

Oncologic Effectiveness and Safety of Splenectomy in Total Gastrectomy for Proximal Gastric Carcinoma: Meta-analysis of Randomized Controlled Trials

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Abstract. *Background/Aim:* The role of splenectomy as an essential component of radical surgery for proximal gastric cancer, from an oncological point of view, is still debated, and no consistent recommendations have been proposed. The aim of this systematic review with meta-analysis was to provide a more robust answer regarding the oncological effectiveness and safety of splenectomy in total gastrectomy for proximal gastric carcinoma. *Materials and Methods:* A systematic review and meta-analysis of randomized controlled trials was planned and performed in accordance with Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement and Cochrane Handbook for Systematic Reviews of Intervention. Patients with a histological diagnosis of gastric adenocarcinoma located in the upper third of the stomach who underwent D2 total gastrectomy with or without splenectomy were selected. The primary outcome was to analyze the influence of splenectomy on the overall survival of patients. Additionally, the mean difference in procedure time, length of hospital stay, number of retrieved lymph nodes, as well as the odds ratio of postoperative complications comparing splenectomy to spleen preservation were investigated in a secondary analysis. *Results:* Overall, four studies with a total of 978 patients met the inclusion criteria.

The pooled analysis showed no difference in overall survival rates between those who underwent spleen preservation compared to the splenectomy-treated group (risk ratio=0.92, 95% confidence interval=0.79 to 1.06, $p=0.277$). Interestingly, all studies reporting overall morbidity data highlighted statistically significant differences in favor of spleen-preservation group (odds ratio=2.11, 95% confidence interval=1.44 to 3.09, $p<0.001$). *Conclusion:* In total, gastrectomy for proximal gastric cancer, splenectomy should not be recommended as it increases operative morbidity without improving survival when compared to spleen preservation. Furthermore, our results may help in planning the updated versions of Gastric Cancer Treatment Guidelines. This meta-analysis, however, points to the urgent need for high-quality, well-designed, large-scale, clinical trials, with short-as well as long-term evaluation comparing splenectomy with spleen-preserving procedures, in a controlled randomized manner to help future research and to establish an evidence-based approach to gastric cancer treatment.

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Gastric cancer, despite decreasing in incidence in recent decades, is still the third leading cause of cancer-related death around the world (1). Interestingly, researchers are facing clinically relevant changes in epidemiological trends according to the location and histotype of gastric cancer: while the overall number of newly diagnosed gastric cancer cases is decreasing, with tumors located in the distal third of the stomach showing the most evident decrease, the incidence of proximal tumors has remained stable or even increased over time (2-5). Similarly, a relative increase in Lauren diffuse histotype tumors has also been registered (5-7). As a result, since the proximal location as well as the

diffuse histotype are associated with higher biological and clinical aggressiveness and worse prognosis, emerging epidemiological trends could lead to a general decrease in overall survival (8-11). Currently, surgical R0 resection with D2 lymph node dissection represents the only curative treatment for non-metastatic proximal gastric cancer (12), while neoadjuvant and adjuvant chemotherapies, as well as chemoradiation, improve outcomes, aiming at reduction of recurrence and extension of survival (13). To this aim, for tumors directly invading the spleen, splenectomy should be considered as a part of standard D2 total gastrectomy (14). In the absence of direct invasion, on the other hand, splenectomy is also performed to ensure complete resection of nodal stations 10 and 11 in surgically challenging and technically demanding cases. Nevertheless, the role of splenectomy as an essential component of radical surgery for proximal gastric cancer, from an oncological point of view, is still debated (12). No consistent recommendations have been proposed since the available data are ambiguous, with some studies reporting slightly, but not significantly better survival with splenectomy (15-17), while conflicting results are reported from other studies (18-20). However, despite all these inconclusive results, the splenectomy rate continues to be high, ranging from 26-48.7% (21-24).

We therefore undertook a systematic review and meta-analysis of currently available data in order to provide a more robust answer regarding the oncological effectiveness and safety of splenectomy in total gastrectomy for proximal gastric carcinoma.

Materials and Methods

Literature search. This systematic review with meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement (25) and the Cochrane Handbook for Systematic Reviews of Interventions (26). A literature search was undertaken in PubMed, Cochrane, Embase and Ovid databases for all articles published up to December 2017 with the follow Medical Subject Headings (MeSH) and key word search: ("gastric cancer" OR "gastric carcinoma" OR "gastric adenocarcinoma" OR "stomach neoplasm" OR "stomach cancer" OR "stomach carcinoma") AND ("splenectomy" OR "spleen resection") AND ("spleen preserving" OR "spleen preservation" OR "splenic preservation") AND (Publication Type:"comparative study" OR "follow-up studies" OR "clinical trial" OR "evaluation studies" OR "randomized controlled trial" OR "controlled clinical trial" OR "research design"). The search was carried out independently by two investigators. The key words were used in all possible combinations to obtain the maximum number of articles. We also reviewed the bibliographies of relevant articles to identify additional publications.

Article selection. The articles were screened for the presence of the following defined eligibility criteria according to the PICO (population, intervention, comparator, outcome) format (27). P-Population: Patients with a histologically diagnosis of gastric

adenocarcinoma located in the upper third of the stomach who underwent surgical treatment without previous chemotherapy or surgery for gastric cancer. I-Intervention: D2 total gastrectomy with splenectomy; C-Comparator: D2 total spleen-preserving gastrectomy; O-Outcomes of interest: prognostic characteristics and postoperative outcomes. Only randomized controlled trials (RCTs) with full text were included. Experimental studies in animal models, single case reports, technical reports, reviews, abstracts and editorials were excluded. When the same population was included in multiple publications, only data from the most recent article were used for meta-analysis.

Data extraction. Two of the Authors (L.M. and F.R.) independently reviewed the formal published versions of all eligible studies for content according to the specified inclusion criteria using a data extraction form based on the Cochrane Consumers and Communication Review Group's data extraction template (26). Disagreements were resolved by discussion or consultation with third Author.

Data recorded included: first author, study design, study setting (single-center or multicenter), country of origin, year of publication, study period, sample size, demographic features, clinicopathological characteristics, operative factors, intra- and postoperative complications, total number of patients assessed in survival analysis, median or mean duration of follow-up, control and intervention groups for estimation of hazard ratio (HR), and overall survival outcomes. Authors of articles were contacted for more detailed data when necessary.

This study did not require ethical approval and informed consent since all analyses were based on the previous published data.

Summary outcome measures. The primary outcome was to analyze the influence of splenectomy on the overall survival of patients with proximal gastric cancer by comparing the prognosis of patients undergoing gastrectomy with splenectomy for proximal gastric cancer with that of patients undergoing spleen-preserving gastrectomy. Additionally, the mean difference in procedure time, length of hospital stay, number of retrieved lymph nodes, as well as the odds ratio of postoperative complications comparing splenectomy to spleen preservation were investigated as a secondary analysis.

Quality assessment. All eligible articles were evaluated independently by two reviewers for risk of bias according to the Quality In Prognosis Study (QUIPS) tool (28). Risk of bias was scored as low, moderate or high for each domain, based on answers to three to six questions for six items: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis. A final grading of low risk of bias was assigned when three or more of the six items were considered to be of high methodological quality; risk of bias was considered high when three or more of the six items were deemed to be of low methodological quality. Otherwise a moderate risk of bias was assigned.

Statistical analysis. Comprehensive Meta-Analysis software version 3.3.070 (Biostat, Englewood, NJ, USA) was used for meta-analysis. In pooled analyses of associations between various demographic and clinicopathological variables and splenectomy/non-splenectomy, effect sizes were calculated as odds ratios (ORs) with 95% confidence intervals. The HR and 95% confidence interval for overall survival were retrieved from each article where possible; otherwise the value was estimated according



PRISMA 2009 Flow Diagram

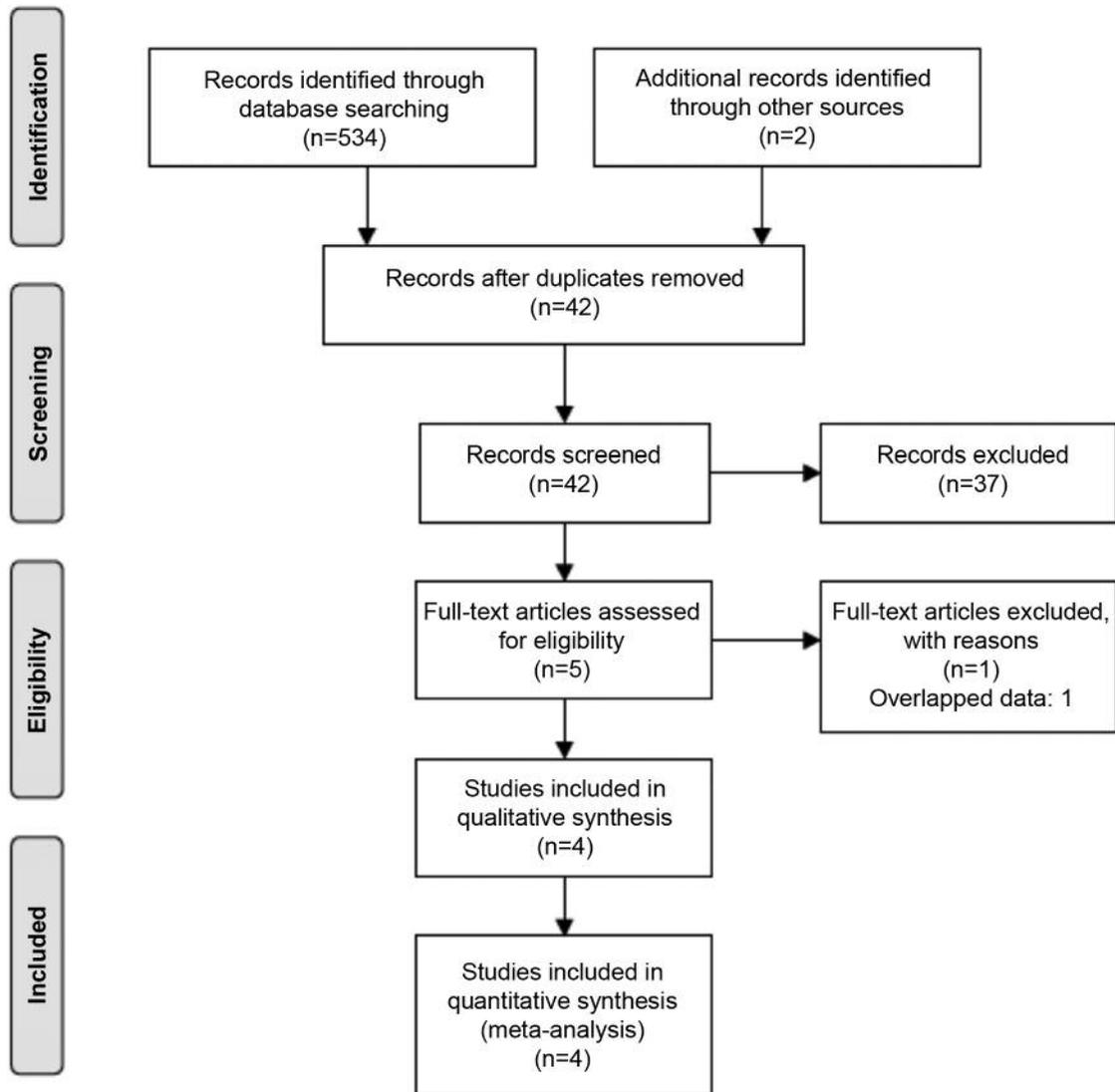


Figure 1. Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) flow chart of study selection.

to the method of Tierney and colleagues (29) using Plot Digitizer version 2.5.1 (<http://plotdigitizer.sourceforge.net/>). The pooled HR was estimated in meta-analysis. Between-study heterogeneity was explored using the Higgins I^2 measure (26). I^2 values of around 25%, 50% and 75% were considered to represent low, moderate and high heterogeneity respectively. When the I^2 value exceeded 50%, the effect size for each study was calculated by a random-effects model using the DerSimonian and Laird approach (26); otherwise, a fixed-effect model was used. A chi-squared-based

Q-test was also performed to check between-study heterogeneity, with values of $p < 0.100$ considered statistically significant. Potential sources of heterogeneity were investigated in subgroup analyses.

Funnel plots to test the publication bias were not performed due to the limited number of studies (fewer than 10) included in each analysis (25). This study did not require ethical approval or informed consent due to analyses being carried out based on the previous published data.

Table I. Characteristics of the included studies.

Author	Study period	Country of origin	Sample size, n (M/F)		Age, years ^a		pT1/T2/T3/T4, n		OS, HR (95% CI)	Follow-up
			Splenectomy	Spleen preservation	Splenectomy	Spleen preservation	Splenectomy	Spleen preservation		
Sano <i>et al.</i> (18)	2002-2009	Japan	254 (196/58)	251 (204/47)	65 (27-75)	65 (30-75)	31/144/78/1	40/155/55/1	0.86 (0.62-1.18)	71.8
Yu <i>et al.</i> (16)	1995-1999	Korea	104 (72/32)	103 (72/31)	57 (24-78)	57 (31-78)	10/56/35/3	9/49/43/2	1.13 (0.87-1.47)	64.8
Csendes <i>et al.</i> (15)	1985-1992	Chile	90 (NR)	97 (NR)		62 (29-80)	NR	NR	1.16 (0.80-1.67)	At least 5 years
Toge <i>et al.</i> (17)	NR	Japan	41 (NR)	38 (NR)	NR	NR	NR	NR	1.28 (0.90-1.81)	At least 5 years

F: Female; M: male; OS: overall survival; NR: not reported; HR: hazard ratio; CI: confidence interval. ^aMedian (range).

Table II. Results of meta-analysis of the secondary outcomes.

Outcomes	Effect size	95% CI	p-Value	Heterogeneity		Effect model
				I ² (%)	p-Value	
Operative time (minutes)	MD: 0.13	-0.01-0.28	0.079	10.5	0.29	Fixed
Hospital stay (days)	MD: 0.06	-0.36-0.48	0.783	77.8	0.034	Random
Retrieved lymph nodes (number)	MD: 0.18	0.03-0.32	0.019	58.8	0.119	Fixed
No. 10 lymph node station	OR: 1.56	0.75-3.27	0.232	22.2	0.257	Fixed
No. 11 lymph node station	OR: 1.21	0.47-3.12	0.690	59.9	0.114	Random
Mortality	OR: 1.06	0.29-3.86	0.925	0	<0.001	Fixed
Postoperative complications	OR: 2.11	1.44-3.09	<0.001	0	0.79	Fixed
SSIs	OR: 1.44	0.72-2.88	0.302	0	0.489	Fixed
Intraperitoneal infection	OR: 2.10	1.15-3.83	0.016	0	0.731	Fixed
Pulmonary complications	OR: 1.68	0.94-2.99	0.292	25.4	0.247	Fixed

MD, Mean difference; OR, odds ratio; CI, confidence interval; SSIs, surgical site infections.

Results

Study selection and characteristics. The initial search produced 534 studies, of which 492 were excluded because of duplication. After checking the relevant bibliography, two additional articles were included. The titles and abstracts of the remaining 42 records were screened and five studies fulfilled criteria for eligibility (Figure 1). Thirty-seven studies that were not related to the comparison between splenectomy and spleen-preserving total gastrectomy for proximal gastric cancer, or that were reviews, non-RCTs, editorial or case reports were excluded. Of the remaining five records, those by Sano *et al.* were included as one study, since they separately published complementary data from the same group of patients (18, 30).

After this screening, 4 RCTs published between 1985 and 2017 were included (15-18). The total number of included patients was 978 (489 in the splenectomy-treated group and

489 in the group with spleen preservation) ranging from 79 to 505 patients per study.

Only one study (505 patients, 51.6%) was multicentric (36 institutions belonging to the Stomach Cancer Study Group of the Japanese Clinical Oncology Group, Japan) (31), while the others were performed at single centers in Eastern populations (286 patients, 29.2%) from Japan (17) and South Korea (16), or in Western populations (187 patients, 19.2%) from Chile (15). The overall proportion of patients who had undergone splenectomy was 50% (489 patients), ranging from 48.1% (15) to 51.9% (17) patients per study. The main characteristics of each study included in the meta-analysis are shown in Table I. Since not all studies reported all variables examined in the meta-analysis, only studies reporting the variable of interest were included for quantitative synthesis to investigate the association of splenectomy with that variable.

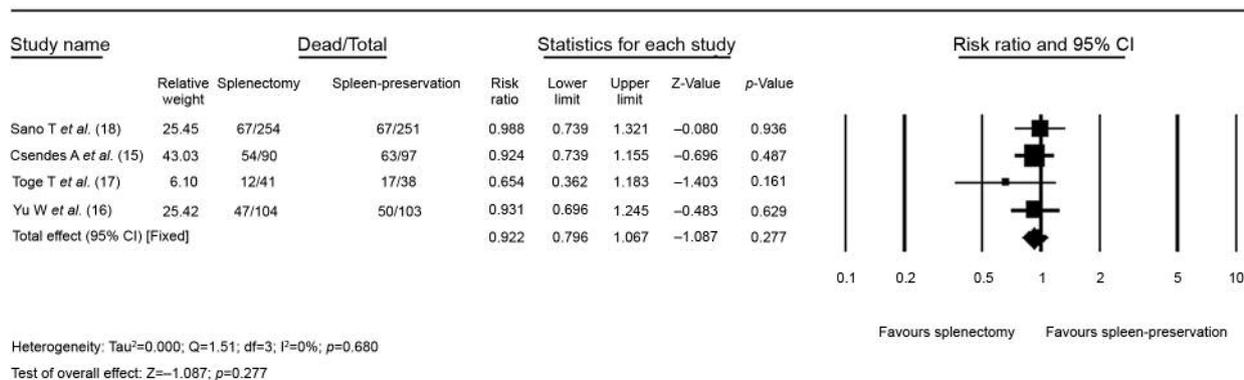


Figure 2. Forest plot of risk ratio with 95% confidence interval (CI) for the effect of splenectomy on overall survival (OS).

Splenectomy and survival of patients with gastric cancer. The range of follow-up was 64.8 to 71.8 months; two studies did not clearly specify the duration of follow-up for survival, reporting a period of at least 5 years (15, 17). All the selected studies found no statistically significant prognostic difference in terms of overall survival between the splenectomy *versus* spleen-preservation groups.

The pooled analysis showed no difference in the overall survival rate between the two groups (risk ratio=0.92, 95% CI=0.79 to 1.06, $p=0.277$) in a fixed-effect model ($I^2=0%$, Cochran's $Q=1.511$) (Figure 2) that was not statistically significant.

Secondary analysis. The mean difference in procedure time, length of hospital stay, number of retrieved lymph nodes, metastasis in no. 10 and no. 11d nodes, as well as the OR of perioperative mortality and postoperative complications comparing splenectomy to spleen preservation were investigated as a secondary analysis (Table II).

Operative time and hospital stay. All selected studies not reporting operative time and hospital stay, with the exclusion of that by Yu *et al.* (16), were pooled in the analysis. No significant difference in operative time between the two groups was found in a fixed-effect model [mean difference (MD)=0.13 min, 95% CI=0.01-0.28 min, $p=0.079$]. Similarly, two studies reporting data on the length of hospital stay (16, 18) and the estimated effect size indicated no significant difference between the groups (MD=0.06; 95% CI=0.36-0.48, $p=0.783$).

Significant heterogeneity was found among the included studies ($I^2=77.8%$, $p<0.05$), and a random-effect analysis model was used.

Number of retrieved lymph nodes. Only two studies (16, 18) with a total of 712 patients presented data for retrieved lymph

nodes and the estimated effect size indicated the number of lymph nodes retrieved was higher in the splenectomy group (MD=0.18, 95% CI=0.03 to 0.32, $p<0.05$). Furthermore, no significant differences with regard to the histological metastasis rate in no. 10 and no. 11d nodes were highlighted between the two groups (15, 16, 18) (Table II).

Perioperative mortality. Two studies reported data regarding in-hospital mortality on a total of 689 patients (15, 18). Overall mortality rate was 1.4% (5/344), ranging from 0.4-4.4% in the splenectomy group, and 1.4% (5/345), ranging from 0.8-3.1% in the group with spleen preservation. The pooled analysis showed no statistically significant differences in perioperative mortality between the two groups (OR=1.06, 95% CI=0.29-3.86, $p=0.925$) in a fixed-effect model ($I^2=0%$, $p<0.001$).

Postoperative complications. All studies reporting overall morbidity highlighted statistically differences in favor of the group with spleen preservation, with a pooled analysis resulting in (OR=2.11, 95% CI=1.44-3.09, $p<0.001$) in a fixed-effect model ($I^2=0%$, $p=0.79$).

Furthermore, an independent meta-analysis for surgical site infections and pulmonary complications was performed; no significant differences between splenectomy and spleen-preservation groups was highlighted. Interestingly, an independent meta-analysis showed that splenectomy was more likely than spleen preservation to result in intraperitoneal complications (OR=2.10, 95% CI=1.15-3.83, $p<0.05$) in a fixed effect model ($I^2=0%$, $p=0.731$).

Quality assessment. Two included studies (15, 18) were scored as being of high methodological quality and the other two (16, 17) of moderate quality according to QUIPS tool (28) (Table III).

Table III. Quality assessment of studies using the Quality In Prognosis Studies assessment tool (28)^a. Risk of bias is shown for each factor for each study.

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Sano <i>et al.</i> (18)	Low	Low	Moderate	Low	Low	Low
Yu <i>et al.</i> (16)	Moderate	High	Moderate	Low	Moderate	Low
Csendes <i>et al.</i> (15)	Low	Moderate	Low	Low	Moderate	Moderate
Toge <i>et al.</i> (17)	High	Moderate	Moderate	Moderate	Moderate	High

^aHigh methodological quality: low risk of bias on three or more items; low methodological quality: high risk of bias on three or more items; moderate methodological quality: all other values.

Discussion

Results from our meta-analysis show that there appears to be no statistically significant prognostic difference in terms of OS between patients treated with splenectomy *versus* those with spleen preservation for curable proximal gastric carcinoma. Furthermore, the pooled operative morbidity outcomes favored the group which underwent spleen-preserving surgery, with mean odds of developing postoperative complications in the splenectomy-treated group being twice as high.

Initially, even if in the absence of any supporting evidence, the Japanese Gastric Cancer Treatment Guidelines suggested splenectomy for achieving clearance of nodal station 10 for potentially curable T2-T4 tumors invading the greater curvature of the upper stomach (14). Four years later, the Japanese Gastric Cancer Association revised their gastric cancer treatment guidelines, recommending splenectomy only for those with T2-T4 tumors either directly invading the spleen or located in the greater curvature of the upper stomach (12).

Several attempts have been made to investigate whether splenectomy is essential from an oncological point of view, but research comparing splenectomy with spleen-preserving surgery for non-metastatic proximal gastric cancer shows diverging outcomes. Wanebo *et al.* identified an adverse effect of splenectomy on prognosis (21), whereas Kanayama *et al.* supported there being a survival advantage (32). Moreover, increased postoperative morbidity and mortality were indicated in several retrospective studies (21, 33, 34). Similarly, they failed to show any survival advantage for splenectomy over spleen preservation (35, 36). These results, however, may be unreliable since the studies were affected by the limitations of their retrospective approach. Four prospective RCTs were conducted to evaluate splenectomy in total gastrectomy. The trial by Yu *et al.* on 207 patients in a single institution showed a slightly but not significantly better overall 5-year survival associated with splenectomy rather than spleen preservation (54.8% *vs.* 48.8%) (16).

Csendes *et al.* prospectively compared the early and late results of total gastrectomy *versus* total gastrectomy plus splenectomy on a total of 187 patients with proximal gastric carcinoma (15). Survival analysis highlighted a 42% 5-year survival rate for those treated with splenectomy as opposed to 36% for the spleen-preservation group, without statistical significance. A better prognosis was also suggested for the splenectomy-treated group of another small-scale Japanese RCT (79 patients) reported in 1985 (17). Furthermore, a meta-analysis by Yang *et al.* concluded that there was no statistically significant survival benefits associated with splenectomy when compared with spleen-preserving surgery and routinely performing splenectomy should not be recommended (37). However, it should be pointed out that the sample size of these RCTs was limited, and a well-designed RCT is necessary to explore the effectiveness of splenectomy, especially for proximal and whole gastric cancer. Recently the largest multi-institutional RCT on a total of 505 patients with gastric cancer was published, showing statistically significant non-inferiority of spleen preservation to splenectomy in 5-year survival rates (76.4% *vs.* 75.1%, *p*=0.025) (12). This prompted us to prepare a systematic review of the literature with meta-analysis of updated available data to provide a more robust answer regarding the oncological effectiveness and safety of splenectomy for the treatment of proximal gastric cancer.

The current meta-analysis involved four studies with 978 patients (489 treated with splenectomy): two of them (15, 18) were of high methodological quality and the other two (16, 17) of moderate quality according to the QUIPS tool (28). The oncological effectiveness, in terms of OS, was the primary outcome of this study. R0 resection with D2 lymphadenectomy is currently recommended as the standard of surgical treatment with curative intent by the Japanese, Korean, Italian, German and British national guidelines, by the European Society for Medical Oncology (ESMO) guidelines, as well as the joint ESMO-European Society of Surgical Oncology (ESSO)-European Society of Radiotherapy and Oncology guidelines (38). However, the

main target of gastric cancer surgery is to preserve postoperative functionality and quality of life, without reducing long-term outcomes by means of a tailored approach (39). To this address, splenectomy in total gastrectomy for proximal resectable gastric cancer is suggested in the case of splenic or pancreatic invasion to achieve R0 resection. Splenectomy should be also performed in the absence of direct infiltration, aiming at complete lymphadenectomy at the splenic hilum (no. 10 station) since 8-20% of cases of proximal gastric cancer metastasize to the lymph nodes in this area and complete dissection can represent a surgical challenge without splenectomy (18, 40-42). According to our results, splenectomy did not affect patient survival compared to spleen-preserving surgery for proximal gastric cancer. Furthermore, even though splenectomy resulted in a higher number of retrieved lymph nodes, no significant differences as regards the histological metastasis rate in no. 10 and no. 11d nodes were highlighted between the two groups. There is no evidence to support that splenectomy improves the survival rate of patients with metastasis to the lymph nodes at the splenic hilum or along the splenic artery (16, 37, 43, 44). Since the frequency of splenic hilar lymph node metastasis is associated with tumor stage, tumor location and nodal status, it could effectively be postulated that proximal gastric cancer not involving the greater curvature has very low possibility of no. 10 lymph node metastasis, and that when it does metastasize to no. 10 nodes, disease is already extensive and the addition of splenectomy to total gastrectomy would be ineffective (35, 45-48). Additionally, long-term T-cell suppression in patients with gastric cancer after total gastrectomy with splenectomy may have a detrimental effect on immune surveillance, worsening survival outcomes (49).

With regard to the safety of splenectomy, operative time, hospital stay and postoperative mortality were equivalent between the two groups. On the other hand, a significant increase in postoperative complications were registered for the splenectomy group. The increased incidence of intraperitoneal infections after splenectomy, hypothetically due to the reduction of immunomodulation splenic activity (33) is of concern. Previous studies have reported higher morbidity rates, especially infectious complications, in patients undergoing splenectomy than those who did not (15, 50, 52). Splenectomy has also been recognized as an independent risk factor influencing postoperative complications (21, 33, 53, 54). Recent European clinical trials of gastrectomy showed that splenectomy associated with extended lymph node dissection may even be harmful because of increased morbidity associated with the procedure (19, 20). Overall, our pooled outcomes on post-procedure complications confirmed these data. The spleen is an important component of the reticuloendothelial system and accounts for 25% of the total lymphoid tissue, contributing to blood cell monitoring and

immune activities (55). Moreover, it is involved in protection from infectious agents by producing opsonins, as well as polyreactive antibodies (44). On this basis, it can be theorized that common complications after splenectomy such as sepsis, abdominal abscess, pneumonia and wound infection, could be caused by a loss of immunological functions following spleen removal (56).

Our study was affected by some limitations. First of all, the number of included RCTs is very low and two of the included studies were only of moderate methodological quality. Additionally, it would be of immense interest to evaluate the prognostic significance of lymph node metastasis at the splenic hilum and along the distal splenic artery for these two groups. Unfortunately, only in the study by Yu *et al.* (16) was this detailed information reported. Lastly, it would have been interesting to investigate the oncologic role of splenectomy for gastric cancer located at and limited to the greater curvature, since these tumors may metastasize only to no. 10 nodes, which can be cured by splenectomy (47, 57, 58). In this regard, only a recent retrospective review of 108 patients with advanced proximal gastric cancer involving the greater curvature showed that splenectomy increases postoperative complication rate without clearly improving survival outcomes (59).

Conclusion

In total gastrectomy for proximal gastric cancer, splenectomy should not be recommended as it increases operative morbidity without improving survival when compared to spleen preservation. Furthermore, our results may help in planning the updated versions of Gastric Cancer Treatment Guidelines. This meta-analysis, however, points to the urgent need for high quality, well-designed, large-scale, clinical trials with short- as well as long-term evaluation comparing splenectomy with spleen-preserving procedures, in a controlled randomized manner, helping future research and establishing an evidence-based approach to gastric cancer treatment.

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Conflicts of Interest

The Authors report no conflicts of interest in regard to this study and they alone are responsible for the content and writing of the article.

Ethical Standards

This study did not require the ethical approval and informed consent since all analyses were based on the previous published data.

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