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Impact of spleen-preserving total gastrectomy on postoperative infectious complications and 5-year overall survival: systematic review and meta-analysis of contemporary randomized clinical trials

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ABSTRACT

Background The role of splenectomy in proximal gastric cancer is still debated. The objective of the present meta-analysis was to provide more-robust evidence about the effect of spleen-preserving total gastrectomy on postoperative infectious complications, overall morbidity, and 5-year overall survival (os).

Methods PubMed, EMBASE, and the Web of Science were consulted . Pooled effect measures were calculated using an inverse-variance weighted or Mantel–Haenszel in random effects meta-analysis. Heterogeneity was evaluated using I^2 index and Cochran Q-test.

Results Three randomized controlled trials published between 2000 and 2018 were included. Overall, 451 patients (50.1%) underwent open total gastrectomy with spleen preservation and 448 (49.9%) underwent open total gastrectomy with splenectomy. The patients ranged in age from 24 to 78 years. No differences were found in the number of harvested lymph nodes ($p = 0.317$), the reoperation rate ($p = 0.871$), or hospital length of stay ($p = 0.347$). The estimated pooled risk ratios for infectious complications, overall morbidity, and mortality were 1.53 [95% confidence interval (CI): 1.09 to 2.14; $p = 0.016$], 1.51 (95% CI: 1.11 to 2.05; $p = 0.008$), and 1.23 (95% CI: 0.40 to 3.71; $p = 0.719$) respectively. The estimated pooled hazard ratio for 5-year os was 1.06 (95% CI: 0.78 to 1.45; $p = 0.707$).

Conclusions Spleen-preserving total gastrectomy should be considered in patients with curable gastric cancer because it is significantly associated with decreased postoperative infectious complications and overall morbidity, with no difference in the 5-year os. Those observations appear worthwhile for establishing better evidence-based treatment for gastric cancer.

Key Words Gastric cancer, splenectomy, spleen preservation, infectious complications, 5-year overall survival

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INTRODUCTION

Gastric cancer is one of the most common cancers worldwide[1]. It has been estimated that almost 1 million new cases of stomach cancer occurred in 2012, making that disease the 5th most common malignancy[2,3]. Despite randomized trials that have failed to demonstrate a survival benefit of D2 nodal dissection[4–6], modified D2 lymphadenectomy with spleen preservation is generally accepted as the standard of care in selected subgroups of patients[7].

Lymph node metastases at the splenic hilum are found in up to 10% of patients with gastric and gastroesophageal junction tumours[8,9]. Some authors have recommended splenectomy to completely dissect the lymph nodes around

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the splenic artery and hilum[10]. However, the effect of splenectomy on long-term prognosis appears to be marginal[11–16]. Furthermore, the importance of the spleen as a part of the immune system and its role in macrophage storage and protection against gram-negative infections are well established[17,18]. Postoperative complications are significantly higher after gastrectomy combined with splenectomy than after gastrectomy alone[19], but the effect of splenectomy on postoperative infectious complications and overall survival (OS) is still unclear.

The aim of the present meta-analysis was to assess the incidence of postoperative infectious complications and the 5-year OS in patients undergoing total gastrectomy with or without splenectomy so as to better define the risk–benefit ratio of those procedures and to guide clinical decision-making.

METHODS

Search Strategy and Study Selection

The study was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement[20]. An extensive literature search spanning 2000–2018 was conducted independently by two authors (AA, SS) to identify published series written in English about spleen-preservation gastrectomy (G) compared with gastrectomy with splenectomy (GS) for proximal gastric cancer. PubMed, EMBASE, and the Web of Science databases were consulted using the terms "stomach cancer" and "splenectomy" or "spleen resection" or "splenic preservation."

Randomized controlled trials (RCTS) that compared the effectiveness or safety of GS and G were included. Abstracts, case reports, case series, retrospective observational studies, and articles not in English were excluded (Figure 1). Two authors (AA, SS) independently extracted data from eligible studies. The extracted data included study characteristics (first author name, year, country, and journal of publication), number of patients, time frame, clinical and demographic characteristics of the patient population, surgical approach, postoperative outcomes, and 5-year OS. Disagreements about study exclusion and data extraction were resolved by consensus; if no agreement could be reached, a third senior author (LB) made the decision.

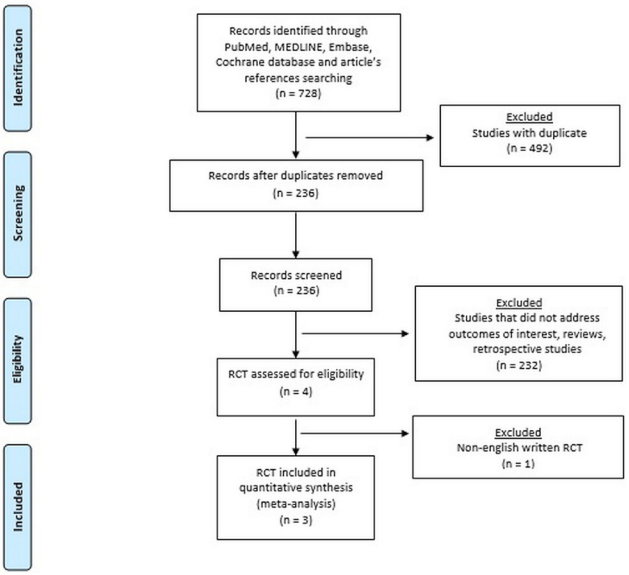

FIGURE 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, 2009) diagram of study selection.

Inclusion and Exclusion Criteria and Surgical Technique

In all included studies, patients with resectable gastric cancer eligible for curative surgery were evaluated by preoperative endoscopy, biopsy, and computed tomography imaging. Patients with early gastric cancer were included for randomization. Patients were randomly allocated to a given treatment after staging laparotomy. Intraoperative pancreatic or splenic tumour infiltration, liver or peritoneal metastasis, station 10 macroscopic lymph node metastasis, Borrmann type 4 (linitis plastica), and positive peritoneal lavage cytology were exclusion criteria. All patients had a D2 lymphadenectomy. In the G group, dissection of station 11 was performed by removing lymph nodes *en bloc* with fatty tissue along the axis of the splenic artery. In the GS group, the spleen was removed *en bloc* with station 10, and the splenic artery was ligated and cut distal to the origin of the great pancreatic artery. The small number of patients with iatrogenic splenic injury were included in the analysis. Gastric tumours other than adenocarcinoma (that is, lymphoma and adenosquamous carcinoma) were excluded.

Outcomes

The primary outcome was the rate of postoperative infectious complications. The secondary outcomes were overall morbidity, postoperative mortality, 5-year OS, operative time, number of lymph nodes harvested, reoperation rate, and length of hospital stay. If an outcome was unclear, we sought further information from the authors of the relevant study. Each infectious complication was defined, identified, and diagnosed in accordance with the U.S. Centers for Disease Control and Prevention guidelines[21].

Study Quality Appraisal

Two authors (AA, SS) independently assessed the methodologic quality of the selected trials. These criteria were used for the assessment:

- Method of randomization
- Allocation concealment
- Baseline comparability of study groups
- Blinding
- Completeness of follow-up

Trials were graded as follows: A, adequate; B, unclear; and C, inadequate on each criterion. Thus, each RCT was graded as having low, moderate, or high risk of bias. Disagreements were resolved by discussion.

Statistical Analysis

The results of the systematic review were summarized qualitatively into a frequentist random effects meta-analysis

of pooled risk ratio and raw mean difference. The inverse-variance method and DerSimonian–Laird estimator for variance of true effect size (τ^2) were applied[22]. Heterogeneity between the studies was evaluated by I^2 index and Cochran Q-test[23]. Statistical heterogeneity was considered significant when the p value was less than 0.10 or the I^2 index was greater than 50%[24]. Wald-type 95% confidence intervals were computed for pooled measures; otherwise, 95% confidence intervals for the I^2 index were calculated according Higgins and Thompson[25]. The prediction interval for the treatment effect of a new study was calculated according to Borenstein[23]. Hazard ratios and relative standard errors for time-to-event outcomes by the Kaplan–Meier method were approximated using the formula described by Parmar[26]. Kaplan–Meyer curves were digitalized using the GetData Graph Digitizer software (http://getdata-graph-digitizer.com/). Variance for continuous outcomes was estimated from ranges according to Hozo *et al.*[27]. Because sample sizes were not the same in all studies, we performed sensitivity analyses by rerunning the analysis, excluding one study each time, to verify the robustness of the overall results. A Z-score test was performed. Two-sided p values were considered statistically significant when less than 0.05. All analyses were carried out using the R software application (version 3.2.2: The R Foundation, Vienna, Austria).

RESULTS

Systematic Review

Three RCTs published between 2000 and 2018 met the inclusion criteria. There was one publication each from Chile, South Korea, and Japan. Figure 2 shows the quality assessment of the trials.

Table I shows demographic, clinical, and surgical variables for the patient sample. Of the 899 included patients, 451 (50.2%) underwent G, and 448 (49.8%) underwent GS. Patients ranged in age from 24 to 78 years, and most were men (90%). Body mass index was reported for the patients in one study. Comorbidities and American Society of Anesthesiologists score were not reported. All patients underwent an open surgical operation, and reconstruction methods were at the surgeon's discretion. Bursectomy was not mandatory. Perioperative care, anesthesia management, and technical details of the operations were not specified.

The operative time ranged from 90 to 485 minutes in the G group and from 112 to 440 minutes in the GS group. Median intraoperative blood loss and perioperative blood transfusions were reported in only one study. The pathologic tumour stage and tumour histology were reported in two studies (Table I). The number of retrieved lymph nodes ranged from 4 to 158 in the G group and from 5 to 156 in the GS group.

The reoperation rate ranged from 1.6% to 9.3% in the G group and from 1.2% to 11.1% in the GS group. Postoperative overall morbidity ranged from 8.7% to 41.2% in the G group and from 15.4% to 50% in the GS group. Only one study specifically reported the rate of anastomotic and pancreatic fistulae. The hospital length of stay ranged from

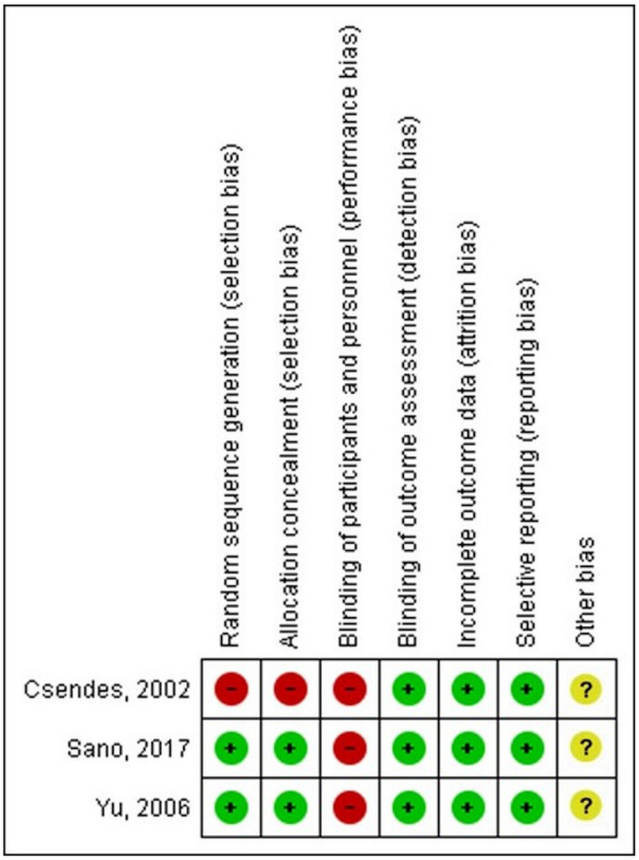

FIGURE 2 Risk of bias was assessed using the Cochrane Risk of Bias tool.

9 to 60 days in the G group and from 9 to 71 days in the GS group. In-hospital mortality ranged from 0.8% to 3.1% in the G group and from 0.4% to 4.4% in the GS group.

Median follow-up duration was reported in two studies and ranged from 64.8 months to 71.8 months. In two studies, aggregated OS was reported; in one study, OS was stratified according to tumour stage. One study reported the 5-year relapse-free survival. The long-term consequences of splenectomy were analyzed in one study, which found no differences in terms of pneumonia and other infections.

Meta-analysis

In addition to the systematic review, we performed a frequentist meta-analysis. Using a random effects model, the estimated pooled risk ratio for postoperative infectious complications (three studies, 899 patients in total) was 1.53 [95% confidence interval (CI): 1.09 to 2.14; $p = 0.016$]. The lower and upper limits of prediction were 0.17 and 13.54 respectively. Heterogeneity was zero ($I^2 = 0\%$; 95% CI: 0.0% to 49.7%; $p = 0.813$), and the τ^2 was 0.0. The sensitivity analysis yielded a risk ratio estimate of 1.52 (95% CI: 1.08 to 2.13; Figure 3).

Using a random effects model, the estimated pooled risk ratio for postoperative overall morbidity (three studies, 899 patients in total) was 1.51 (95% CI: 1.11 to 2.05; $p = 0.008$). The lower and upper limits of prediction were 0.08 and 27.57 respectively. Heterogeneity was nonsignificant ($I^2 = 39.1\%$; 95% CI: 0.0% to 81.1%; $p = 0.194$), and the τ^2 was

TABLE I Demographics and clinical data for the 899 study patients

Variable	Splenectomy with total gastrectomy					
	Csendes *et al.*, 2002[15] Chile		Yu *et al.*, 2006[16] South Korea		Sano *et al.*, 2017[19] Japan	
	Yes	No	Yes	No	Yes	No
Patients *(n)*	90	97	104	103	254	251
Sex *(n)*						
Men	60	65	72	72	196	204
Women	30	32	32	31	58	47
Age (years)						
Mean	62.7	62.7	57	57	65	65
Range			24–78	31–78	27–75	30–75
Stage *(n)*						
I			35	28	94	108
II	Not reported	Not reported	21	24	74	70
III			27	27	70	53
IV			21	24	16	20
Histology *(n)*						
Differentiated	Not reported	Not reported	33	33	118	136
Undifferentiated			71	70	136	115
Operative time (minutes)						
Mean	218	208	Not reported	Not reported	231	224
Range	120–440	90–450			112–440	108–485
Retrieved nodes *(n)*						
Median	30		40	40	64	59
Range	22–38		5–93	4–94	19–156	16–158
Reoperation *(n)*	10	9	Not reported	Not reported	3	4
Infectious complications *(n)*	35	24	8	7	23	14
Overall morbidity *(n)*	45	40	16	9	77	42
Mortality *(n)*	4	3	2	1	1	2
5-Year overall survival (%)	41.9	36.2	54.8	48.5	73.6	74.5

0.02. The sensitivity analysis yielded a risk ratio estimate of 1.55 (95% CI: 1.2 to 1.94; Figure 4).

Using a random effects model, the estimated pooled mean difference for hospital length of stay (two studies, 394 patients in total) was 1.50 (95% CI: –1.63 to 4.63; $p = 0.347$). Heterogeneity was moderate ($I^2 = 54.2\%$; 95% CI: 0.0% to 88.7%; $p = 0.139$), and the τ^2 was 2.7.

Using a random effects model, the estimated pooled mean difference for harvested lymph nodes (two studies, 712 patients in total) was 2.50 (95% CI: –2.40 to 7.40; $p = 0.317$). Heterogeneity was moderate ($I^2 = 65.7\%$; 95% CI: 0.0% to 92.2%; $p = 0.087$), and the τ^2 was 8.2.

Using a random effects model, the estimated pooled risk ratio for reoperation (two studies, 692 patients in total) was 1.06 (95% CI: 0.51 to 2.23; $p = 0.871$). Heterogeneity was zero ($I^2 = 0\%$, $p = 0.583$), and the τ^2 was 0.0.

Using a random effects model, the estimated pooled risk ratio for mortality (three studies, 899 patients in total) was 1.23 (95% CI: 0.40 to 3.71; $p = 0.719$). The lower and upper limits of prediction were 0.01 and 1620.4 respectively. Heterogeneity was zero ($I^2 = 0\%$; 95% CI: 0.0% to 72.4%; $p = 0.685$), and the τ^2 was 0.0. The sensitivity analysis yielded a risk ratio estimate of 1.21 (95% CI: 0.42 to 3.55; Figure 5).

Using a random effects model, the estimated pooled hazard ratio for 5-year OS (two studies, 713 patients in total) was 1.06 (95% CI: 0.78 to 1.45; $p = 0.707$). Heterogeneity was zero ($I^2 = 0\%$, $p = 0.430$), and the τ^2 was 0.0 (Figure 6).

DISCUSSION

In the meta-analysis, we show that the rates of postoperative infectious complications and of overall morbidity were significantly lower in patients undergoing G for carcinoma of the upper third of the stomach. In contrast, no differences were found in the number of harvested lymph nodes, the reoperation rate, hospital length of stay, overall mortality, or 5-year OS.

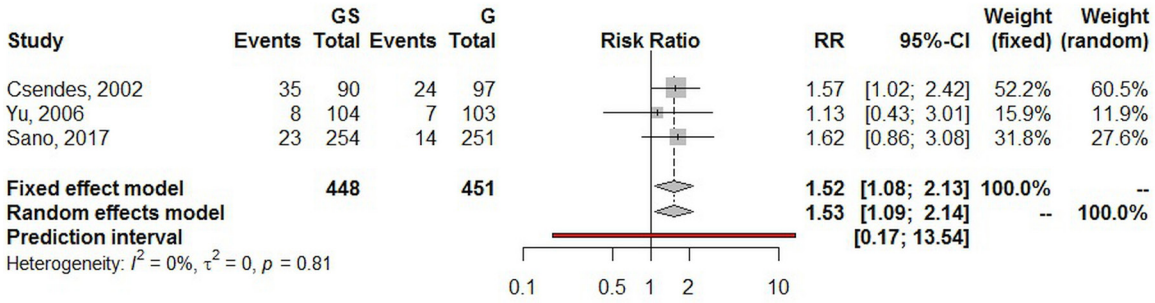

FIGURE 3 Forest plot of postoperative infectious complications. GS = total gastrectomy with splenectomy; G = total gastrectomy; RR = risk ratio; CI = confidence interval.

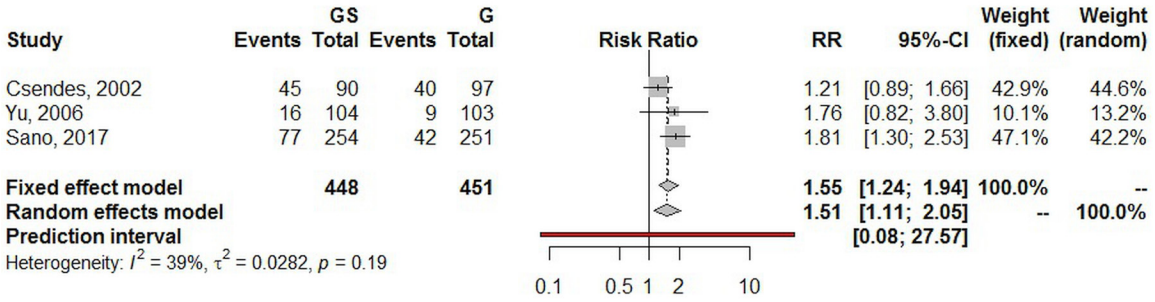

FIGURE 4 Forest plot of overall morbidity. GS = total gastrectomy with splenectomy; G = total gastrectomy; RR = risk ratio; CI = confidence interval.

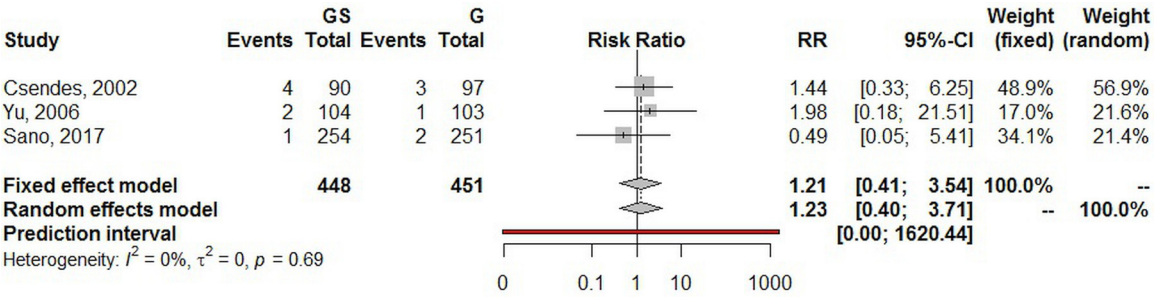

FIGURE 5 Forest plot of mortality. GS = total gastrectomy with splenectomy; G = total gastrectomy; RR = risk ratio; CI = confidence interval.

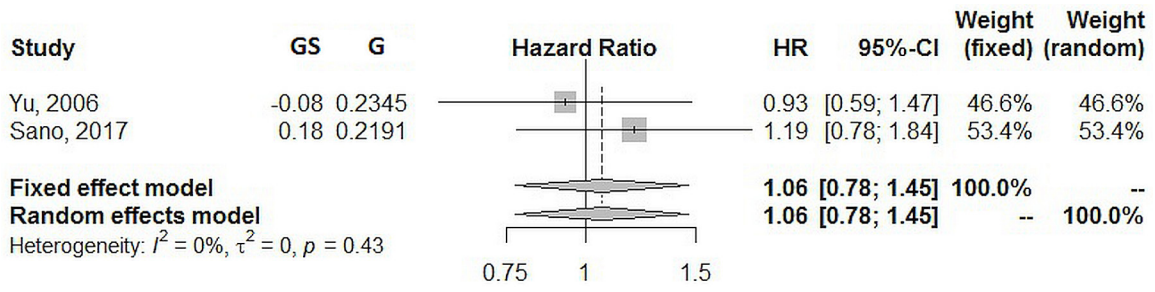

FIGURE 6 Forest plot of 5-year overall survival. GS = total gastrectomy with splenectomy; G = total gastrectomy; HR = hazard ratio; CI = confidence interval.

The spleen is part of the reticuloendothelial system, and its contribution to systemic immunologic surveillance through the synthesis of opsonins and antibodies is crucial. Postoperative infectious complications after splenectomy have previously been postulated to potentially be attributable to a partial loss of immunologic function[28,29].

Postoperative surgical site infection (SSI) is one of the most common complications after gastrectomy. It can lead to prolonged hospital stay and increased health care costs, and can also adversely affect OS and disease-free survival[30,31]. The incidence of postoperative SSI after elective gastrectomy has been reported to be up to 20%, combining superficial and deep incisional SSI[32]. A recent study from Japan involving 685 patients undergoing open elective total or distal gastrectomy showed a 6.1% overall incidence of superficial incisional SSI[33]. The incidence of organ or space SSI was significant and was reported to be higher after total gastrectomy than after distal gastrectomy (10.4% vs. 5.8%). In a recent national clinical database study in Japan that included 39,253 patients who underwent total gastrectomy, the overall SSI rate was 8.1%, and splenectomy was a risk factor for postoperative SSI, anastomotic leak, and pancreatic fistula[34]. In our systematic review, the overall aggregated incidence of postoperative infectious complications was 12.3%, and the estimated pooled risk ratio in the GS group compared with the G group was 1.53 (95% CI: 1.09 to 2.14; $p = 0.016$), thus reflecting the importance of splenic preservation in maintaining immunomodulation activity to prevent postoperative infectious complications. Notably, heterogeneity in the analysis was zero, adding significance to the result.

Our estimated pooled risk ratio for postoperative overall morbidity in the GS group compared with the G group was 1.51 ($p = 0.008$), an observation that is in line with previous RCTS[15,16,19] and easily understandable, given the fact that surgical complications are influenced by the extent of the surgical procedure itself. As seen in previous studies, no statistically significant differences were found in terms of harvested lymph nodes, reoperation rate, and hospital length of stay[35].

For gastric cancer, R0 resection with D2 lymphadenectomy is recommended as the standard curative surgical treatment[36,37]. In Asian countries, extended lymph node dissection is regarded as essential in the treatment of gastric cancer, and splenectomy has been suggested to achieve complete clearance of nodal station 10 in patients with curable T2–4 cancers invading the greater gastric curvature[36]. However, in Western countries, trials from the Netherlands, the U.K. Medical Research Council, and Italy[38–40] failed to demonstrate any initial survival advantage with D2 resection. It has been postulated that, after splenectomy, long-term T-cell suppression, with consequent immunosuppression, could negatively affect immune surveillance, leading to worse OS[41].

Despite those findings, consensus opinion is that medically fit patients should undergo D2 dissection at a high-volume centre[38]. Previous retrospective and single-centre studies set out to examine the effect of splenectomy on 5-year OS, but results were contrasting, incomplete, and biased[42–45]. To overcome those limitations, three RCTS were conducted contemporaneously. Csendes *et al.*[15] found a trend toward a better 5-year OS rate in patients who underwent GS than in patients who underwent spleen-preserving G (42% vs. 36%). Similarly, Yu and colleagues[16] described a slightly better 5-year OS rate in patients who underwent GS (54.8% vs. 48.8%). In both studies, the results were not statistically significant. Recently, in a large multicentre RCT, Sano *et al.*[19] found statistically significant noninferiority for spleen-preserving G compared with GS (76.4% vs. 75.1%, $p = 0.025$). Our study produced similar results, with an estimated pooled 5-year OS hazard ratio of 1.06 ($p = 0.707$), and no differences between the two groups. Notably, heterogeneity was zero, thus conferring additional credibility to that outcome.

The results of our study might not be generalizable given that the patients came mainly from Asia and South America and the surgery was performed at high-volume centres with appropriate surgical expertise. Because the data were aggregated, the confounding effects of tumour stage and perioperative chemotherapy on OS could not be determined. In addition, no specific data about comorbidities and American Society of Anesthesiologists score were reported, and so no inferences could be drawn concerning an association with survival. However, despite those limitations, our systematic review and meta-analysis includes only contemporary RCTS and represents the first meta-analysis focusing on postoperative infectious complications and the hazard ratio for 5-year OS. Moreover, heterogeneity relating to the primary study outcome was zero.

CONCLUSIONS

Spleen-preserving open total gastrectomy has the potential to significantly lower rates of postoperative infectious complications and overall morbidity, with no difference in 5-year OS. Although the interaction between postoperative infectious complications and long-term prognosis after open gastrectomy with or without splenectomy remains unclear, splenectomies are expected to decline in number into the future. Because minimally invasive surgery is becoming a recommended option for gastric cancer and appears to be comparable to open gastrectomy in short- and long-term results, further studies are required to evaluate the potential value of the laparoscopic approach in further reducing the risk of infectious complications and improving long-term survival.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

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