Original Article

Efficacy of the No. 10 lymphadenectomy with spleen preservation on patients with gastric cancer and/or esophagogastric junction adenocarcinoma who underwent total gastrectomy: a systematic review and meta-analysis

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Background: Surgery with total gastrectomy and D2 lymph node dissection (LND) has been recommended as the standard treatment for patients with advanced upper and middle gastric carcinoma and/or Siewert type II/III adenocarcinoma of the esophagogastric junction (AEG). However, whether the No. 10 lymph node (No. 10 LN, also known as splenic hilar LN) should be dissected in total gastrectomy remains controversial. We aimed to evaluate whether the No. 10 LND with spleen preservation has survival benefit for patients with gastric cancer and/or AEG who underwent the total gastrectomy.

Methods: The PubMed, Embase, the Cochrane Library, ClinicalTrials.gov and American Society of Clinical Oncology.org (ASCO.org) were electronically searched to identify eligible studies. The primary outcome was the survival rate, and secondary outcomes included the disease-free survival (DFS) rate and side effects. The Review Manager 5.3.5 software was used for the meta-analysis. The odds ratio (OR) and mean difference with 95% confidence interval (CI) were calculated. The statistical heterogeneity was assessed using chi-square (χ^2) and I^2 tests.

Results: Eight studies enrolling a total of 4,131 patients were eligible for our review. The meta-analysis results demonstrated that the No. 10 LND group was significantly better than the non-No. 10 LND group in terms of the 3- (OR =0.71, 95% CI: 0.62–0.81, P<0.00001) and the 5-year (OR =0.66, 95% CI: 0.58–0.75, P<0.00001) survival rates but not in the 1-year survival rate (OR =0.91, 95% CI: 0.75–1.11, P=0.36). The DFS rates in the No. 10 LND group were significantly increased after 1 (OR =0.76, 95% CI: 0.61–0.93, P=0.008), 3 (OR =0.69, 95% CI: 0.60–0.81, P<0.00001), and 5 (OR =0.66, 95% CI: 0.56–0.76, P<0.00001) years compared with those in the non-No. 10 LND group.

Discussion: Evidence shows that the No. 10 LND with spleen preservation can improve the survival and the DFS rates for patients with gastric cancer and/or Siewert type II/III AEG who underwent the total gastrectomy. High-quality prospective trials are expected.

Keywords: No. 10 lymphadenectomy; gastric cancer; adenocarcinoma of the esophagogastric junction (AEG); total gastrectomy; systematic review

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Introduction

Gastric cancer is responsible for over one million new cases in 2020, and is listed as the fourth most common malignancy and one of the most common causes of cancer-related death worldwide (1,2). According to the Japanese Gastric Cancer Treatment Guideline (JGCTG) 2010 (version 3), surgery with total gastrectomy and D2 lymph node dissection (LND) is recommended as the standard treatment for patients with advanced upper and middle gastric carcinoma in East Asia (3). The advanced Siewert type II/III adenocarcinoma of the esophagogastric junction (AEG) is suggested with the same treatment with proximal gastric cancer as their anatomical position and biological behavior are quite similar (3).

Nevertheless, whether the No. 10 lymph node (No.10 LN, also known as splenic hilar LN) should be dissected in total gastrectomy remains controversial. The incidence rate of No. 10 lymph node metastasis (LNM) is reported to be 9.0–27.9% in the advanced upper and middle gastric cancers (4-7) and 4.8–15.0% in the Siewert type II/III AEG (8-11). Thus, the No. 10 LND is recommended to be added in the total gastrectomy (12).

However, some studies consider that undergoing the No. 10 LND is unnecessary, for the No. 10 LNM is considered as one of the incurable factors of prognosis and the No. 10 LND does not have a survival benefit (13,14). Shin *et al.* (15) have reported that patients with the No. 10 LNM have worse survival than patients without the No. 10 LNM and does not gain survival benefit from the No. 10 LND. Recently, the No. 10 LN has been deleted from the definition of D2 LND in total gastrectomy according to the JGCTG 2018 (5th edition) by the Japanese Gastric Cancer Association (16).

The aim of the present study was to perform a systematic review of randomized controlled trials (RCTs) or cohort studies to evaluate the effects of No. 10 LND with spleen preservation on patients with gastric cancer and/or Siewert type II/III AEG who have undergone total gastrectomy. We present the following article in accordance with the PRISMA reporting checklist (17) (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-522/rc).

Methods

Search strategy and selection criteria

The PubMed, Embase, the Cochrane Library, ClinicalTrials.gov and American Society of Clinical Oncology.org (ASCO.org) were searched until January 2022 for relevant citations. A combination of the following terms was used to complete the search: "gastric cancer", "cardiac carcinoma", "esophagogastric junction carcinoma", "No. 10 lymphadenectomy", "splenic hilar lymphadenectomy", "No. 10 lymph node", "splenic hilar lymph node", and "gastrectomy". Manual searches included scanning of reference lists in relevant articles. No language restriction was applied.

Eligible trials were RCTs or cohort studies that compared the No. 10 LND with the non-No.10 LND for patients with gastric cancer and/or Siewert type II/III AEG who underwent the total gastrectomy. Moreover, data concerning the survival rate should be reported in studies. Studies were excluded if they met the following criteria: (I) intraoperative evidence of peritoneal dissemination or distant metastasis; (II) combined major organ resection (except necessary organ resection, such as splenectomy or pancreatectomy, because of intraoperative organ injury, the intraoperative detection of invasion of the pancreas or spleen, or to enable the en bloc dissection of evident metastatic No. 10 LNs); (III) incomplete pathological data; (IV) and neoadjuvant therapy.

Study selection

Two authors (MXC, BWX) independently selected literature. A third author (BXK) resolved any discrepancies if the first two authors disagreed. The full text of each potentially eligible study was evaluated for inclusion or exclusion in accordance with the selection criteria of the two independent reviewers (YF and YXK).

Data extraction

Two authors (XLS and YBW) independently extracted the data using predefined data extraction forms. Extracted data included study details, study population characteristics, interventions, and outcomes from each eligible trial. All relevant texts, tables, and figures were reviewed for data extraction. Any disagreement in data extraction was resolved by a third reviewer (YYL).

Quality assessment

The methodological quality of cohort studies was assessed by using of the Newcastle-Ottawa Scale (18). A "star system" was applied in each study in accordance with three broad perspectives: selection of cases (0–4 stars), comparability

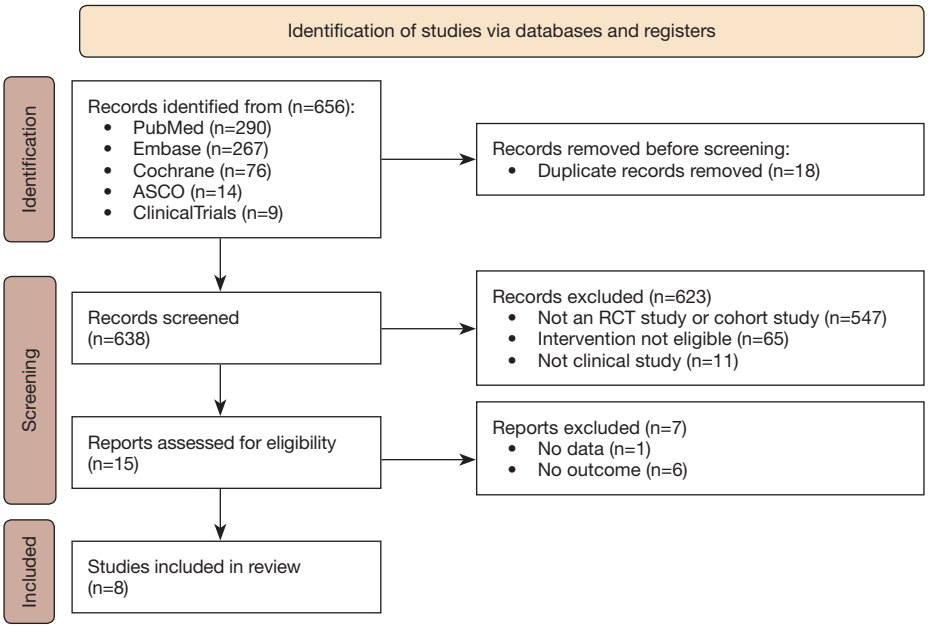

Figure 1 Flow diagram summarizing study identification and selection. ASCO, American Society of Clinical Oncology; RCT, randomized controlled trials.

of groups (0–2 stars), and assessment of outcome (0–3 stars). The quality of each study was graded as either "high quality" (8–9 stars) or "moderate quality" (5–7 stars). The quality of the included RCTs was assessed using the modified Jadad standard. Three items were included in the specified criteria of the RCTs: randomization (0–2 points), dropout or withdrawal (0–1 point), and allocation concealment (0–2 points) (19). A blind approach was discarded in RCTs because of the intrinsic nature of the intervention. Studies that received an Jadad score of 3 or higher were classified as high-quality studies. Two authors (YYL and YXK) independently ranked and assessed each study.

Outcome measures

The primary outcome was overall survival rate that was assessed in the included study. This endpoint was measured over one, three, or five years, depending on the size of the study and the length of the follow-up. The disease-free survival (DFS) rate at each time point, complications and mortality associated with the No. 10 LND were the secondary outcomes.

Statistical analysis

A meta-analysis of outcomes by combining various studies was performed using the Review Manager (RevMan) software, version 5.3.5 (The Cochrane Collaboration, Software Update, Oxford). The effect measures of interest were odds ratio (OR) and mean difference with 95% confidence interval (CI). The statistical heterogeneity was assessed using chi-square (χ^2) and I^2 tests. I^2 <25%, 25%≤ I^2 ≤50%, and I^2 >50% reflected small, moderate, and large inconsistencies, respectively. Sub-group analyses or sensitivity analyses was undertaken to attempt to explain heterogeneities if existed. The ability to conduct subgroup analyses depended on whether the required information was reported in the included studies. The location of tumor was considered for possible subgroup analysis. Sensitivity analyses were carried out only in high quality trials to avoid errors caused by poor quality studies. The publication bias was performed using the Begg's funnel plots and Egger's tests if the number of included studies was more than 10 (20,21). P<0.05 was considered significant.

Results

Selection of trials

From the 656 citations identified using database searches, 18 duplicate studies and 623 reviews, case reports, letters, editorials, and irrelevant articles were excluded (*Figure 1*).

Furthermore, 7 out of the 15 remaining trials with potential relevance were excluded from the study after reading the full text. One study referred to the posterior No. 10 LND (22); and six studies did not reveal sufficient outcome information to perform analysis (23-28). Finally, eight retrospective cohort studies involving 4,131 patients were included in the study (14,29-35).

Among the included studies, 1,929 patients were in the No. 10+ group (No. 10 LND was conducted for patients with gastric cancer and/or Siewert type II/III AEG who underwent the total gastrectomy) and 2,202 patients were in the No. 10– group (No. 10 LND was not conducted for patients with gastric cancer and/or Siewert type II/III AEG who underwent total gastrectomy). For the study by Park *et al.* (14), only the data of arms fulfilled the included criteria and were extracted for meta-analysis. In the study of Bian *et al.* (30), although the data fulfilled the included criteria was limited in the patients with negative No. 4s LNs, we performed a sensitivity analysis and found the result be influenced slightly by the confinement of patients with negative No. 4s LNs. Thus, we included this study for meta-analysis. The average age of patients was 58.9 years, and 74.8% of the patients were male (*Table 1*). The percentages of TNM stages I–IV of the tumors were 11.0%, 25.7%, 59.5%, and 3.8%, respectively, for patients with the No. 10 LND, and 16.1%, 25.9%, 54.3%, and 3.7%, respectively, for patients without the No. 10 LND. The mean tumor size of gastric cancer and/or Siewert type II/III AEG was 5.9 cm. The mean duration of follow-up was 70.7 months.

Qualitative analysis of studies

As *Table 2* shows, among the eight cohort studies, 7 were of high quality (14,29,30,32-35), and 1 was of moderate quality (31).

Survival rate

Overall survival rate

The meta-analysis results showed that the No. 10 LND significantly improved the 3- [eight studies (14,29-35) reported this data, OR =0.71, 95% CI: 0.62–0.81, P<0.00001; heterogeneity: I^2 =39%, P=0.12 for χ^2] and 5-year [eight studies (14,29-35) reported this data, OR =0.66, 95% CI: 0.58–0.75, P<0.00001; heterogeneity: I^2 =24%, P=0.23 for χ^2] survival rates but not the 1-year survival rate [eight studies (14,29-35) reported this data, OR =0.91, 95% CI: 0.75–1.11, P=0.36; heterogeneity: I^2 =53%, P=0.04 for χ^2; *Figure 2*].

Survival rate of patients with gastric cancer after surgical resection with total gastrectomy

The pooled meta-analysis results demonstrated that the No. 10 LND significantly improved the 3- [six studies (14,30,32-35) reported this data, OR =0.76, 95% CI: 0.65–0.90, P=0.001; heterogeneity: I^2 =32%, P=0.19 for χ^2] and 5-year [seven studies (14,29,30,32-35) reported this data, OR =0.70, 95% CI: 0.60–0.82, P<0.00001; heterogeneity: I^2 =13%, P=0.33 for χ^2] survival rates but not the 1-year survival rate [six studies (14,30,32-35) reported this data, OR =0.95, 95% CI: 0.74–1.21, P=0.67; heterogeneity: I^2 =61%, P=0.02 for χ^2; *Figure 3A*].

Survival rate of patients with gastric cancer and type III AEG after surgical resection with total gastrectomy

The overall survival rates in patients with the No. 10 LND were significantly higher than those in patients without the No. 10 LND after 3 [seven studies (14,30-35) reported this data, OR =0.72, 95% CI: 0.57–0.90, P=0.004; heterogeneity: I^2 =54%, P=0.04 for χ^2], and 5 years [eight studies (14,29-35) reported this data, OR =0.64, 95% CI: 0.53–0.79, P<0.0001; heterogeneity: I^2 =49%, P=0.06 for χ^2], but not 1 year [seven studies (14,30-35) reported this data, OR =0.92, 95% CI: 0.62–1.37, P=0.69; heterogeneity: I^2 =63%, P=0.01 for χ^2; *Figure 3B*].

DFS rate

Overall DFS rate

The meta-analysis showed significant differences between the two groups, and the result favored the No. 10+ group with 1- [five studies (30-33,35) reported this data, OR =0.76, 95% CI: 0.61–0.93, P=0.008; heterogeneity: I^2 =0, P=0.61 for χ^2], 3- [five studies (30-33,35) reported this data, OR =0.69, 95% CI: 0.60–0.81, P<0.00001; heterogeneity: I^2 =0%, P=0.55 for χ^2], and 5-year [five studies (30-33,35) reported this data, OR =0.66, 95% CI: 0.56–0.76, P<0.00001; heterogeneity: I^2 =5%, P=0.38 for χ^2] DFS rates (*Figure 4*).

DFS rate of patients with gastric cancer after surgical resection with total gastrectomy

Results showed that the No. 10 LND was associated with a significant improvement in the 1- [four studies (30,32,33,35) reported this data, OR =0.79, 95% CI: 0.62–0.99, P=0.04; heterogeneity: I^2 =0%, P=0.54 for χ^2], 3- [four studies (30,32,33,35) reported this data, OR =0.72, 95% CI: 0.60–0.85, P=0.0002; heterogeneity: I^2 =0%, P=0.47 for χ^2], and

Table 1 Basic characteristics of the included studies

Study	Year	Country	Study type	Arms	Sample size (n)	Sex, M/F (n)	Age (year)	Tumor size (cm)	Tumor location (upper third and AEG/middle third/lower third/entire and linitisplastica)	Pathological differentiation (differentiated/undifferentiated)	TNM stage[†] (I/II/III/IV)	Follow-up duration (month)
Bian	2016	China	Retrospective	No. 10+[‡]	260	185/75	NC	NC	NC	39/221	5/59/196/0	62
				No. 10−[§]	243	170/73	NC	NC	NC	48/195	6/58/179/0	62
Huang	2017	China	Retrospective	No. 10+	198	155/43	61.9	6.1	80/75/0/43	NC	9/49/140/0	60
				No. 10–	198	154/44	61.1	5.9	83/80/0/35	NC	15/45/138/0	60
Lin	2021	China	Retrospective	No. 10+	354	280/74	62.3	5.3	161/122/0/71	275/79	61/90/203/0	60
				No. 10–	354	286/68	63.1	5.3	155/146/0/53	289/65	73/85/196/0	60
Liu	2021	China	Retrospective	No. 10+	237	165/72	58.0	6.8	148/60/19/10	68/169	20/44/156/17	91.2
				No. 10–	237	172/65	58.1	7.0	138/64/22/13	68/169	20/34/163/20	91.2
Lv	2016	China	Retrospective	No. 10+	293	241/52	NC	4.9	293/0/0/0	NC	52/87/154/0	47
				No. 10–	401	335/66	NC	4.9	401/0/0/0	NC	81/104/216/0	47
Oh	2021	Korea	Retrospective	No. 10+	288	194/94	56.1	7.5	NC	88/200	NC	60
				No. 10–	288	198/90	56.1	7.5	NC	89/199	NC	60
Park	2019	Korea	Retrospective	No. 10+	79	58/21	55.5	NC	NC	NC	22/57/0/0	93.3
				No. 10–	248	168/80	55.1	NC	NC	NC	100/148/0/0	93.3
Yang	2014	China	Retrospective	No. 10+	220	163/57	NC	NC	104/64/41/11	35/185	12/35/128/45	89.5
				No. 10–	233	166/67	NC	NC	64/85/51/33	25/208	14/22/146/51	96

[†], TNM stage was according to seventh American Joint Committee on Cancer staging system for gastric cancer; [‡], No. 10 lymph node dissection; [§], non-No. 10 lymph node dissection. M/F, male/female; AEG, adenocarcinoma of the esophagogastric junction; TNM, tumor-node-metastasis; NC, not clear.

Table 2 Quality assessment of included cohort studies

Study	Selection				Comparability		Outcome			Score
	1	2	3	4	5A	5B	6	7	8	
Bian 2016	*†	*	*	*	*	*	*	*	*	*********‡
Huang 2017	*	*	*	*	*	*	*	*	*	*********
Lin 2021	*	*	*	*	*	*	*	*	*	*********
Liu 2021	*	*	*	*	*	*	*	*	*	*********
Lv 2016	*	*	*	*			*	*	*	*******
Oh 2021	*	*	*	*	*	*	*	*	*	*********
Park 2019	*	*	*	*	*		*	*	*	********
Yang 2014	*	*	*	*	*	*	*	*	*	*********

1, representativeness of the exposed cohort; 2, non-exposed cohort drawn from the same community; 3, ascertainment of exposure; 4, outcome of interest not present at start of study; 5A, comparability of cohorts on the basis of tumor categories; 5B, comparability of cohorts on the other factors; 6, assessment of outcomes; 7, follow-up long enough for outcomes to occur; 8, adequacy of follow up of cohorts; †, each star represents if an individual criterion within the subsection was fulfilled; ‡, score for study quality. The quality of each included cohort study was graded as either "high quality" (8–9 stars) or "moderate quality" (5–7 stars).

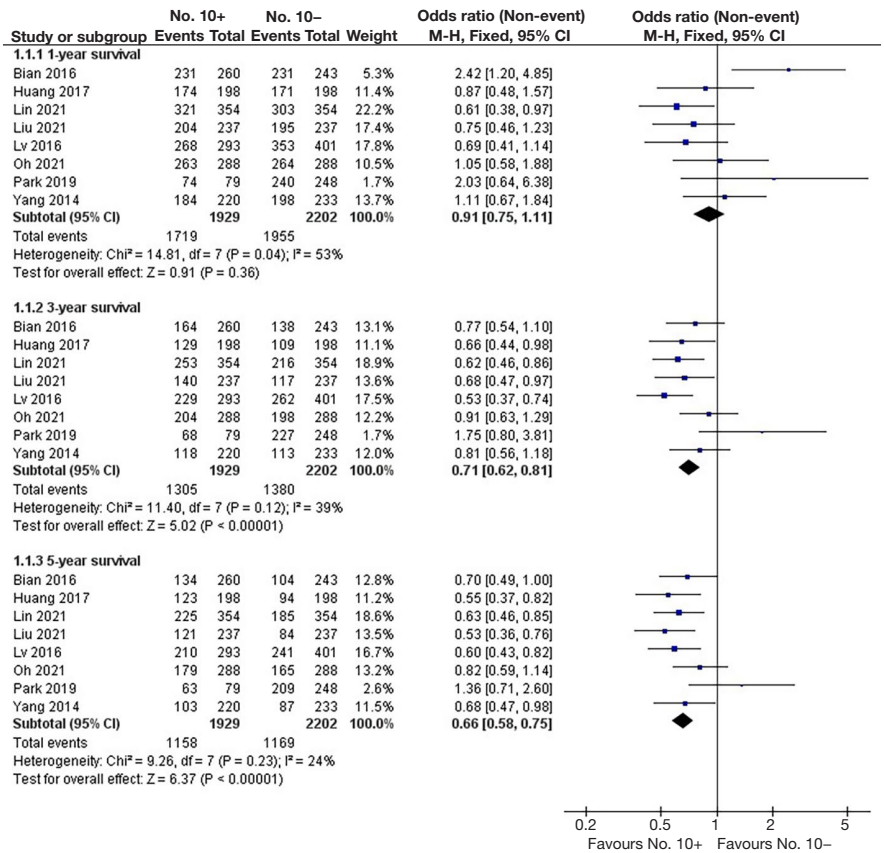

Figure 2 Meta-analysis of overall survival in trials comparing No. 10 LND versus non-No. 10 LND for patients with gastric cancer and/or Siewert type II/III AEG who have undergone total gastrectomy. No. 10 LND, No. 10 lymph node dissection; AEG, adenocarcinoma of the esophagogastric junction; No. 10+, No. 10 lymph node dissection group; No. 10–, non-No. 10 lymph node dissection group; M-H, Mantel-Haenszel; CI, confidence interval.

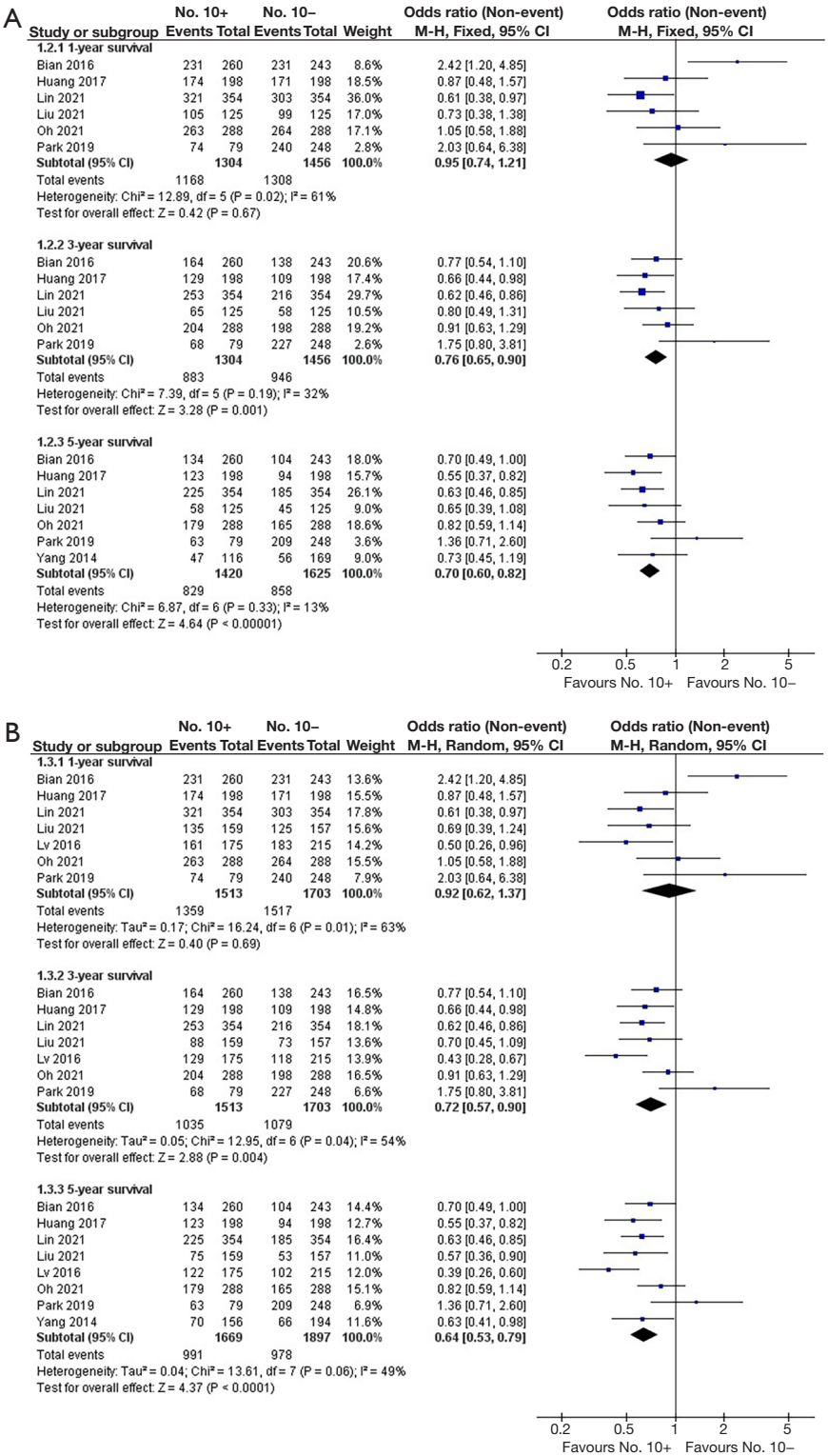

Figure 3 Meta-analysis of survival in trials comparing No. 10 LND versus non-No. 10 LND for: (A) patients with gastric cancer who have undergone total gastrectomy; (B) patients with gastric cancer and/or Siewert type III AEG who have undergone total gastrectomy. No. 10 LND, No. 10 lymph node dissection; AEG, adenocarcinoma of the esophagogastric junction; No. 10+, No. 10 lymph node dissection group; No. 10–, non-No. 10 lymph node dissection group; M-H, Mantel-Haenszel; CI, confidence interval.

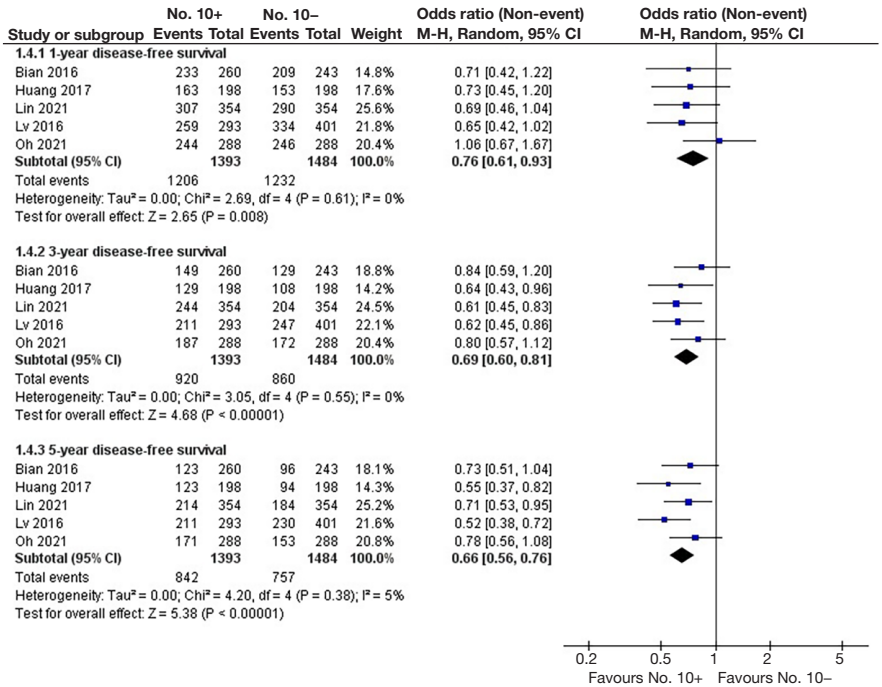

Figure 4 Meta-analysis of overall DFS in trials comparing No. 10 LND versus non-No. 10 LND for patients with gastric cancer and/or Siewert type II/III AEG who have undergone total gastrectomy. DFS, disease-free survival; No. 10 LND, No. 10 lymph node dissection; AEG, adenocarcinoma of the esophagogastric junction; No. 10+, No. 10 lymph node dissection group; No. 10–, non-No. 10 lymph node dissection group; M-H, Mantel-Haenszel; CI, confidence interval.

5-year [four studies (30,32,33,35) reported this data, OR =0.70, 95% CI: 0.59–0.83, P<0.0001; heterogeneity: I^2 =0%, P=0.62 for χ^2] DFS rates (*Figure 5A*).

DFS rate of patients with gastric cancer and type III AEG after surgical resection with total gastrectomy

The DFS rate in the No. 10+ group was significantly higher after 1 [five studies (30-33,35) reported this data, OR =0.72, 95% CI: 0.55–0.93, P=0.01; heterogeneity: I^2 =30%, P=0.22 for χ^2], 3 [five studies (30-33,35) reported this data, OR =0.66, 95% CI: 0.53–0.82, P=0.0001; heterogeneity: I^2 =43%, P=0.14 for χ^2], and 5 years [five studies (30-33,35) reported this data, OR =0.61, 95% CI: 0.46–0.80, P=0.0004; heterogeneity: I^2 =67%, P=0.02 for χ^2] than that in the No. 10– group (*Figure 5B*).

Safety

The most frequent side effects correlated with the No. 10 LND that were reported in the trials were iatrogenic spleen injury, intraoperative blood loss, pancreas-related complications, and peritoneal bleeding. The pooled meta-analysis results demonstrated that there was no significant difference between the two groups in the complications with grade I-II [five studies (31-35) reported this data, OR =1.20, 95% CI: 0.96–1.51, P=0.12; heterogeneity: I^2 =10%, P=0.35 for χ^2], complications with grade III-IV [five studies (31-35) reported this data, OR =1.30, 95% CI: 0.91–1.85, P=0.16; heterogeneity: I^2 =21%, P=0.28 for χ^2], and mortality [five studies (29,30,32-34) reported this data, OR =1.59, 95% CI: 0.52–4.87, P=0.42; heterogeneity: I^2 =0%, P=0.72 for χ^2, *Figure 6*].

Discussion

This systematic review shows that the No. 10 LND with spleen preservation can significantly improve the overall survival and the DFS rates of patients with gastric cancer and/or Siewert type II/III AEG who have undergone the total gastrectomy.

Given the special anatomical position of the spleen and various complicated splenic hilum vessels, the exposure and the vascularization of splenic vessels are difficult to perform. Moreover, pancreas-related complications and bleeding

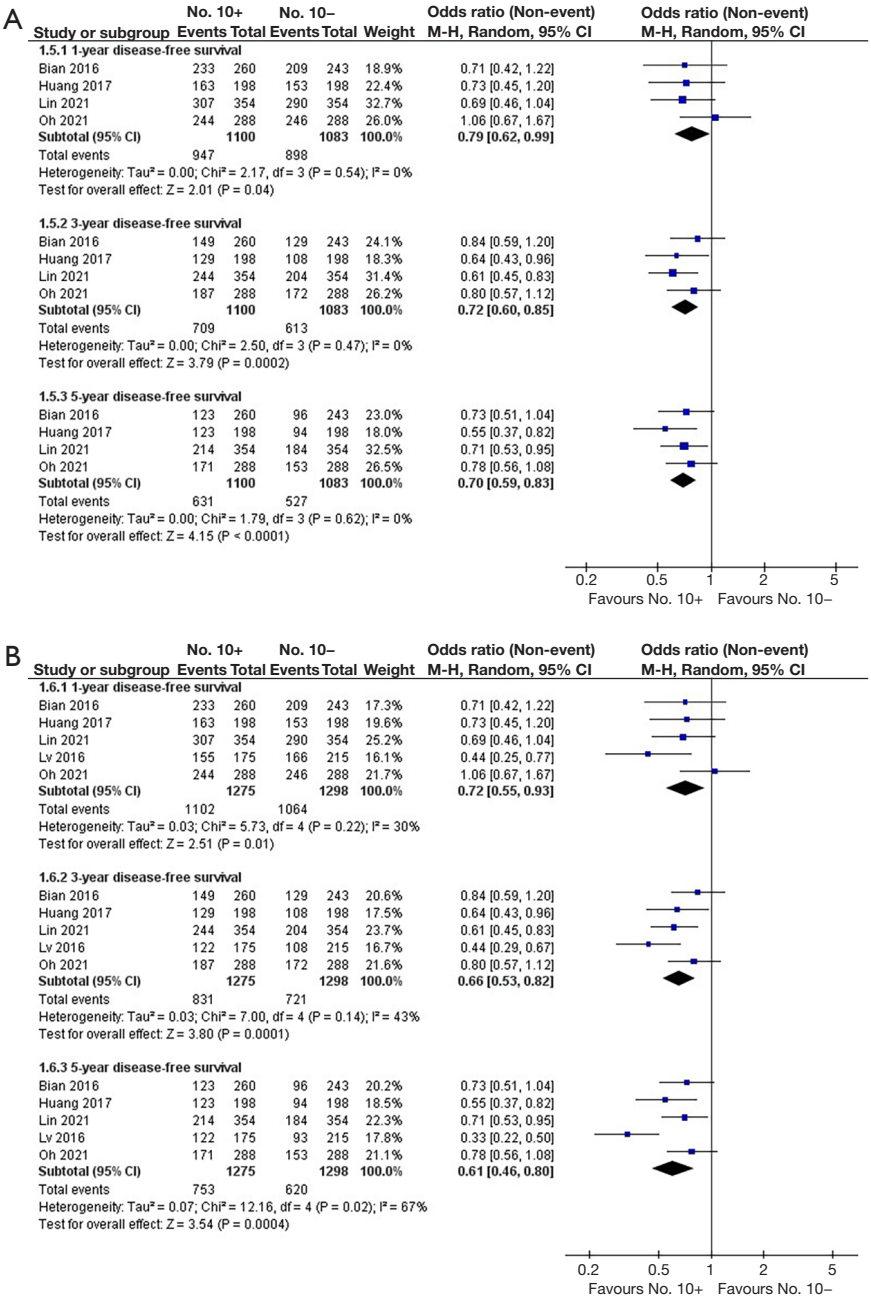

Figure 5 Meta-analysis of DFS in trials comparing No. 10 LND versus non-No. 10 LND for: (A) patients with gastric cancer who have undergone total gastrectomy; (B) patients with gastric cancer and/or Siewert type III AEG who have undergone total gastrectomy. DFS, disease-free survival; No. 10 LND, No. 10 lymph node dissection; AEG, adenocarcinoma of the esophagogastric junction; No. 10+, No. 10 lymph node dissection group; No. 10–, non-No. 10 lymph node dissection group; M-H, Mantel-Haenszel; CI, confidence interval.

may be present. Thus, surgeons have preferred splenectomy to facilitate the No. 10 LND for the total gastrectomy in previous years (36,37). However, the total gastrectomy combined with the resection of spleen is reported to result in higher morbidity, larger blood loss, and could not show a superiority on survival rates compared with that of splenic preservation (38,39). Moreover, the loss of the antitumor and the anti-infection functions of the spleen's immunologic

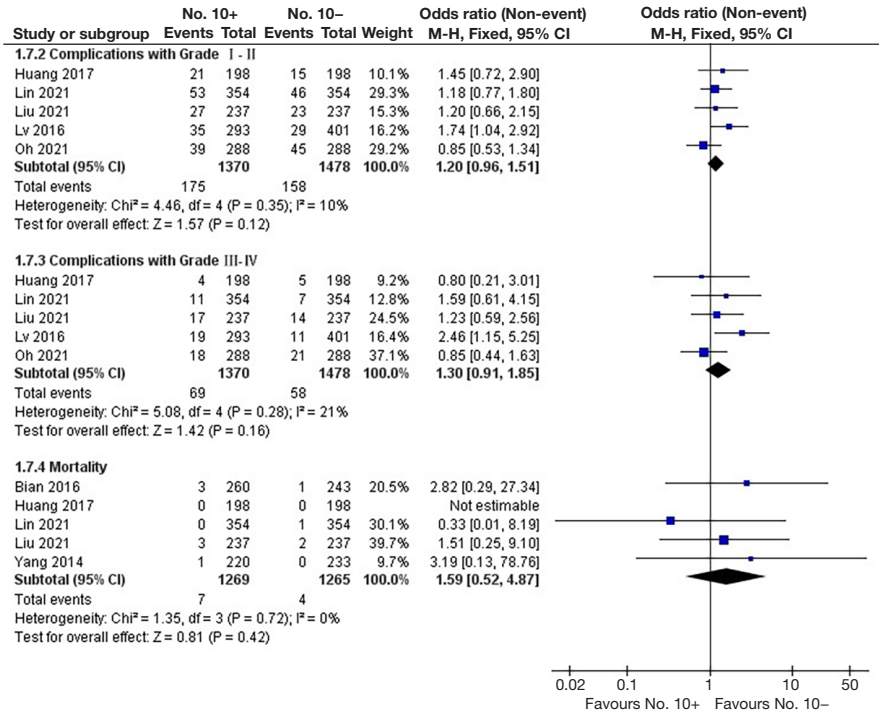

Figure 6 Meta-analysis of safety in trials comparing No. 10 LND versus non-No. 10 LND for patients with gastric cancer and/or Siewert type II/III AEG who have undergone total gastrectomy. No. 10 LND, No. 10 lymph node dissection; AEG, adenocarcinoma of the esophagogastric junction; No. 10+, No. 10 lymph node dissection group; No. 10–, non-No. 10 lymph node dissection group; M-H, Mantel-Haenszel; CI, confidence interval.

effect is a negative effect for patients with splenectomy. Sano *et al.* (40,41) have compared the prognosis of patients with splenectomy and spleen preservation (without intentional No. 10 dissection); found that the 5-year overall survival rates of two arms are 75.1% and 76.4%, respectively (P>0.05); and confirmed the noninferiority of the spleen preservation. However, this study was limited to patients with upper gastric cancer without invasion to the greater curvature. Regarding proximal gastric cancer invading the greater curvature, one retrospective study in Japan reported that no significant survival benefit was observed in the splenectomy group comparing with spleen preservation (without intentional No. 10 dissection) group [5-year OS rate of 63.7% *vs.* 73.6% and 5-year relapse-free survival (RFS) rate of 60.2% *vs.* 67.3%], and splenectomy was associated with a higher morbidity rate (30.2% *vs.* 13.3%) (42). Yang *et al.* (43) have conducted a meta-analysis and found that splenectomy did not increase 5-year overall survival rate but had significantly higher incidence of postoperative complications. For the above reasons, the laparoscopic spleen-preserving No. 10 LND is first reported by Huang *et al.* and has been gradually accepted and adopted by an increasing number of surgeons as a technically safe and feasible procedure (44).

In this study, the significant benefit of the No. 10 LND is observed, which is similar to the result reported by Huang *et al.* (32). Several reasons can account for the decreased mortality. First, the No. 10 LNM is closely linked with the prognosis of patients (15,45). Shin *et al.* (15) have reported that the 5-year survival rate for patients in the hilar node metastasis group (11.04%) is significantly lower than that in the non-metastasis group (51.57%, P<0.001). Takayama *et al.* (45) have also reported that the prognosis of patients with positive No. 10 LNs is significantly worse than that of patients with negative No. 10 LNs. Although the No. 10 LND with splenectomy is demonstrated to have no superiority in terms of safety and prognosis over the non-No. 10 LND, many studies have verified that the spleen-preserving No. 10 LND, whether in the laparoscopic or the open form, is safe (46,47). Yang *et al.* (29) have reported that no spleen-preserving LND-related complication, such as intraperitoneal hemorrhage or pancreatic leakage, has

occurred in the two groups, except one patient from the 10D+ group who has experienced intraoperative splenic injury. Zheng *et al.* (26) have conducted a prospective multicenter study to evaluate the technical safety and feasibility of laparoscopic spleen-preserving No. 10 LND for 242 patients with total gastrectomy. Results show that the major complication rate is 3.3% (8/242), but No. 10 LND-related complications are not observed (26). Thus, without morbidity and mortality, the spleen-preserving No. 10 LND may bring increased dissection of the positive No. 10 LNs and possibly favorable prognosis. Zheng *et al.* (26) have reported that the average numbers of laparoscopic spleen-preserving No. 10 LND and metastases are 2.4 and 0.1, respectively, and the rate of the No. 10 LNM is 8.1% among patients with advanced gastric cancer (18/223). Second, the No. 10 LNM is found to be significantly associated with positive No. 4s LN in several studies (30,48,49). Bian *et al.* (30) have found that the negative predictive efficacy of No. 4s LN status for no metastasis to No. 10 LN is 98.09%. Aoyagi *et al.* (48) have reported that Nos. 4sa and 4sb LNM are significant parameters for the No. 10 LNM ($P<0.001$ and $P=0.006$, respectively) with a logistic regression analysis. Besides, No. 4s LNs are found be upstream of No. 10 LNs (50). Thus, based on the above, the status of negative No. 4s LN may be an indicator for predicting no metastasis to No. 10 LN, and No. 10 LND may gain survival benefits for the patients with No. 4s metastasis. If No. 4s LNs are identified as positive by using intraoperative visualization or pathological examination, the No. 10 LND may be recommended. Third, the greater curvature is found as the common tumor location in patients with No. 10 LNM (38.5%) followed by posterior wall (27.8%), and encircling involvement (22.8%) (4). The serosa-negative tumors located at the lesser curvature and anterior wall are observed with no No. 10 LNM (4). Watanabe *et al.* (51) have found that the incidence of the No. 10 LNM is 15.9% in patients with tumors invading the greater curvature from a retrospective data of 421 patients' outcomes after the total gastrectomy for proximal advanced gastric cancer, and the index to estimate the benefit from the No. 10 LND is 5.6, indicating a certain survival benefit. The greater curvature invasion is verified to be a risk factor of the No. 10 LNM, and therefore it had clinical significance of No. 10 LND for these patients with advanced gastric cancer invading the greater curvature line (38,51). Maezawa *et al.* (52) have found the substantially higher T1 of the No. 10 LN than the other regional nodes, such as Nos. 8a, 11p, and 11d, in locally advanced proximal gastric cancer invading the greater curvature. Authors recommend the No. 10 LND as a part of the D2 dissection for proximal gastric cancer invading the greater curvature (52).

The meta-analyses show that the DFS rates for patients with the No. 10 LND have significantly better prognosis compared with those for patients without the No. 10 LND. Three studies are not included in the meta-analyses because of insufficient data (14,29,34). However, Park *et al.* (14) have observed a RFS rate and found no difference in the RFS rates between the two groups. The DFS rate, which is closely correlated to relapse and distant metastasis, generally denotes the length of time the patient survives without any signs or symptoms after primary treatment for a cancer (53). The presence of the No. 10 LNM is one of the independent predictors of distant metastasis after the R0 surgical resection, indicating that the non-No. 10 LND patients with potentially positive No. 10 LN have a high risk for the presence of distant LNM and therefore a lower DFS, but a limited risk for the presence of relapse *in situ* (6). Thus, the relative effect of the No. 10 LND may be less remarkable for RFS than DFS.

Considering the discrepancies of Siewert type II AEG, Siewert type III AEG, and stomach cancer, subgroup analysis according to the location of tumor are performed. The results of subset analyses showed that the survival and DFS rates of the patients with gastric cancer are consistent with those of the patients with gastric cancer and/or type II/III AEG. Results indicate that the tumor, whether located in the stomach or below 1 centimeter above the esophagogastric junction, is not crucial in the prognosis of patients. The finding maybe because the biological behavior and the anatomical position of the Siewert type II/III AEG are quite similar to those of advanced proximal gastric cancer, which has a similar prognosis while the total gastrectomy and the D2 lymphadenectomy are performed (54). The subgroup analyses on the tumor of gastric cancer and/or Siewert type III AEG indicate that the No. 10 LND significantly improves the overall survival and the DFS rates of patients with gastric cancer and/or the Siewert type III AEG who have undergone total gastrectomy. However, the validity of meta-analysis may be affected by significant heterogeneity and limited sample sizes. The subset analyses according to tumor size, tumor stage, and degree of pathological differentiation are not conducted because of insufficient information. The result of meta-analysis of safety in trials comparing No. 10 LND versus non-No. 10 LND indicates that No. 10 LND is a safe way for patients with gastric cancer and/or Siewert type II/III AEG who have undergone

total gastrectomy.

The current study has several potential limitations. First, there are important heterogeneities among studies. Sensitivity and subgroup analyses have failed to eliminate the significance. There are many differences across studies that serve as sources of heterogeneity, including variation in sample sizes, variation in the baseline of tumor characteristics (e.g., tumor differentiation, stage, and size), and length of follow-up period. Second, the publication bias may exist because of the relatively limited database. The quality of the current study may be influenced by none of the available RCTs included. We speculate that the reason may be that for surgeons, performing surgical intervention with randomized and blinded ways is a difficult and unethical task. Nevertheless, the meta-analyses of well-designed non-RCTs are demonstrated to have similar accuracy to RCTs (55). There may be duplicate patients due to several overlaps in terms of institution and operation year, in which the patients underwent total gastrectomy (29,31-34). However, we failed to eliminate the duplicate data because of the insufficient reported information in the included studies. Nevertheless, we conducted sensitivity analyses of the studies that may have contained duplicate patients to verify the stability of the results. The analysis results indicated that the survival outcomes in this study are slightly influenced by potential duplicate patients. Besides, there may exist potentially confounding selection bias from the non-No. 10 LND group introduced by the retrospective nature of the included studies, because it is difficult to analyze and draw a conclusion regarding the No. 10 LN metastasis and staging without lymphadenectomy. The improved comprehensive approach of imaging diagnosis, intraoperative diagnosis on LN metastasis and staging can be expected in the future (56). In addition, the chemotherapy is a prognostic factor of patients with gastric cancer and/or Siewert type II/III AEG who have undergone the total gastrectomy. Hence, patients who have received postoperative chemotherapy during the period of the clinical researches may influence the results. Therefore, the results of current study should be interpreted cautiously.

Conclusions

The No. 10 LND with spleen preservation is a safe approach to improve the survival of patients with gastric cancer and/or Siewert type II/III AEG who have undergone total gastrectomy. Further high-quality prospective trials are urgently needed to verify this outcome.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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