

Review Article



Advantages of Splenic Hilar Lymph Node Dissection in Proximal Gastric Cancer Surgery

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ABSTRACT

Gastrectomy with lymph node dissection remains the gold standard for curative treatment of gastric cancer. Dissection of splenic hilar lymph nodes has been included as a part of D2 lymph node dissection for proximal gastric cancer. Previously, pancreatoco-splenectomy has been performed for dissecting splenic hilar lymph nodes, followed by pancreas-preserving splenectomy and spleen-preserving lymphadenectomy. However, the necessity of routine splenectomy or splenic hilar lymph node dissection has been under debate due to the increased morbidity caused by splenectomy and the poor prognostic feature of splenic hilar lymph node metastasis. In contrast, the relatively high incidence of splenic hilar lymph node metastasis, survival advantage, and therapeutic value of splenic hilar lymph node dissection in some patient subgroups, as well as the effective use of novel technologies, still supports the necessity and applicability of splenic hilar lymph node dissection. In this review, we aimed to evaluate the need for splenic hilar lymph node dissection and suggest the subgroup of patients with favorable outcomes.

Keywords: Stomach neoplasms; Splenectomy; Spleen preservation; Lymph node dissection; Prognosis

INTRODUCTION

Surgical resection of the primary tumor with its lymphatics remains the gold standard for curative treatment of gastric adenocarcinoma. Earlier studies aiming to improve prognosis in gastric cancer patients have investigated the lymphatic flow by using activated carbon particles or India ink injection [1-4]. The possible lymphatic spread of the tumor was determined with the lymphangiogram results, incidence of lymph node metastasis, and potential survival benefit of the systematic dissection of the lymphatic flow; moreover, radical surgery for gastric cancer has been standardized based on these data.

Comprehensive investigations have demonstrated that the stomach has a sophisticated lymphatic flow, and gastric tumors follow various spreading patterns according to the tumor location or biology [3-6]. The lymphatic flow of upper body tumors, specifically those located along the

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Conflict of Interest

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greater curvature, is drained to splenic hilar lymph nodes via the left gastroepiploic artery, short gastric artery, celiac artery, and posterior gastric artery [4,7]. Therefore, splenic hilar lymph nodes, which are also classified as number 10 lymph nodes, were defined as one of the regional lymph node groups (N2 group) of gastric cancer (except for lower, lower/middle tumors, which are classified as N3 group) [4,8]. In a study that analyzed the lymph node metastasis pattern in 1,931 gastric cancer patients, the incidence of splenic hilar lymph node metastasis was 9%, with the 5-year survival rate of 12% [9]. This study also confirmed that the incidence of splenic hilar lymph node metastasis for proximal tumors located at the greater curvature is substantially high (32%), whereas that of the tumors along the lesser curvature or on the anterior/posterior walls is only up to 6%. Okajima and Isozaki [10] reported that the incidence of the splenic hilar lymph node metastasis according to the location of gastric cancer was 26.7%, 15.5%, and 1.9% for tumors located in whole stomach, upper body and mid body, respectively; however, no metastases were found in the splenic hilar lymph nodes with cancer of the lower third part of the stomach. In this context, total gastrectomy with splenectomy for dissecting splenic hilar lymph nodes was accepted as a part of curative gastrectomy for proximal gastric cancer [11].

THE INCIDENCE AND RISK FACTORS FOR SPLENIC HILAR LYMPH NODES METASTASIS

Following the adoption of splenic hilar lymph node dissection as a part of D2 lymph node dissection for proximal gastric cancer, the incidence of splenic hilar lymph node metastasis in gastric cancer has been published repeatedly. This incidence in various series, and metastasis rates according to the cross-sectional tumor location, Borrmann classification, depth of invasion, and pathological stage are summarized in **Tables 1–3** [7,12-26]. In these series, the incidence of splenic hilar lymph node metastasis was reported to be 8.1%–27.9%, and 571 (11.7%) of the 4,900 included patients presented this metastasis. The incidence was higher in majority of the studies for tumors located at a greater curvature or encircling tumors, Borrmann III–IV class, deeper T stage, and advanced pathological stage. Additional clinical factors including younger age, female sex, increased tumor size, poorly differentiated or undifferentiated tumors, advanced N stage, presence of lymphovascular invasion, and presence of distant metastasis were also identified as risk factors for the splenic hilar lymph node metastasis [7,14-18,20,21,25].

In a study by Sasada et al. [7], splenic hilar lymph node metastasis was detected in 31 (15.4%) of 201 patients who underwent total gastrectomy and splenectomy for proximal gastric

Table 1. The incidence of #10LN according to the cross-sectional tumor location

Author	Year	Country	No. of patients with #10LN metastasis/No. of all patients	#10LN metastasis incidence	Cross-sectional tumor location				
					GC	LC	AW	PW	Encircling
Mönig et al. [12]	2001	Germany	11/112	9.8%	37.5%	1.5%	0	0	13.3%
Sasada et al. [7]	2009	Japan	31/201	15.4%	38.5%	2.6%	5.3%	27.8%	22.8%
Shin et al. [14]	2009	Korea	41/319	12.9%	15.6%	9.7%	20.8%	12.0%	23.1%
Aoyagi et al. [15]	2010	Japan	20/191	10.5%	38.1%	0	6.3%	8.6%	17.4%
Kosuga et al. [16]	2011	Japan	30/280	10.7%	19.4%	7.2%			16.2%
Chen et al. [18]	2014	China	18/205	8.8%	18.2%	3.8%	0	13.3%	13.3%
Sun et al. [20]	2015	China	16/150	10.7%	17.8%	4.1%			10.7%
Watanabe et al. [22]	2016	Japan	39/421	9.3%	15.9%	6.2%			
Son et al. [23]	2017	Korea	87/602	14.5%	28.8%	9.7%	15.6%	12.3%	45.0%
Jeong et al. [25]	2019	Korea	63/665	9.5%	19.4%	3.5%	8.1%	7.4%	25.7%
Yura et al. [26]	2019	Japan	48/593	8.1%	15.1%	4.2%			

#10LN = number 10 lymph nodes; GC = greater curvature; LC = lesser curvature; AW = anterior wall; PW = posterior wall.

Splenic Hilar Nodal Dissection

Table 2. The incidence of #10LN according to the Borrmann classification

Author	Year	Country	No. of patients with #10LN metastasis/No. of all patients	#10LN metastasis incidence	Borrmann			
					I	II	III	IV
Mönig et al. [12]	2001	Germany	11/112	9.8%	0	0	1.8%	52.6%
Shin et al. [14]	2009	Korea	41/319	12.9%	11.1%	7.5%	12.2%	34.1%
Aoyagi et al. [15]	2010	Japan	20/191	10.5%	16.7%	4.3%	12.7%	14.3%
Kosuga et al. [16]	2011	Japan	30/280	10.7%	5.3%			26.4%
Zhu et al. [17]	2012	China	74/265	27.9%	14.9%		32.3%	
Chen et al. [18]	2014	China	18/205	8.8%	0	10.5%	3.8%	21.7%
Watanabe et al. [22]	2016	Japan	39/421	9.3%	17.1%			14.2%
Son et al. [23]	2017	Korea	87/602	14.5%	10.5%	6.5%	13.1%	24.5%

#10LN = number 10 lymph nodes.

Table 3. The incidence of #10LN according to the depth of invasion and stage

Author	Year	Country	No. of patients with #10LN metastasis/No. of all patients	#10LN metastasis incidence	Depth of invasion				Stage			
					M/SM	MP	SS	SE	1	2	3	4
Mönig et al. [12]	2001	Germany	11/112	9.8%					0	0	9.1%	35.7%
Ooki et al. [13]	2008	Japan	18/196	9.2%	2.4%	4.3%	8.5%	18.4%				
Sasada et al. [7]	2009	Japan	31/201	15.4%	0	5.3%	6.5%	27.2%				
Shin et al. [14]	2009	Korea	41/319	12.9%	0	0	9.7%	22.2%	0	4.5%	9.5%	43.8%
Aoyagi et al. [15]	2010	Japan	20/191	10.5%	9.1%	0	10.5%	12.9%	0	2.5%	6.3%	34.1%
Kosuga et al. [16]	2011	Japan	30/280	10.7%	0	3.2%	11.3%	13.4%				
Zhu et al. [17]	2012	China	74/265	27.9%	0	7.7%	17.8%	32.0%				
Chen et al. [18]	2014	China	18/205	8.8%	8.3%	0	4.5%	10.6%	0	2.9%	8.5%	23.5%
Sun et al. [20]	2015	China	16/150	10.7%	0	1.3%	14.3%	34.8%				
Watanabe et al. [22]	2016	Japan	39/421	9.3%	15.0%			16.7%				
Son et al. [23]	2017	Korea	87/602	14.5%	0	3.1%	4.7%	19.2%	0	2.1%	25.1%	
Jeong et al. [25]	2019	Korea	63/665	9.5%	0	0	5.6%	19.7%	0	0	13.5%	38.3%

#10LN = number 10 lymph nodes; M = mucosa; SM = submucosa; MP = muscularis propria; SS = subserosa; SE = serosa.

cancer. In multivariate analysis of their study, age was the only predictive factor, whereas the presence of distant metastasis, tumor size, differentiation, and macroscopic type were not. The most important finding of their study was the relationship between the frequency of lymph node metastasis and the splenic hilum, cross-sectional tumor location, and T stage. Splenic hilar lymph node metastasis was more common in patients with tumor located at the greater curvature (38.5%), posterior wall (27.8%), encircling involvement (22.8%), and this incidence increased with elevation in the T stage (27.2% for serosa-positive tumors). No splenic hilar lymph node metastasis was observed for patients with serosa-negative tumors located at the lesser curvature and anterior wall.

Aoyagi et al. reported that cross-sectional tumor location and pathological stage were associated with splenic hilar lymph node metastasis. In contrast, age, T stage, N stage, and the number of lymph node metastasis were not [15]. In their study, the incidence of splenic hilar lymph node metastasis was 38.1% (8 of 21 patients) for the greater curvature tumors and 17.4% (8 of 46 patients) for encircling tumors. No splenic hilar lymph node metastasis was observed in patients with lesser curvature tumors (none of 73 patients). Splenic hilar lymph node metastasis was not observed in stage-I tumor patients (none of 25 patients); however, it was observed in 34.1% (14 of 41 patients) stage-IV patients. The authors also demonstrated the correlation between positivity in #4sa, #4sb, or #11 lymph nodes and the splenic hilar lymph node metastasis.

One of the highest incidences for splenic hilar lymph node metastasis was observed in a study, which enrolled 265 patients subjected to gastrectomy combined with splenectomy (curative or palliative intent), of which 74 (27.9%) patients had splenic hilar lymph node metastasis (23.5%

for patients who underwent R0 resection) [17]. Younger age, Borrmann III–IV lesions, Lauren diffuse-type histology, lymphovascular invasion, T stage, N stage, presence of nonregional lymph node metastasis, and peritoneal cytology positivity as significant risk factors correlated with splenic hilar lymph node metastasis. Among these, T stage, N stage, and the presence of distant lymph node metastasis were independent risk factors. While no splenic hilar lymph node metastasis was observed in early gastric cancer, 28.9% (41 of 142 patients) of serosa positive tumors and 39.3% (24 of 61 patients) of tumors with adjacent organ invasions had splenic hilar lymph node metastasis. Moreover, splenic hilar lymph node metastasis was identified in 49.3% (33 of 67 patients) of patients with 7–15 positive lymph nodes, 82.4% (28 of 34 patients) of patients with >15 positive lymph nodes, and 72.8% (16 of 22 patients) with distant lymph node (#13, #14a, and those beyond #15) metastasis.

In another study, the risk factors related to splenic hilar lymph node metastasis in patients with advanced cancer, T stage, differentiation, tumor size, cross-sectional location, and Borrmann type were associated with the splenic hilar lymph node metastasis; however, multivariate analysis demonstrated that only T stage and tumor size act as the independent factors [20]. Incidences of splenic hilar lymph node metastasis were 1.3%, 14.3%, and 34.8% for T2, T3, and T4 tumors, respectively. Splenic hilar lymph node metastasis was observed in only 3 of 89 (3.4%) patients with tumors smaller than 5 cm and in 13 of 61 (21.3%) patients with larger tumors. In this study, they highlighted the importance of preoperative risk prediction for developing a rational surgical strategy for advanced gastric cancer.

In 2017, Hong et al. [21] designed a modeling system to predict the risk of splenic hilar lymph node metastasis for advanced upper gastric cancer. Tumor size, cT stage, and cN stage are considered as independent risk factors for patients undergoing curative gastrectomy with spleen-preserving splenic hilar lymph node dissection excluding stump cancer, tumors invading the adjacent organs, and M1 disease. To create a scoring system, patients were divided into three groups (low, intermediate, and high risk) by using the following factors: 2 points for ≥ 5 cm tumor size, 1 point for serosal involvement, and 1 point for lymph node positivity. The incidences of splenic hilar lymph node metastasis were 2.8%, 13.9%, and 34.9%, for low, intermediate, and high-risk groups, respectively. Moreover, an algorithm based on the scoring system for splenic hilar lymph node management was proposed.

SURVIVAL BENEFIT OF NUMBER 10 LYMPH NODE DISSECTION

Several studies have compared the survival outcomes of patients with and without splenic hilar lymph node metastasis. Moreover, the therapeutic value of splenic hilar lymph node dissection was evaluated as a form of the therapeutic index (TI), which was calculated by multiplying the splenic hilar lymph node metastasis incidence by the 5-year overall survival in patients suffering from this disorder [27].

In patients who underwent total gastrectomy plus splenectomy, 5-year survival rates were reported as 5.4%–26% for patients with splenic hilar lymph node metastasis, and majority of the studies have reported poor outcomes in patients with splenic hilar lymph node metastasis compared to the patients without it [7,14,17,25,28]. Subsequent studies have also investigated the efficacy of dissecting splenic hilar lymph nodes in subgroups, not all patients. The 5-year survival rate has been reported up to 51.3% in the subgroups. No survival difference was

found in few studies, whereas some studies argued the potential benefits of splenic hilar lymph node dissection in the subgroups.

In Aoyagi's study [15], the presence of splenic hilar lymph node metastasis did not reveal survival difference for stages IIIB and IV patients. In a study by Kosuga et al. [16], no significant difference was observed in 5-year survival between patients with splenic hilar lymph node metastasis and those without it (51.3% and 42.1%, respectively). The overall TI of the projected benefits from splenic hilar lymph node dissection was 5.49 (incidence was 10.7%). In subgroups of greater curvature and Borrmann-IV cancers, therapeutic indices were 19.4 and 12.9, respectively; however, encircling tumors (TI=1.62) and tumors invading the adjacent organs (TI=0) demonstrated quite low therapeutic value from splenic hilar lymph node dissection.

We recently investigated the impact of splenic hilar lymph node metastasis on prognosis in patients with advanced gastric cancer [23]. To this end, we analyzed 602 patients who underwent total gastrectomy with D2 lymph node dissection. We evaluated the subgroups of patients with metastasis to the splenic hilar lymph node, patients with metastasis to extraperigastric stations (#8a, #9, #11, or #12a), and patients with distant metastasis. 5-year overall survival in patients with splenic hilar lymph node metastasis was 24.1% (54.8% for patients without splenic hilar lymph node metastasis) and the TI for splenic hilar lymph node was 3.5; however, no significant differences were observed in the overall survival between patients with splenic hilar lymph node metastasis and those with metastasis to extraperigastric stations. Overall survival in patients with splenic hilar lymph node metastasis was better than that of patients with splenic hilar lymph node plus distant metastasis, and that of patients with distant metastasis but without splenic hilar lymph node metastasis. Moreover, the peritoneum was the most common recurrence site, despite involvement of any extraperigastric lymph nodes. This study revealed that dissection of splenic hilar lymph node provides a similar prognosis to that achieved with the dissection of extraperigastric lymph nodes in patients who underwent total gastrectomy for advanced gastric cancer.

Three studies from Japan investigated the value of splenic hilar lymph node dissection in proximal gastric cancer by dividing the patients into two groups as a greater curvature group (with tumors involving the greater curvature) and a nongreater curvature group (without tumors involving the greater curvature) [22,24,26]. In the first study by Watanabe et al. [22], the incidence of splenic hilar lymph node metastasis in the greater curvature group was 15.9% (6.2% for nongreater curvature group, $P=0.032$). In the greater curvature group, 5-year overall survival rates with and without splenic hilar lymph node metastasis were 35.4% and 43.1%, respectively ($P=0.135$), and these rates in the nongreater curvature group were 32.8% and 66.5%, respectively ($P<0.001$). The TI of splenic hilar lymph node was 5.6 in the greater curvature group and 2.0 in the nongreater curvature group. The greater curvature group was further analyzed in the study, and patients aged <65 years (TI=8.2), with Borrmann-IV (TI=7.1), and with <T4 stage (TI=10.0) demonstrated relatively higher therapeutic indices.

Maezawa et al. [24] investigated the efficacy of splenic hilar lymph node dissection by comparing it to that of the other regional nodes in locally advanced proximal gastric cancer invading the greater curvature. The incidence of splenic hilar lymph node metastasis, 5-year overall survival, and TI were 13.4%, 30%, and 4.02%, respectively. The most important finding of the study was the substantially higher TI of splenic hilar lymph node than those of #8a, #11p, and #11d. The authors suggest that the presence of splenic hilar lymph node is

higher than that of the #11 lymph nodes, and they recommended the removal of the splenic hilar lymph nodes as a part of D2 dissection for proximal gastric cancer detected in the greater curvature.

A recent study evaluated the efficacy of splenic hilar lymph node dissection for advanced gastric cancer invading the greater curvature [26,29]. No statistically significant difference was observed in 5-year survival for the patients with and without splenic hilar lymph node metastasis in the greater curvature group, whereas significant difference was observed in the nongreater curvature group. The TI of the splenic hilar lymph node station was 7.1 in the greater curvature group, and higher than those of the essential components of D2 dissection, including #5, #6, #8a, #9, #11p, #11d, and #12.

In addition to the observational studies, randomized comparative studies evaluating the impact of splenic hilar lymph node dissection were also published. The first randomized study in English literature was the Chilean study published in 2002 [30]. Herein, the authors compared total gastrectomy versus total gastrectomy with pancreas-preserving splenectomy in patients with gastric cancer. Patients with macroscopic metastasis at the splenic hilum and macroscopic findings of spleen invasion have not been included. Splenic hilar lymph node metastasis was detected in 8 (9%) of 90 patients in total gastrectomy plus splenectomy group. The 5-year survival rates were not statistically different between groups (36% in total gastrectomy group and 42% in total gastrectomy plus splenectomy group). The authors concluded that splenectomy does not influence the survival after total gastrectomy in early stages and may be performed only in selected patients with an advanced-stage disease.

The most systematic randomized study to evaluate splenectomy in total gastrectomy for proximal gastric cancer was published by the Stomach Cancer Study Group of the Japan Clinical Oncology Group in 2017 (JCOG0110) [31]. In this noninferiority trial, 505 patients from 36 institutions were randomized to splenectomy or spleen preservation groups. The 5-year overall survival rates were 75.1% and 76.4% for the splenectomy and the spleen preservation group, respectively. Statistically significant noninferiority of spleen preservation was presented, and the authors concluded that splenectomy should be avoided; however, certain crucial points were highlighted in the study design. Patients with the tumor invading the greater curvature, those with gastric remnant cancer, those with Borrmann-IV, and patients with gross lymph node metastasis at splenic hilum were excluded from the study, that is, patients at high risk for splenic hilar lymph node metastasis were eliminated. Moreover, only advanced cancer was supposed to be included; 14.1% of the included patients had pathological T1 tumors. Therefore, the incidence of splenic hilar lymph node metastasis was quite low (2.4%) in the splenectomy group, compared to the previous studies [32,33]. In 58 of 254 patients in the spleen preservation group, splenic hilar lymph node dissection or sampling was performed without splenectomy. Considering the strict eligibility study criteria, the results should not be extrapolated to all gastric cancer patients, and certain questions still need to be answered.

FEASIBILITY OF SPLENIC HILAR LYMPH NODE DISSECTION WITHOUT SPLENECTOMY

Removal of the spleen, which is a part of the immune system, has been questioned due to its possible effects on short- and long-term outcomes. Although several surgeons have routinely

performed splenectomy for the removal of splenic hilar lymph nodes, it is possible to remove the same group of lymph nodes by preserving the spleen and splenic vessels. A randomized study comparing spleen-preserving splenic hilar lymph node dissection and splenectomy for proximal gastric cancer demonstrated that a similar number of lymph nodes could be removed with both approaches, and that no survival advantage of splenectomy exists over spleen-preserving dissection [34]. In subsequent studies, spleen-preserving dissection was commonly performed with open or laparoscopic approach [35-38]. Interim report of a randomized trial comparing the laparoscopic and open spleen preserving splenic hilar lymph node dissection demonstrated that operative time, number of harvested lymph nodes including splenic hilar lymph node, time taken for splenic hilar lymph node dissection, as well as the complication rates are comparable between the groups [39]. In addition to the successful applications of laparoscopic splenic hilar lymph node dissection, robotic surgery is known to be a feasible and safe approach for spleen-preserving splenic hilar lymph node dissection [40,41]. Image-guided surgery with the assistance of 3D simulation and fluorescent lymphography-guided lymph node dissection are also tools that assist surgeons regarding the appropriate anatomy of the splenic vessels before surgery and in identifying all necessary lymph nodes [42-45].

SUMMARY

Several factors determine the direction and timing of the lymphatic spread of gastric cancer. The splenic hilar lymph node group is one of the essential targets in the surgical treatment of proximal gastric cancer, and published studies have reported various incidences of splenic hilar metastasis and survival rates for patients with splenic hilar lymph node metastasis. The overall incidence of splenic hilar lymph node metastasis was reported up to 27.9% in gastric cancer, and a correlation was observed between the risk of splenic hilar lymph node metastasis and several clinicopathological factors including age, cross-sectional tumor location, tumor size, T stage, N stage, and pathological stage. All these factors except for the tumor location are parts of advanced or systemic disease and they mostly reflect poor prognosis for gastric cancer patients. Thus, studies exploring long-term outcomes of splenic hilar lymph node dissection failed to present a survival benefit. It is rational to use a cross-sectional tumor location as the best candidate variable in selecting patients who would benefit from the splenic hilar lymph node dissection. The recent randomized trial, which has a strict eligibility criteria, concluded that routine splenic hilar lymph node dissection is not required in all patients requiring total gastrectomy; however, no convincing evidence is available to ignore the benefit of splenic hilar lymph node dissection in patients with a high risk of splenic hilum lymph node metastasis.

CONCLUSIONS

The potential benefit of splenic hilar lymph node dissection becomes more pronounced when demonstrated by the relatively higher TI, specifically in tumors involving greater curvature of the proximal stomach and conceivably for Borrmann type IV tumors. Therefore, the dissection of splenic hilar lymph node should be considered and allowed to be a part of curative surgery in selected patient groups, if R0 resection is intended.

REFERENCES

1. Takahashi T, Sawai K, Hagiwara A, Takahashi S, Seiki K, Tokuda H. Type-oriented therapy for gastric cancer effective for lymph node metastasis: management of lymph node metastasis using activated carbon particles adsorbing an anticancer agent. *Semin Surg Oncol* 1991;7:378-383.
[PUBMED](#) | [CROSSREF](#)
2. Coller FA, Kay EB, McIntyre RS. Regional lymphatic metastases of carcinoma of the stomach. *Arch Surg* 1941;43:748-761.
[CROSSREF](#)
3. Pissas A, Sarrazin R, Dyon JF, Bouchet Y. The lymphatic vessels of the stomach in man. *Folia Morphol (Praha)* 1982;30:363-365.
[PUBMED](#)
4. Maruyama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. *World J Surg* 1987;11:418-425.
[PUBMED](#) | [CROSSREF](#)
5. Son T, Hyung WJ, Kim JW, Kim HI, An JY, Cheong JH, et al. Anatomic extent of metastatic lymph nodes: still important for gastric cancer prognosis. *Ann Surg Oncol* 2014;21:899-907.
[PUBMED](#) | [CROSSREF](#)
6. Choi YY, An JY, Guner A, Kang DR, Cho I, Kwon IG, et al. Skip lymph node metastasis in gastric cancer: is it skipping or skipped? *Gastric Cancer* 2016;19:206-215.
[PUBMED](#) | [CROSSREF](#)
7. Sasada S, Ninomiya M, Nishizaki M, Harano M, Ojima Y, Matsukawa H, et al. Frequency of lymph node metastasis to the splenic hilus and effect of splenectomy in proximal gastric cancer. *Anticancer Res* 2009;29:3347-3351.
[PUBMED](#)
8. Kajitani T. The general rules for the gastric cancer study in surgery and pathology. Part I. Clinical classification. *Jpn J Surg* 1981;11:127-139.
[PUBMED](#) | [CROSSREF](#)
9. Maruyama K, Guntvén P, Okabayashi K, Sasako M, Kinoshita T. Lymph node metastases of gastric cancer. General pattern in 1931 patients. *Ann Surg* 1989;210:596-602.
[PUBMED](#) | [CROSSREF](#)
10. Okajima K, Isozaki H. Splenectomy for treatment of gastric cancer: Japanese experience. *World J Surg* 1995;19:537-540.
[PUBMED](#) | [CROSSREF](#)
11. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma - 2nd English edition -. *Gastric Cancer* 1998;1:10-24.
[PUBMED](#) | [CROSSREF](#)
12. Mönig SP, Collet PH, Baldus SE, Schmackpfeffer K, Schröder W, Thiele J, et al. Splenectomy in proximal gastric cancer: frequency of lymph node metastasis to the splenic hilus. *J Surg Oncol* 2001;76:89-92.
[PUBMED](#) | [CROSSREF](#)
13. Ooki A, Yamashita K, Kikuchi S, Sakuramoto S, Katada N, Hutawatari N, et al. Clinical significance of total gastrectomy for proximal gastric cancer. *Anticancer Res* 2008;28:2875-2883.
[PUBMED](#)
14. Shin SH, Jung H, Choi SH, An JY, Choi MG, Noh JH, et al. Clinical significance of splenic hilar lymph node metastasis in proximal gastric cancer. *Ann Surg Oncol* 2009;16:1304-1309.
[PUBMED](#) | [CROSSREF](#)
15. Aoyagi K, Kouhiji K, Miyagi M, Imaizumi T, Kizaki J, Shirouzu K. Prognosis of metastatic splenic hilum lymph node in patients with gastric cancer after total gastrectomy and splenectomy. *World J Hepatol* 2010;2:81-86.
[PUBMED](#) | [CROSSREF](#)
16. Kosuga T, Ichikawa D, Okamoto K, Komatsu S, Shiozaki A, Fujiwara H, et al. Survival benefits from splenic hilar lymph node dissection by splenectomy in gastric cancer patients: relative comparison of the benefits in subgroups of patients. *Gastric Cancer* 2011;14:172-177.
[PUBMED](#) | [CROSSREF](#)
17. Zhu GL, Sun Z, Wang ZN, Xu YY, Huang BJ, Xu Y, et al. Splenic hilar lymph node metastasis independently predicts poor survival for patients with gastric cancers in the upper and/or the middle third of the stomach. *J Surg Oncol* 2012;105:786-792.
[PUBMED](#) | [CROSSREF](#)

18. Chen XL, Yang K, Zhang WH, Chen XZ, Zhang B, Chen ZX, et al. Metastasis, risk factors and prognostic significance of splenic hilar lymph nodes in gastric adenocarcinoma. *PLoS One* 2014;9:e99650.
[PUBMED](#) | [CROSSREF](#)
19. Yang K, Zhang WH, Chen XZ, Chen XL, Zhang B, Chen ZX, et al. Survival benefit and safety of no. 10 lymphadenectomy for gastric cancer patients with total gastrectomy. *Medicine (Baltimore)* 2014;93:e158.
[PUBMED](#) | [CROSSREF](#)
20. Sun Z, Wang Q, Yu X, Ou C, Yao L, Liu K, et al. Risk factors associated with splenic hilar lymph node metastasis in patients with advanced gastric cancer in northwest China. *Int J Clin Exp Med* 2015;8:21358-21364.
[PUBMED](#)
21. Hong ZL, Chen QY, Zheng CH, Li P, Xie JW, Wang JB, et al. A preoperative scoring system to predict the risk of No.10 lymph node metastasis for advanced upper gastric cancer: a large case report based on a single-center study. *Oncotarget* 2017;8:80050-80060.
[PUBMED](#) | [CROSSREF](#)
22. Watanabe M, Kinoshita T, Enomoto N, Shibasaki H, Nishida T. Clinical significance of splenic hilar dissection with splenectomy in advanced proximal gastric cancer: an analysis at a single institution in Japan. *World J Surg* 2016;40:1165-1171.
[PUBMED](#) | [CROSSREF](#)
23. Son T, Kwon IG, Lee JH, Choi YY, Kim HI, Cheong JH, et al. Impact of splenic hilar lymph node metastasis on prognosis in patients with advanced gastric cancer. *Oncotarget* 2017;8:84515-84528.
[PUBMED](#) | [CROSSREF](#)
24. Maezawa Y, Aoyama T, Yamada T, Kano K, Hayashi T, Sato T, et al. Priority of lymph node dissection for proximal gastric cancer invading the greater curvature. *Gastric Cancer* 2018;21:569-572.
[PUBMED](#) | [CROSSREF](#)
25. Jeong O, Jung MR, Ryu SY. Clinicopathological features and prognostic impact of splenic hilar lymph node metastasis in proximal gastric carcinoma. *Eur J Surg Oncol* 2019;45:432-438.
[PUBMED](#) | [CROSSREF](#)
26. Yura M, Yoshikawa T, Otsuki S, Yamagata Y, Morita S, Katai H, et al. The therapeutic survival benefit of splenic hilar nodal dissection for advanced proximal gastric cancer invading the greater curvature. *Ann Surg Oncol* 2019;26:829-835.
[PUBMED](#) | [CROSSREF](#)
27. Sasako M, McCulloch P, Kinoshita T, Maruyama K. New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. *Br J Surg* 1995;82:346-351.
[PUBMED](#) | [CROSSREF](#)
28. Nashimoto A, Yabusaki H, Matsuki A. The significance of splenectomy for advanced proximal gastric cancer. *Int J Surg Oncol* 2012;2012:301530.
[PUBMED](#) | [CROSSREF](#)
29. Yura M, Yoshikawa T. ASO author reflections: splenic hilar nodal dissection for proximal advanced gastric cancer. *Ann Surg Oncol* 2019;26:588-589.
[PUBMED](#) | [CROSSREF](#)
30. Csendes A, Burdiles P, Rojas J, Braghetto I, Diaz JC, Maluenda F. A prospective randomized study comparing D2 total gastrectomy versus D2 total gastrectomy plus splenectomy in 187 patients with gastric carcinoma. *Surgery* 2002;131:401-407.
[PUBMED](#) | [CROSSREF](#)
31. Sano T, Sasako M, Mizusawa J, Yamamoto S, Katai H, Yoshikawa T, et al. Randomized controlled trial to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma. *Ann Surg* 2017;265:277-283.
[PUBMED](#) | [CROSSREF](#)
32. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008;359:453-462.
[PUBMED](#) | [CROSSREF](#)
33. Kinoshita T. Splenic hilar dissection in the treatment of proximal advanced gastric cancer: what is an adequate strategy? *Transl Gastroenterol Hepatol* 2016;1:72.
[PUBMED](#) | [CROSSREF](#)
34. Yu W, Choi GS, Chung HY. Randomized clinical trial of splenectomy versus splenic preservation in patients with proximal gastric cancer. *Br J Surg* 2006;93:559-563.
[PUBMED](#) | [CROSSREF](#)
35. Hyung WJ, Lim JS, Song J, Choi SH, Noh SH. Laparoscopic spleen-preserving splenic hilar lymph node dissection during total gastrectomy for gastric cancer. *J Am Coll Surg* 2008;207:e6-e11.
[PUBMED](#) | [CROSSREF](#)

36. Huang CM, Chen QY, Lin JX, Zheng CH, Li P, Xie JW, et al. Laparoscopic spleen-preserving splenic hilar lymphadenectomy performed by following the perigastric fascias and the intrafascial space for advanced upper-third gastric cancer. *PLoS One* 2014;9:e90345.
[PUBMED](#) | [CROSSREF](#)
37. Ji X, Fu T, Bu ZD, Zhang J, Wu XJ, Zong XL, et al. Comparison of different methods of splenic hilar lymph node dissection for advanced upper- and/or middle-third gastric cancer. *BMC Cancer* 2016;16:765.
[PUBMED](#) | [CROSSREF](#)
38. Huang CM, Huang ZN, Zheng CH, Li P, Xie JW, Wang JB, et al. Huang's three-step maneuver shortens the learning curve of laparoscopic spleen-preserving splenic hilar lymphadenectomy. *Surg Oncol* 2017;26:389-394.
[PUBMED](#) | [CROSSREF](#)
39. Guo X, Peng Z, Lv X, Cui J, Zhang K, Li J, et al. Randomized controlled trial comparing short-term outcomes of laparoscopic and open spleen-preserving splenic hilar lymphadenectomy for advanced proximal gastric cancer: an interim report. *J Surg Oncol* 2018;118:1264-1270.
[PUBMED](#) | [CROSSREF](#)
40. Yang K, Cho M, Roh CK, Seo WJ, Choi S, Son T, et al. Robotic spleen-preserving splenic hilar lymph node dissection during total gastrectomy for gastric cancer. *Surg Endosc* 2019;33:2357-2363.
[PUBMED](#) | [CROSSREF](#)
41. Son T, Lee JH, Kim YM, Kim HI, Noh SH, Hyung WJ. Robotic spleen-preserving total gastrectomy for gastric cancer: comparison with conventional laparoscopic procedure. *Surg Endosc* 2014;28:2606-2615.
[PUBMED](#) | [CROSSREF](#)
42. Wang JB, Huang CM, Zheng CH, Li P, Xie JW, Lin JX, et al. Role of 3DCT in laparoscopic total gastrectomy with spleen-preserving splenic lymph node dissection. *World J Gastroenterol* 2014;20:4797-4805.
[PUBMED](#) | [CROSSREF](#)
43. Kinoshita T, Shibasaki H, Enomoto N, Sahara Y, Sunagawa H, Nishida T. Laparoscopic splenic hilar lymph node dissection for proximal gastric cancer using integrated three-dimensional anatomic simulation software. *Surg Endosc* 2016;30:2613-2619.
[PUBMED](#) | [CROSSREF](#)
44. Kwon IG, Son T, Kim HI, Hyung WJ. Fluorescent lymphography-guided lymphadenectomy during robotic radical gastrectomy for gastric cancer. *JAMA Surg* 2019;154:150-158.
[PUBMED](#) | [CROSSREF](#)
45. Kim YM, Baek SE, Lim JS, Hyung WJ. Clinical application of image-enhanced minimally invasive robotic surgery for gastric cancer: a prospective observational study. *J Gastrointest Surg* 2013;17:304-312.
[PUBMED](#) | [CROSSREF](#)