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Lack of Oncological Benefit from Bursectomy in Radical Gastrectomy: A Systematic Review

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Keywords
Gastrectomy · Bursectomy · Gastric cancer · Adenocarcinoma

Abstract
Background: Resection of the omental bursa has been suggested to reduce peritoneal recurrence and facilitate a complete oncological resection during a gastrectomy. The addition of this procedure increases technical complexity and prolongs the procedure. Published data regarding the oncological benefit of this procedure are conflicting. We hypothesized that a bursectomy during a radical gastrectomy does not improve overall survival. ***Methods:*** In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline, a comprehensive literature search of 3 electronic databases (PubMed, Scopus, and Embase) was conducted to identify the clinical studies that compared bursectomy with no-bursectomy in radical gastrectomy for gastric adenocarcinoma. Qualitative and quantitative data synthesis was performed using RevMan software. A random-/fixed-effect modeling was used depending upon the heterogeneity. Bias and quality assessment tools were applied. The study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42019116556). ***Results:*** Of 8 studies assessing the role of bursectomy in gastric adenocarcinoma, 6 (75%) were included – of which 2 (33%) are randomized controlled trials. Of 2,904 patients, 1,273 (%) underwent a bursectomy. There was no statistically significant difference in either overall survival (hazard ratio [HR] = 0.89, 95% CI 0.75–1.06, I^2 = 14%) or disease recurrence (HR = 1.01, 95% CI 0.84–1.20, I^2 = 22%) in the bursectomy group compared to the no-bursectomy group. ***Conclusion:*** There is no additional oncological benefit of adding bursectomy to radical gastrectomy in all patients with gastric adenocarcinoma.

Introduction

Gastric cancer is the fifth most common and third most lethal cancer worldwide, with 783,000 deaths in 2018 [1]. Gastrectomy with regional lymphadenectomy is the preferred surgical treatment for nonmetastatic gastric adenocarcinoma [2]. Despite multimodal treatment, the majority of patients with advanced nonmetastatic cancer recur with the peritoneal disease (29–56%) [3–6].

Omental bursectomy involves the dissection of the peritoneal lining covering the pancreas and anterior plane of transverse mesocolon along with omentectomy. Omental bursectomy was developed as a part of radical

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gastrectomy to achieve – (a) complete elimination of the microscopic disease from the greater omentum, the lesser sac, and the pancreas; (b) complete clearance of the subpyloric lymph nodes; and (c) clean meticulous dissection of celiac-based lymph node basin [7–9].

Despite having the theoretical benefit of removing all micrometastatic diseases during gastrectomy, there is equipoise regarding the therapeutic value of a bursectomy [10]. Previous studies have demonstrated improvement in survival among patients who underwent bursectomy [11, 12]. Subsequent studies have questioned the oncological benefit, and a recent well-designed RCT demonstrated no oncological benefit [13].

The bursectomy requires technical expertise and adds time and potential morbidity to a gastrectomy. Facing a consecutive change of the operative access toward minimal invasive techniques in the treatment of gastric cancer, more traditional operative steps, such as bursectomy, are reevaluated regarding their oncological benefit to optimize and standardize surgical procedures. Therefore, it is imperative to understand its oncological value before performing a routine bursectomy. This systematic review and meta-analysis aim to synthesize currently available conflicting data to ascertain the oncological benefit of a bursectomy in addition to a gastrectomy.

Methods

The protocol of this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number – CRD42019116556. This review was completed following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines [14, 15].

Search Strategy

A comprehensive search strategy was developed following a consensus among the coauthors in collaboration with an external expert. The search strategy used variations in text words – ("stomach neoplasm" OR "stomach cancer" OR "gastric cancer" OR "gastric neoplasm") AND ("omental bursa" OR bursectomy OR omentectomy) – found in the title, abstract, or keyword fields to retrieve articles referring to the benefit of bursectomy during radical gastrectomy performed for gastric cancer. A total of 3 electronic databases – MEDLINE (PubMed), Embase, and Scopus – were searched from their inception to March 2020.

Inclusion/Exclusion Criteria for the Studies

Following criteria were used for studies to be suitable for inclusion in the systematic review:

- Clinical trials and observational studies including patients with operable nonmetastatic gastric cancer.
- Studies reporting (or having data to calculate) hazard ratio (HR) for overall survival (OS) in patients undergoing bursectomy versus no-bursectomy.
- Studies reported in the English language.

Studies reporting recurrent gastric cancer or gastric tumors other than adenocarcinoma were not included in the systematic review.

Data Extraction

Two authors (P.K.G. and A.J.) searched the electronic databases and screened all the titles and abstracts from the selected articles. Any disagreement was resolved by consensus among the authors. The full texts of the selected articles were analyzed by the 3 authors (P.K.G., A.J., and R.K.). The relevant information was extracted using a predefined data extraction sheet.

Assessment of the Quality of the Studies

Quality assessment of the selected studies was performed independently by the 2 reviewers. The Cochrane Risk-of-Bias Tool [16] for eligible RCTs and the methodological index for nonrandomized studies [17] for nonrandomized studies were used to assess the quality of studies.

Statistical Analysis

Review manager (Cochrane Collaboration's software) version RevMan 5.3 was used for analysis [18]. The generic inverse variance method was used to calculate the estimate of OS and disease recurrence in patients undergoing bursectomy in radical gastrectomy. The data were entered as a natural logarithm of relative effect size and standard error of the mean for each of the studies. Both fixed- and random-effects models were used to pool the data according to the result of a statistical heterogeneity test. Heterogeneity between studies was evaluated using the Cochran Q Statistic and the I^2 test, with $p < 0.05$ indicating significant heterogeneity.

Results

Literature Review

The search strategy retrieved 436 articles, of which 20 were included for initial review (Fig. 1). Of 8 studies, there were 3 publications from the Osaka-Bursectomy trial – (a) Imamura et al. [19] reported operative morbidity and mortality data, (b) Fujita et al. [20] reported the interim analysis of the trial, and (c) Hirao et al. [11] published the long-term outcomes of the trial. Six studies – 4 nonrandomized and 2 randomized – fulfilled inclusion and exclusion criteria and were included in the review (Table 1). A total of 2,904 patients were included in the meta-analysis – 1,273 had bursectomy and 1,631 did not undergo bursectomy during radical gastrectomy.

Quality Assessment

Online supplementary Figure S1 (for all online suppl. material, see www.karger.com/doi/10.1159/000517654) displays the assessment of the quality of RCTs included in the review using the Cochrane Risk-of-Bias Tool. All nonrandomized studies included in this systematic review were assessed to have a medium quality with a methodological index for nonrandomized study median score of 17.5 out of 24. Low quality was due to lack of prospective data collection, calculation of the study size, and incomplete follow-up. Online supplementary Table S2 il-

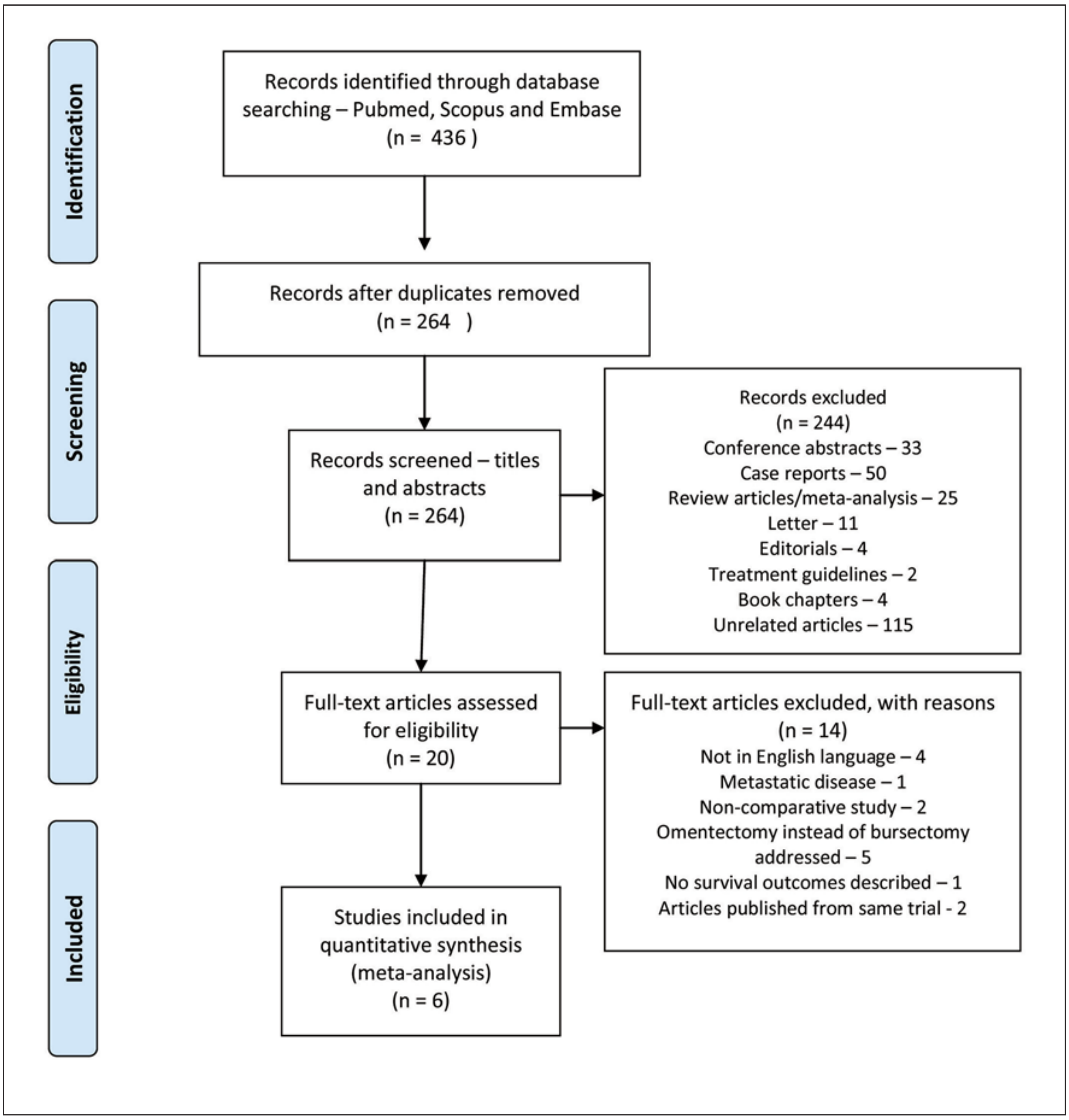

Fig. 1. Flowchart of PRISMA diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Studies examining the role of bursectomy during gastrectomy for advanced gastric cancer

S. No.	Author	Publication year	Study period	Nation	Study design	Sample size		Inclusion criteria	Outcome
						bursectomy	no-bursectomy		
1	Eom et al. [22]	2013	2001–2006	Korea	Retrospective comparative study	107	363	cT2–T3M0	DFS, OS
2	Hu et al. [12]	2020	2012–2013	China	Retrospective comparative study	180	180	cT1–4N0–3M0	DFS, OS
3	Kochi et al. [21]	2014	2004–2010	Japan	Retrospective comparative study	121	133	Stage IA–IIIC	DFS, OS
4	Zhang et al. [9]	2015	2012–2013	China	Retrospective comparative study	159	247	pT2–T4N0–N3M0	DFS, OS
5	Hirao et al. [11]	2015	2002–2007	Japan	Randomized controlled trial	104	106	cT2–T3N0–N1M0	OS
6	Kurokawa et al. [13]	2018	2010–2015	Japan	Randomized controlled trial	602	602	cT3–4bN (not bulky) M0[a]	DFS, OS

OS, overall survival; DFS, disease-free survival; JCGC, Japanese Classification of Gastric Carcinoma. [a] As per the 14th edition of the JCGC.

Table 2. Surgical and oncological outcomes for patients undergoing gastrectomy with or without bursectomy

Characteristic	Eom et al. [22]		Hu et al. [12]		Kochi et al. [21]		Zhang et al. [9]		Hirao et al. [11]		Kurokawa et al. [13]	
	B+ (n = 107)	B– (n = 363)	B+ (n = 180)	B– (n = 180)	B+ (n = 121)	B– (n = 133)	B+ (n = 159)	B– (n = 247)	B+ (n = 104)	B– (n = 106)	B+ (n = 602)	B– (n = 602)
Operative time, mean minutes (SD)	262.8 (52.1) $p < 0.001$	211.9 (51.2)	**2.45 (0.39) $p = 0.074$	**2.32 (0.25)	*311 (180–570) $p = 0.001$	*264 (123–560)	260.1 (43.4) $p < 0.001$	227.9 (48.6)	*222 (134–488) $p = 0.368$	*221 (111–360)	*254 (212–297) $p < 0.0001$	*222 (182–167)
Blood loss, mean ml (SD)	NA	NA	120 (22.3) $p = 0.869$	100 (19.7)	*296 (33–2,250) $p = 0.001$	*179 (20–1,340)	201.1 (53.7) $p = 0.729$	198.9 (63.5)	*475 (80–3,970) $p = 0.047$	*350 (55–2,901)	*330 (183–530) $p < 0.0001$	*230 (130–410)
Hospital stay, mean days (SD)	11.6 (4.4) $p = 0.106$	12.4 (5.6)	NA	NA	*16 (8–59) $p = 0.17$	*14 (8–99)	11.4 (4.4) $p = 0.850$	11.4 (4.4)	*16 $p = 0.744$	*15	NA	NA
Harvested lymph nodes, mean (SD)	57.6 (16.5) $p < 0.001$	48.5 (16.6)	19.23 (5.23) $p = 0.059$	18 (4.24)	*19 (4–69) $p = 0.33$	*21 (4–100)	40.6 (17.5) $p < 0.001$	25.4 (9.9)	*38 (11–98) $p = 0.417$	*37 (7–97)	*47 (37–60) $p = 0.44$	*48 (37–62)
Positive lymph nodes, mean (SD)	8.9 (9.9) $p = 0.024$	6.7 (8.9)	NA	NA	*2 (0–34) $p = 0.08$	*3 (0–56)	7.5 (8.7) $p = 0.045$	5.9 (6.4)	NA	NA	NA	NA
Complications, n (%)	26 (24.3%) $p = 0.656$	96 (26.5%)	23 (12.8%) $p = 0.626$	20 (11.1%)	29 (24.0%) $p = 0.77$	34 (25.6%)	37 (23.3%) $p = 0.179$	44 (17.8%)	15 (14.3%) $p = 1.000$	15 (14.3%)	77 (13%) $p = 0.25$	64 (11%)
Surgery-related mortality	0 $p = 1$	1 (0.3%)	3 (1.7%) $p = 0.5$	2 (1.1%)	0 p = NS	1 (0.8%)	0 p = NA	1 (0.4%)	1 (0.95%) $p = 1.00$	1 (0.95%)	1 (<1%) $p = 0.22$	5 (%1)

SD, standard deviation; NA, not available. * Median (range); B+, with bursectomy; B–, without bursectomy. ** Mean operating time in hours.

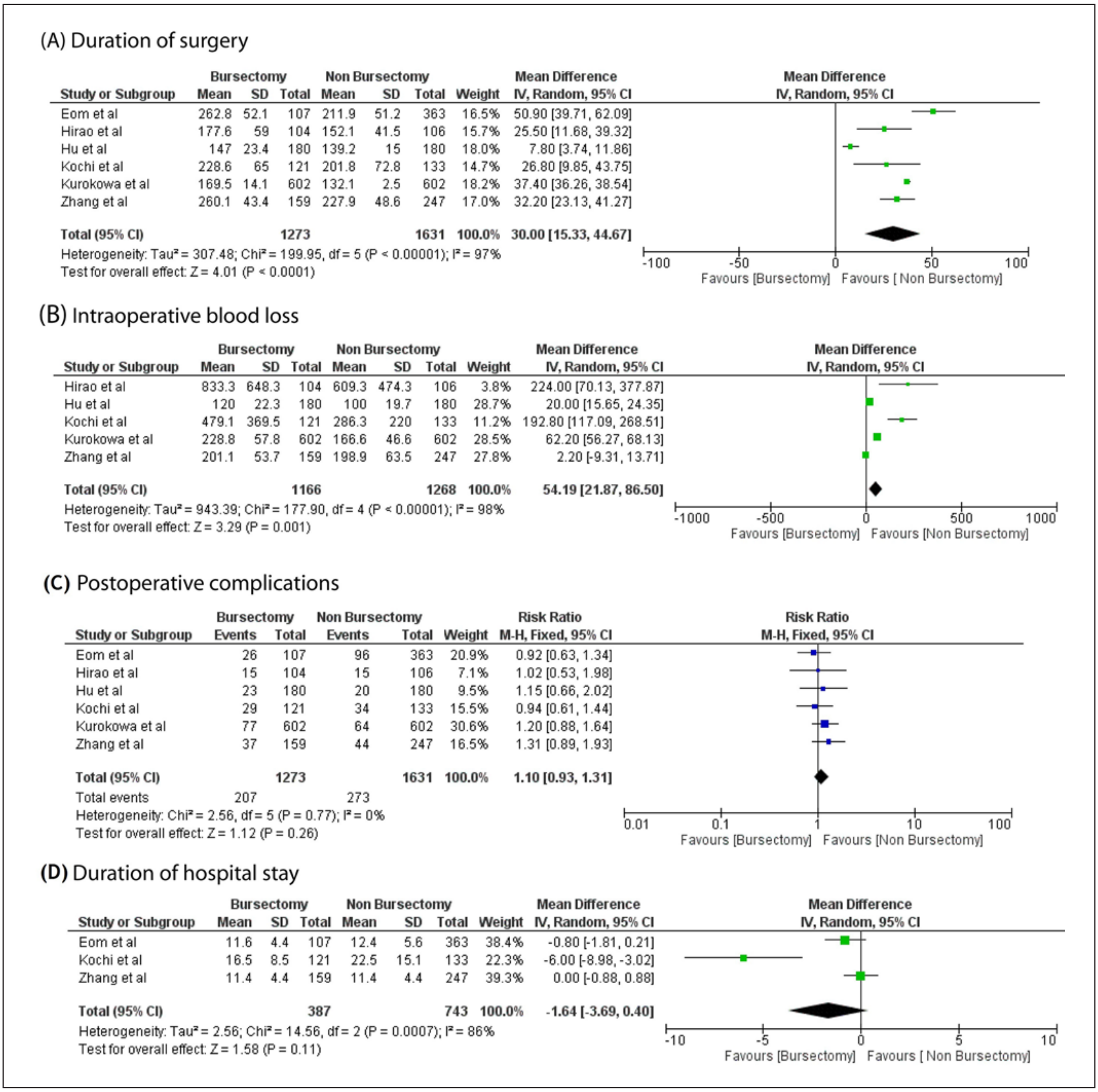

Fig. 2. Forest plot for comparison: duration of surgery (**A**), intraoperative blood loss (**B**), postoperative complications (**C**), duration of hospital stay (**D**).

lustrates the detailed information on the quality assessment of nonrandomized studies. A formal assessment of the publication bias was not performed due to the small number of studies (<10).

Surgery-Related Factors

Table 2 highlights the difference in various surgery-related outcomes when bursectomy was added to standard radical gastrectomy. Four of the 6 studies (3 nonrandomized and 1 randomized) reported that bursectomy increased the duration of surgery significantly (mean difference of 30.00 min, 95% CI 15.33–44.67, p value <0.0001) (Fig. 2A) [9, 13, 21]. Five out of the 6 studies reported the difference in the blood loss when bursectomy was added – 3 of them highlighted that there was a significantly higher blood loss with bursectomy [13, 19, 21]. Overall, bursectomy led to an additional blood loss of 54 mL (95% CI 21–86, p value 0.001) (Fig. 2B). None of the studies

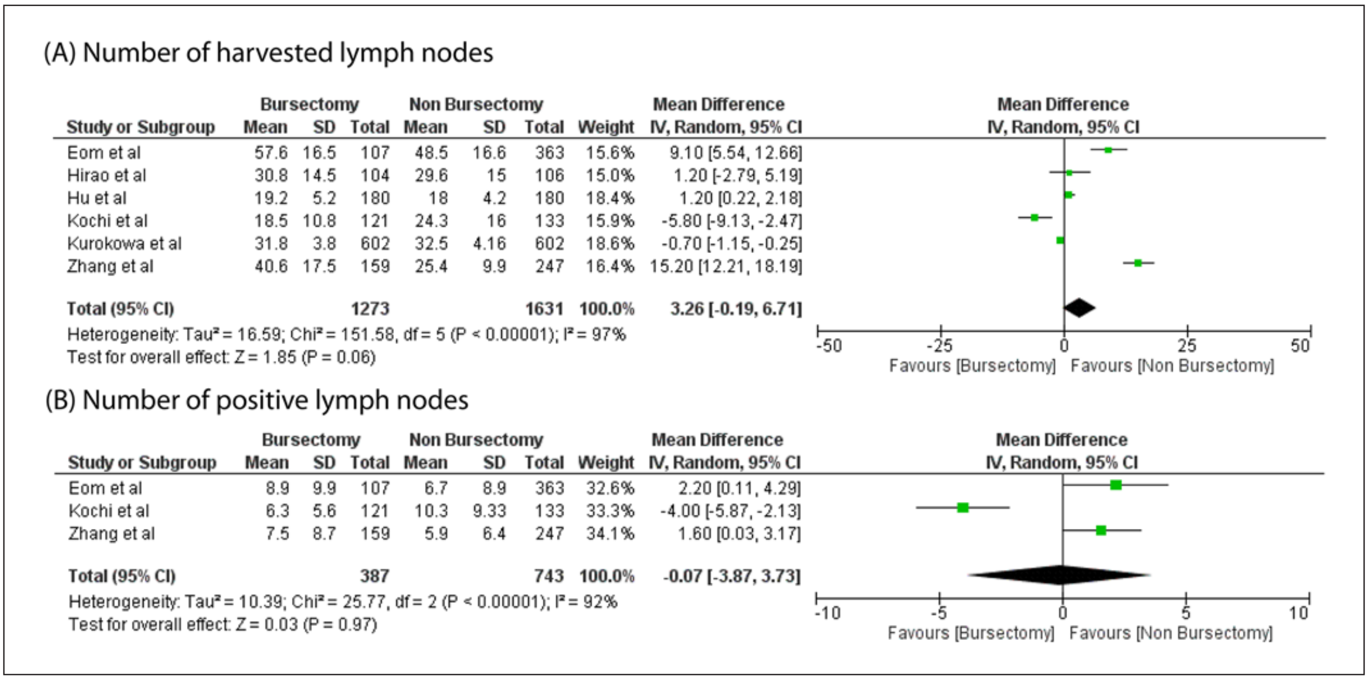

Fig. 3. Forest plot for comparison: number of lymph nodes harvested (**A**), number of metastatic lymph nodes (**B**).

showed that bursectomy resulted in higher postoperative complications – either morbidity or mortality (Fig. 2C). Four studies – Zhang et al. [9], Imamura et al. [19], Kochi et al. [21], and Eom et al. [22] – compared the hospital stay in 2 groups of patients with or without bursectomy; however, none of the studies could find any statistically significant difference (Fig. 2D).

Pathological Outcomes

Out of all 6, 2 studies – Zhang et al. [9] and Eom et al. [22] – could show that bursectomy leads to a significantly higher lymph node yield (10–15 more nodes) in a radical gastrectomy than in its absence. However, none of the RCTs revealed that the addition of bursectomy would add to a higher lymph node harvest. Overall, there was a trend toward a higher lymph node harvest with bursectomy (mean difference of 3.26, 95% CI 0.19–6.71, *p* value 0.06) (Fig. 3A). Moreover, none of the studies showed that bursectomy was associated with a higher yield of metastatic lymph nodes (Fig. 3B).

Survival Outcomes

Figure 4 displays the forest plots for comparison in 2 groups – bursectomy and no-bursectomy – for OS and disease-free survival (DFS). There was no statistically significant difference in either OS (HR = 0.89, 95% CI 0.75–1.06) or DFS (HR = 1.01, 95% CI 0.84–1.20) in the bursectomy group compared to the no-bursectomy group. None of the studies reported any statistically significant increase in disease recurrences when bursectomy was omitted in radical gastrectomy (Table 3). There were conflicting results about the survival benefit of bursectomy in patients with advanced disease (T3/T4). Two studies – Kurokawa et al. [13] and Kochi et al. [21] (all patients in their studies had advanced T3/T4 disease) – reported no survival benefit when bursectomy was carried out in advanced tumors (T3/T4 stages); however, Hu et al. [12] highlighted that there was a significant difference in a 3-year OS (62.2 vs. 45.7%, *p* value 0.039) if bursectomy was added to the radical gastrectomy. Hirao et al. [11] reported that bursectomy led to a difference of almost 20% in the 5-year OS in patients with pT3 or T4 gastric cancer, though the difference failed to attain statistical significance (55.5 vs. 34.8%; HR = 0.54, 95% CI 0.26–1.12, *p* value 0.096).

Discussion

Our study demonstrates that bursectomy with gastrectomy does not improve OS or DFS. The basic premise of the bursectomy is its potential to clear the micrometastatic disease from the lesser bursa and the anterior surface of the pancreas, and it is generally considered to lower the disease recurrence in the serosa-positive disease. Three of the 6 studies (Kurokawa et al. [13], Kochi et al. [21], and Eom et al. [22]) failed to find any significant difference in a 3-year OS in patients with the serosa-positive disease. Both Kurokawa et al. [13] and Kochi et al. [21] did not find any significant difference in a 3-year DFS in

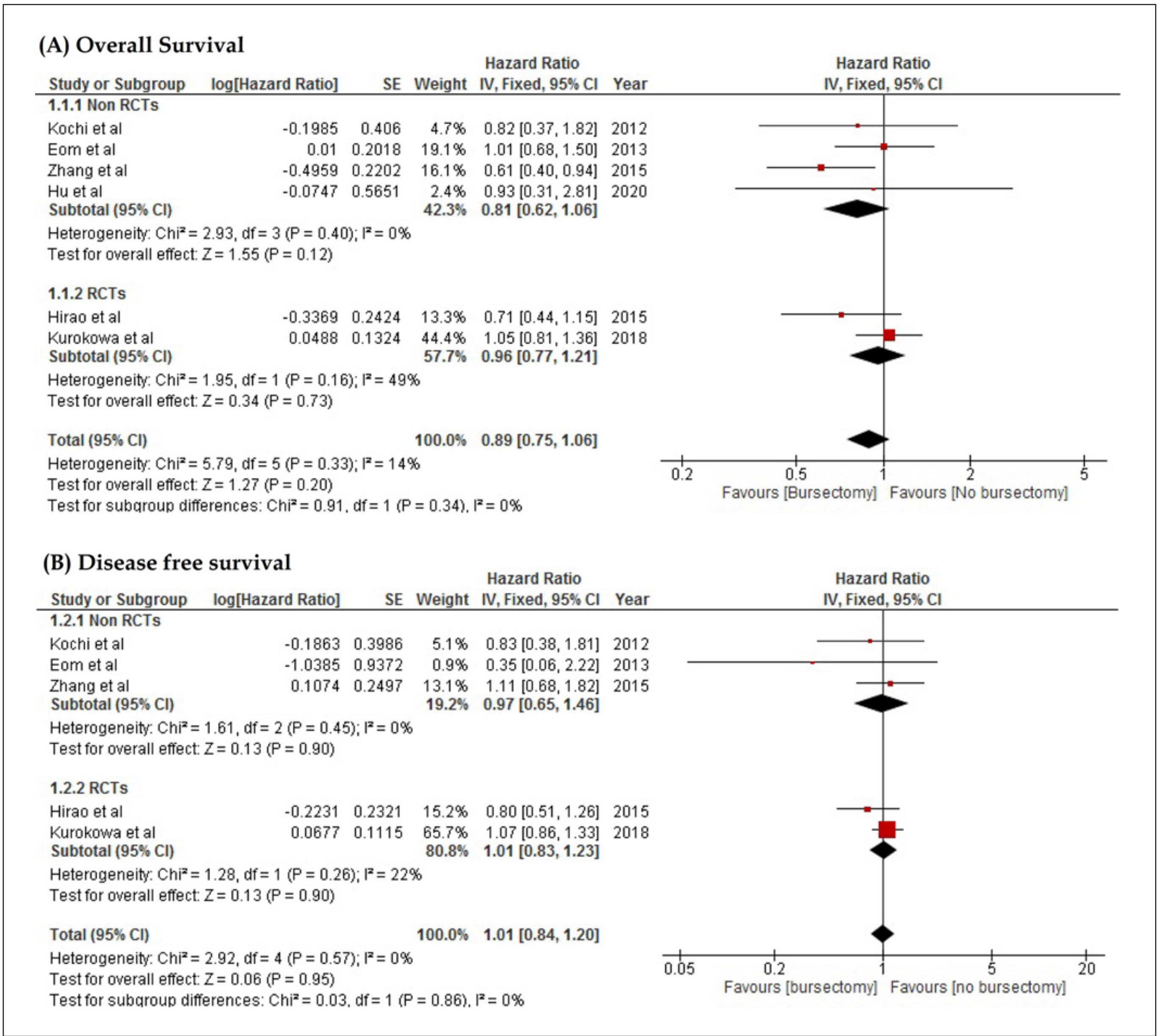

Fig. 4. Forest plot for comparison: OS (**A**), DFS (**B**). RCTs, randomized controlled trials; OS, overall survival; DFS, disease-free survival.

patients with T3/T4 disease. Eom et al. [22] also performed a subgroup analysis of 229 patients with clinical stage III/IV as the surgeons decided the need to perform bursectomy based on the clinical stage; they highlighted that bursectomy did not improve OS in this cohort of patients also (HR 1.16, 95% CI 0.68–1.98, *p* value 0.582). However, Hirao et al. [11] and Hu et al. [12] suggested that bursectomy may have a therapeutic value in this cohort of patients with T3/T4 gastric cancer. Hu et al. [12] demonstrated that bursectomy led to a survival benefit in almost 17% of patients with T4 gastric cancer (5-year OS of 62.2 vs. 45.7%, *p* value 0.039). Similarly, Hirao et al. [11] also observed a gain of almost 20% in the 5-year OS in patients with pT3 or T4 gastric cancer when radical gastrectomy was accompanied by bursectomy, though the difference was not statistically significant [11]. Despite these data, the pooled effect suggests no improvement in OS or DFS and we would advocate against routine bursectomy for advanced gastric cancer. However, this needs to be highlighted that the patient population in various trials was heterogeneous – Hirao et al. [11] and Eom et al. [22] did not include any patient with clinical T4 disease, and the other studies also did not have a uniform representation of T3/T4 patients.

Nodal involvement is considered an important surrogate marker of the prognosis of gastric cancer. Long-term results of the landmark Dutch trial [23] highlighted that D2 lymphadenectomy is the recommended surgical ap-

Table 3. Survival outcomes in various studies

Characteristic	Eom et al. [22]		Hu et al. [12]		Kochi et al. [21]		Zhang et al. [9]		Hirao et al. [11]		Kurokawa et al. [13]	
	B+ (n = 107)	B– (n = 363)	B+ (n = 180)	B– (n = 180)	B+ (n = 121)	B– (n = 133)	B+ (n = 159)	B– (n = 247)	B+ (n = 104)	B– (n = 106)	B+ (n = 602)	B– (n = 602)
Recurrence, n (%)	34 (31.8%) p = 0.268	95 (26.2%)	NA NA	NA	8 (6.6%) p = 0.64	7 (5.3%)	25 (15.7%) p = 0.667	35 (14.2%)	24 p = 0.745	26	150 (24.9%) p = 0.227	134 (22.2%)
5-year OS	NA NA	NA	71.3 p = 0.894	69.1	85.80% HR = 0.82 (95% CI 0.37–1.74; p = 0.60)	80.80%	NA NA	NA	77.50% HR = 0.71 (95% CI 0.44–1.14)	71.30%	76.9% HR = 1.05 (95% CI 0.81–1.37; p = 0.65)	76.7%
5-year DFS	NA NA	NA	NA	NA	87.80% HR = 0.83 (95% CI 0.38–1.77; p = 0.63)	82.90%	NA NA	NA	73.70% HR = 0.8 (95% CI 0.50–1.25)	66.60%	68.0% HR = 1.07 (95% CI 0.86–1.33; p = 0.54)	69.3%
OS in T3/T4 disease	NA HR 1.16 (95% CI 0.68–1.98; p = 0.58)	NA	**62.2% p = 0.039	**45.7%	*67.60% HR = 0.64 (95% CI 0.24–1.79; p = 0.37)	*61.50%	NA	NA	**55.5% HR = 0.54 (95% CI 0.26–1.12; p = 0.096)	**34.8%	***83.3% One sided; p = 0.68	***86.0%

B+, with bursectomy; B–, without bursectomy; NA, not available; HR, hazard ratio; OS, overall survival; DFS, disease-free survival. * 3-year OS for T3 disease; ** 5-year OS for T3/T4 disease; *** 3-year OS for T3–T4 disease.

proach for patients with resectable (curable) gastric cancer in high-volume centers that have adequate expertise to perform it. Bursectomy is classically thought to result in a higher lymph node yield considering a more meticulous dissection of station 6 and celiac-based N2 lymph node basin. The present meta-analysis did not identify that bursectomy increases the lymph node harvest. Moreover, none of the studies reported that bursectomy led to a higher yield of metastatic lymph nodes. As all the studies were carried out in the centers performing D2 lymphadenectomy, it seems that bursectomy alone would not further improve the extent of lymphadenectomy in the hands of expert surgeons.

The present meta-analysis highlights that the bursectomy adds 30 min to the duration of the surgery and results in an additional blood loss of around 50 mL. However, adequate surgical experience with the technique of bursectomy may diminish these operative differences [11–13, 21].

Procedure-related complications are equally essential considerations while recommending a surgical intervention; unusually high morbidity or mortality may even forbid a surgical intervention, which is otherwise oncologically beneficial. The Osaka-Bursectomy trial highlighted that bursectomy is a surgically challenging technique to master for surgeons worldwide as removing the mesocolon and the pancreatic capsule may be physically detrimental to the pancreas/colon and increases the risk of intraoperative and postoperative complications [8]. As the safety of the surgical treatments strongly depends upon the surgeon's experience, all the studies included in the present meta-analysis showed the procedure-related mortality of 1% or less. Only Hu et al. [12] documented the bursectomy-related mortality of 1.7% ($n = 3/180$). Postoperative morbidity varied significantly among the studies ranging from 12.8 [12] to 24.3% [22]; however, none of the studies reported that bursectomy was associated with a higher rate of postoperative complications. The most feared complication after bursectomy remains the pancreatic fistula because bursectomy requires resection of the capsule covering the pancreas. The Osaka-Bursectomy trial [19] highlighted that bursectomy was not associated with a higher incidence of pancreatic fistula than the no-bursectomy group – median drain fluid amylase levels on the postoperative day 1 were similar in both the groups (282 IU/L in the bursectomy group vs. 314 IU/L in the no-bursectomy group, $p = 0.543$). Higher levels of drain fluid amylase levels in both the groups may be explained by the lymph node dissection adjacent to the pancreas and may not be related to the removal of a pancreatic capsule itself. Duration of hospital stay is another surrogate marker of the safety of a surgical procedure; none of the studies showed that bursectomy caused the patients to stay longer in the hospital than those who did not undergo bursectomy.

The present systematic review has many strengths – (a) the majority of the studies have a good sample size (>100), (b) presence of 2 large RCTs, and (c) uniform reporting of outcome data in almost all studies. The limitations of this systematic review and meta-analysis are – (a) the limited number of published studies addressing the role of bursectomy, (b) exclusion of the studies published in a language other than English, (c) heterogeneity among the studies, and (d) all the studies comparing the role of bursectomy conducted in eastern Asia.

Conclusion

Though bursectomy does not increase postoperative morbidity and mortality, the present meta-analysis suggests a lack of benefit for OS and recurrence-free survival in patients with gastric adenocarcinoma. However, the role of bursectomy in patients with T3/T4 gastric cancer is still far from clarity; further trials preferably outside Asia are warranted to clear the air and inspire confidence in the minds of the surgeons before they bid adieu to a classical surgical technique.

Acknowledgments

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Statement of Ethics

The study was conducted in accordance with the International Conference on Harmonization E6 requirements for Good Clinical Practice and with the ethical principles outlined in the Declaration of Helsinki.

Conflict of Interest Statement

All the authors declare no relevant conflicts of interest.

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None to declare.

Author Contributions

Conception and design: P.K.G., A.J., R.K., B.R.; collection and assembly of data: P.K.G., A.J., K.K.T.; statistical analysis: P.K.G., A.J.; data interpretation: all authors; manuscript writing: all authors; final approval of the article: all authors; accountable for all aspects of the work: all authors.

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