5	−167.739	−323.302 to −12.176	0.035	84.8 (0.001)	−0.482	−2.010 to 1.046	0.536	68.3 (0.013)	−3.931	−5.886 to −1.976	0.001	85.0 (0.001)	45.129	−12.412 to 102.671	0.124	90.1 (0.001)
≥60	10/10/11/11	−102.782	−163.468 to −42.095	0.001	93.2 (0.001)	−1.259	−2.245 to −0.273	0.012	77.1 (0.001)	−3.439	−4.633 to −2.245	0.001	88.1 (0.001)	−11.310	−42.376 to 19.756	0.476	97.0 (0.001)
By publication year																	
≥2019	12/13/13/13	−83.009	−134.517 to −31.500	0.002	88.8 (0.001)	−1.239	−2.018 to −0.460	0.002	74.4 (0.001)	−3.224	−3.940 to −2.507	0.001	71.4 (0.001)	13.415	−9.862 to 36.692	0.259	93.9 (0.001)
<2019	3/2/3/3	−117.194	−521.784 to −90.668	0.005	93.0 (0.001)	1.019	−1.725 to 3.763	0.467	54.2 (0.140)	−6.104	−11.944 to −0.265	0.040	96.4 (0.001)	−29.452	−152.363 to 93.459	0.639	98.6 (0.001)
By follow-up period																	
<36 months	8/8/8/8	−87.037	−123.289 to −50.784	0.001	22.4 (0.251)	−1.240	−2.365 to −0.114	0.031	66.1 (0.004)	−3.242	−4.689 to −1.794	0.001	83.7 (0.001)	18.102	−21.573 to 57.776	0.371	91.1 (0.001)
≥36 months	5/4/5/5	−180.698	−316.050 to −45.346	0.009	94.7 (0.001)	0.514	−1.543 to 2.572	0.624	71.6 (0.014)	−4.908	−7.669 to −2.147	0.001	93.4 (0.001)	−25.547	−80.035 to 28.941	0.358	98.2 (0.001)
NA	2/3/3/3	−121.087	−351.679 to 109.506	0.303	96.3 (0.001)	−2.018	−3.953 to −0.082	0.041	87.5 (0.001)	−3.204	−4.176 to −2.233	0.001	47.4 (0.149)	23.500	−54.737 to 101.737	0.556	98.0 (0.001)

†, studies reporting intra-operative blood loss/number of harvested LNs/post-operative hospital stay/operation time. LN, lymph node; WMD, weighted mean difference; CI, confidence interval; I^2, inconsistency index; IGBC, incidental gallbladder cancer; NA, not available.

Table 6 Subgroup analyses comparing laparoscopic surgery with open surgery in terms of postoperative morbidity, recurrence rate and port-site metastasis rate for the management of gallbladder cancer

Subgroups	Studies[†], n	Postoperative morbidity				Recurrence rate				Port-site metastasis rate			
		OR	95% CI	P	I^2 (%) (P)	OR	95% CI	P	I^2 (%) (P)	OR	95% CI	P	I^2 (%) (P)
By ethnicity													
Asia	14/15/12	0.550	0.362 to 0.837	0.005	19.6 (0.240)	1.156	0.539 to 2.477	0.710	80.3 (0.001)	1.486	0.685 to 3.223	0.316	0.0 (0.966)
America	1/2/1	0.906	0.441 to 1.861	0.787	–	0.782	0.103 to 5.936	0.812	87.2 (0.005)	1.739	0.104 to 29.144	0.700	–
Europe	–/3/3	–	–	–	–	0.756	0.546 to 1.049	0.094	0.0 (0.974)	1.701	0.795 to 3.640	0.171	0.0 (0.691)
By proportion of IGBC													
All	3/7/6	0.776	0.430 to 1.399	0.399	0.0 (0.712)	0.629	0.390 to 1.015	0.058	37.0 (0.146)	1.830	0.926 to 3.617	0.082	0.0 (0.526)
Mix	6/6/4	0.426	0.167 to 1.088	0.075	64.3 (0.016)	1.665	0.309 to 8.987	0.553	90.2 (0.001)	1.440	0.348 to 5.955	0.615	0.0 (0.996)
NA	6/7/6	0.639	0.354 to 1.153	0.137	0.0 (0.891)	1.210	0.671 to 2.179	0.527	23.8 (0.247)	1.209	0.414 to 3.529	0.728	0.0 (0.998)
By proportion of Tis & T1 & T2													
All	7/8/5	0.395	0.186 to 0.839	0.016	30.4 (0.196)	1.190	0.320 to 4.431	0.795	86.2 (0.001)	1.556	0.452 to 5.351	0.483	0.0 (0.886)
Mix	7/11/10	0.716	0.456 to 1.124	0.147	15.0 (0.316)	0.779	0.504 to 1.202	0.259	47.5 (0.040)	1.594	0.871 to 2.915	0.130	0.0 (0.926)
NA	1/1/1	0.679	0.162 to 2.835	0.595	–	1.605	0.158 to 16.314	0.689	–	1.917	0.115 to 32.008	0.651	–
By total sample size													
<60	5/9/9	0.464	0.122 to 1.762	0.259	66.7 (0.017)	0.674	0.372 to 1.223	0.195	0.0 (0.595)	1.812	0.724 to 4.539	0.204	0.0 (0.803)
≥60	10/11/7	0.583	0.403 to 0.844	0.004	0.0 (0.815)	1.042	0.599 to 1.814	0.519	87.7 (0.001)	1.498	0.779 to 2.881	0.226	0.0 (1.000)
By publication year													
≥2019	12/10/7	0.609	0.394 to 0.944	0.026	32.6 (0.130)	1.140	0.445 to 2.924	0.785	88.3 (0.001)	1.269	0.468 to 3.442	0.639	0.0 (1.000)
<2019	3/10/9	0.596	0.407 to 0.871	0.137	0.0 (0.675)	1.042	0.599 to 1.814	0.478	7.7 (0.371)	1.750	0.932 to 3.287	0.082	0.0 (0.814)
<36 months	8/8/7	0.541	0.261 to 1.124	0.100	50.76 (0.048)	0.954	0.597 to 1.525	0.846	0.0 (0.517)	1.716	0.641 to 4.591	0.282	0.0 (0.990)
≥36 months	5/6/5	0.723	0.425 to 1.228	0.230	0.0 (0.647)	0.411	0.254 to 0.666	0.001	0.0 (0.668)	0.882	0.248 to 3.137	0.846	0.0 (0.976)
NA	2/6/4	0.502	0.230 to 1.095	0.083	0.0 (0.624)	2.829	0.721 to 11.097	0.136	92.3 (0.001)	1.869	0.900 to 3.885	0.094	0.0 (0.466)

[†], studies reporting postoperative morbidity/recurrence rate/port-site metastasis rate. OR, odds ratio; CI, confidence interval; I^2, inconsistency index; IGBC, incidental gallbladder cancer; NA, not available.

nononcologic surgery for incidental GBC can affect survival and lead to a worse prognosis (46), which was confirmed in this study after restricting analysis to patients with incidental GBC, showing that LS was associated with better overall survival and T2-stage survival than OS. However, we failed to support the superiority of LS over OS for early T-stage GBC, which led us to speculate that this superiority was not entirely attributable to early T-stage of incidental GBC. Nevertheless, we cannot exclude the possibility that selection of LS for patients with incidental GBC in good general conditions accounts for the advantages of LS in our overall analyses, and we agree that further validations in large-scale, well-designed comparative studies are required.

There is evidence that N status is one of the strongest prognostic determinants in patients undergoing operations for GBC (47), and regional lymphadenectomy can improve survival outcomes (48). As recommended by Dou *et al.* (49), relatively-early GBC cases (Tis-T1a or T1b-T2) should be selected in the beginning to accumulate operational experience and standardize surgical process, and gradually transit to advanced stage (T3) GBC cases. In other words, surgeons carrying out LS for GBC should have extensive experience in laparoscopic liver resection, bilioenterostomy, and lymph node dissection, which form an important basis for the safe and smooth implementation of LS. In our overall analyses, LS was found to be associated with less harvested LNs, and in the subgroup involving GBC patients at Tis & T1 & T2, LS had significantly fewer harvested LNs than OS, consistent with the findings by Ong *et al.* in a Swiss nationwide population-based analysis (50). The reasons behind the small number of harvested LNs might be due to lack of awareness that LN removal is a crucial component of oncologic resections, technical inability to perform lymphadenectomy, and learning curve of surgeons. For instance, it is suggested that learning curve of pure LS was about seven cases if surgeons had sufficient experience in laparoscopic hepatectomy (22). Also, minimally invasive technology can perform equally well in terms of the number of harvesting nodes (51,52). Taking this information together, it can be speculated that these findings might, at least in part, be influenced by the beginning of the learning curve. As recommended by expert consensus statement (53), at least 6 LNs should be resected in GBC radical surgery. Considering the fact that 3 of 15 studies reporting harvested LNs had resected less than 6 LNs, we here suggest the implementation of LS at high-volume centers with specialized experience. Therefore, the superiority of LS over OS in better survival and lower LNs observed in this systematic review and meta-analysis might be, at least in part, explained by the preference of LS in GBC patients at earlier stages, with less LN metastasis, and better general conditions.

Tumor recurrence is another important factor impacting postoperative survival of GBC. However, in this systematic review and meta-analysis, we failed to detect any hints of significance in recurrence and PSM rates between patients undergoing LS and OS. Recently, growing concerns have been expressed over PSM, an indicator of poor prognosis (54), when applying LS for the management of GBC. Some experts in this field claimed that PSM rate was comparable between LS and OS pending improved recognition of GBC and implementation of plastic bags to remove resected gallbladder (3). In support of this claim, 11 of 16 eligible studies in this systematic review and meta-analysis reported no occurrence of PSM. Actually in surgical practice, PSM cannot be totally avoided, and it is essential to enhance surgical skills and enrich practical experience of LS to avoid PSM occurrence to the outmost extent.

Finally, several limitations should be addressed for this systematic review and meta-analysis. Firstly, this study is based on retrospective cohorts, and recall bias cannot be fully ruled out. Secondly, because only published studies written in the English were synthesized and the "grey" literature was not covered, publication bias might be possible. As reflected by funnel plots and statistical tests, the possibility of publication bias was high for survival of T2 stage at 1-year and postoperative morbidity, likely due to lack of statistical power from limited numbers or small sizes of studies meta-analyzed. Thirdly, although a wide panel of subgroup analyses were conducted to seek potential sources of between-study heterogeneity, some unaccounted residual confounders such as surgical procedures were not taken into consideration. Fourthly, as a meta-analysis cannot replace studies from high-volume centers involving large sample sizes, we agree that more well-designed studies are required to derive a more precise estimate of clinically important outcomes when comparing LS with OS in the management of GBC patients.

Conclusions

Taken together, our findings indicated that LS statistically had better 2-year survival rates, less intraoperative bleeding, shorter hospitalization times, and lower rates of complications than OS. However, due to the impact of incidental GBC, unaccounted heterogeneity, publication

bias, and lack of high-quality randomized controlled trials, the superiority of LS over OS remains a subject of debate. Moreover, uncertainties such as lymph node dissection and port-site metastasis have not been fully understood, and the safety of LS still remains an open question. More recently, laparoscopic radical surgery for GBC has gained increasing popularity at major hepatobiliary centers. We believe that the confusion on different treatment options for GBC will be gradually cleared up with the accruing evidence to outline the pros and cons of each option.

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Footnote

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