Risk factors of lymph node metastasis in the splenic hilum of gastric cancer patients: A meta-analysis

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Abstract

Background It remains controversial whether splenic hilum lymph nodes (SHLNs) should be excised in radical gastrectomy with D2 lymph node dissection. In this study, we evaluated the role of clinicopathological features in patients with gastric cancer in predicting splenic hilum lymph nodes metastasis.

Methods We searched the Medline, Embase, PubMed and Web of Science databases from inception to May 2020 and consulted related references. 15 articles with a total of 4377 patients were included finally. The odds ratios (ORs) of each risk factor and the corresponding 95% confidence interval (CI) were determined using Revman 5.3 software.

Results Meta-analysis showed that tumor size greater than 5 cm ($p < 0.01$), tumor localization in the greater curvature ($p < 0.01$), diffuse type (Lauren's type) ($p < 0.01$), Borrman type 3–4 ($p < 0.01$), poor differentiation and undifferentiation ($p < 0.01$), depth of invasion T3–T4 ($p < 0.01$), number of lymph node metastases N2–N3 ($p < 0.01$), distance metastasis M1 ($p < 0.01$), TNM stage 3–4 ($p < 0.01$), vascular invasion ($p = 0.01$), and lymphatic invasion ($p < 0.01$) were risk factors of SHLNs metastasis. Moreover, No. 1-, 2-, 3-, 4sa-, 4sb-, 4d-, 6-, 7-, 9-, 11-, and 16-positive lymph node metastasis are strongly associated with splenic hilum lymph nodes metastasis.

Conclusions Tumor size, tumor location, Lauren's type, Borrman type, degree of differentiation, T stage, N stage, M stage, TNM stage, vascular invasion, lymphatic infiltration, and other positive lymph nodes metastasis were risk factors for SHLNs.

Introduction

Despite a downward trend in mortality, gastric cancer (GC) is the still the third leading cause of cancer deaths and the fifth most diagnosed cancer.[1] Surgical resection is the only way to cure GC. According to the Japanese Gastric Cancer Treatment Guidelines, standard gastrectomy involves at least a two-third resection of the stomach with D2 lymph node dissection. Meanwhile, the No. 10 lymph node is also within the scope of resection in proximal GC.[2] The deep anatomical position of the splenic hilum leads to narrowing of the operative space. Because of the fragility of the spleen and the variability of splenic hilum vessels, it is difficult to perform splenic hilum lymph node dissection.[3] Although splenectomy could completely remove splenic hilum lymph nodes (SHLNs), splenectomy for lymph node dissection remains controversial. A large scale randomized controlled trial showed that there was no significant difference in the 5-year survival rate between the splenectomy group and the spleen-preserving group. However, there was higher morbidity and increased blood loss in the splenectomy group.[4] When SHLNs metastasis occurs, the prognosis is worse than that without metastasis.[5] The survival benefits of preventive splenic hilum lymphadenectomy are controversial.[3,6] Therefore, we systematically reviewed the risk factors of SHLNs metastasis to evaluate whether perform spleen-preserving splenic hilum lymph node dissection should be performed in high-risk patients with SHLNs metastasis.

Materials And Methods

Search strategy

We searched Medline, Embase, Web of Science, and PubMed databases from inception to July 2019 and read the relevant references to investigate the literature. We used the following search terms: Stomach Neoplasms, Stomach Neoplasm, Gastric Neoplasm, Cancer of Stomach, Stomach Cancer, Gastric Cancer, Lymph Nodes, Lymph Node, No. 10, Splenic Hilar, Splenic Hilum, Metastasis. The combination of Medicine Subject Headings and keywords were used to search, and there was no language restriction.

Inclusion and exclusion criteria

Inclusion criteria: (1) Study patients were diagnosed with gastric cancer in each institution, and underwent proximal/total gastrectomy with D2/D3 lymphadenectomy; (2) Case control studies; (3) The literature contained information on risk factors for splenic lymph node metastasis; (4) Newcastle-Ottawa quality assessment scale (NOS) score greater than 5 points.

Exclusion criteria: (1) Patients who suffered from residual GC, gastroesophageal junctional cancer, or gastric stromal tumor; (2) Overviews, case studies, or abstracts; (3) Studies that did not include original data and/or lacked a control group or key information that could not be obtained despite contacting the author; (4) Literature originated from the same institution contemporaneously.

Literature screening, data extraction, and quality evaluation

All of the included studies were imported into Endnote X9 software. After reviewing the full text, the studies were screened according to inclusion and exclusion criteria.We designed an information extraction table and extracted relevant information as follows: author name, publication date, country, number of cases, age, gender, tumor size, tumor location, Lauren classification, Borrman classification, tumor differentiation, depth of tumor invasion, number of lymph node metastases, distance metastasis, TNM stage, neurological invasion, vascular invasion, lymphatic invasion, and other positive groups of lymph node metastasis.Quality evaluation was performed using NOS.[7,8] When the NOS score was greater than 7 points, it was rated as high quality literature. When the score was less than 5 points, it was rated as low quality literature. The remainder of the studies were rated as medium quality literature.All operations were performed independently by two researchers. In the event of a disagreement, a third researcher resolved the dispute.

Statistical analysis

Dichotomous variable data was represented by a forest plot using odds ratios (ORs) and 95% confidence intervals (CIs). Q test and the I^2 statistic were used to measure the degree of heterogeneity of the combined data. Random effect model was used when $I^2 > 50\%$ and/or $p < 0.01$; otherwise a fixed effect model was used. Sensitivity analysis was conducted by eliminating studies one by one and changing the

effect model to test the stability of combined data. A funnel plot was used to evaluate publication bias. $p < 0.05$ was considered to be statistically significant.

Results

Study selection

We retrieved a total of 308 articles from Medline (n = 39), Embase (n = 121), PubMed (n = 103), and Web of Science (n = 45), and read the relevant references to obtain three studies. After excluding 154 duplicates, we reviewed the titles and abstracts of the remaining studies and excluded 113 unrelated articles. After excluding review articles and studies that analyzd patient data from the same institution in the same time period, irrelevant data, and unavailable data, 15 articles were eventually included (figure 1). A total of 4377 patients with GC underwent gastrectomy and lymphadenectomy in the included studies. Of these studies, seven were performed in China, five in Japan, two in South Korea, and one in Germany. All of the studies contained at least one risk factor for SHLNs metastasis. General characteristics and quality assessments of the included studies are listed in Table 1.

Fig 1. Flow diagram of the search and selection process.

Age

Five studies included 159 of the total 927 patients aged < 60 years with No. 10 LN+ and 179 of 896 patients aged > 60 years with No. 10 LN+ (OR = 0.90, 95% CI = 0.54–1.48, I^2 = 63%, p = 0.67). There were no significant differences between the two groups (figure 2a). Because of the heterogeneity, we conducted sensitivity analysis by eliminating studies one by one, and found that the heterogeneity decreased significantly when Aoyagi (2010) was removed (I^2 = 18%).

Sex

Thirteen studies, with 2888 males and 1132 females, were included in the gender analysis, which revealed that were no significant differences between males and females (OR = 0.88, 95% CI = 0.72–1.07, I^2 = 24%, p = 0.19) (figure 2b).

Tumor size

Five studies were included in the analysis of tumor size. Because of the difference in the statistics analyzing tumor diameter, we divided the information into two groups (> 5 cm vs. < 5 cm and > 10 cm vs. < 10 cm). There was no significant difference between the groups of > 10 cm and < 10 cm, and the

studies had high heterogeneity (OR = 0.58, 95% CI = 0.21–1.58, I^2 = 71%, p = 0.28). However, when the tumor diameter was demarcated by 5 cm, there was a significant difference between the two groups, and the studies had no heterogeneity (OR = 4.89, 95% CI = 2.98–8.03, I^2 = 0%, p < 0.01) (figure 2c).

Tumor location

Eleven studies, containing 341 patients with tumors located in the greater curvature (Gre) and 2809 with tumors located in other locations, were included in the analysis of tumor location. There was a significant difference between tumors found in the greater curvature and those found elsewhere (OR = 3.10, 95% CI = 1.92–5.02, I^2 = 54%, p < 0.01) (figure 2d). We conducted sensitivity analysis by eliminating studies one by one, and found that the heterogeneity did not change significantly following elimination of any of the studies.

Lauren's type

Four articles containing 929 patients mentioned Lauren's type, which included diffuse and intestinal types. After the data was combined, the results showed a significant difference between diffuse and intestinal types (OR = 2.91, 95% CI = 1.84–4.59, I^2 = 0%, p < 0.01) (figure 2e).

Borrman type

Nine articles included information regarding Borrman's type. Borrman classification is divided into four types: type I, type II, type III, and type IV. We combined types I–III and analyzed the data comparing types I–III and type IV. The heterogeneity of the two groups was small and there was a significant difference between the groups (OR = 2.49, 95% CI = 1.84–3.37, I^2 = 0%, p < 0.01) (figure 2f).

Histological differentiation

Data on histological differentiation was included in 12 studies. We set the poorly differentiated and undifferentiated types as the exposure group, and the moderately differentiated and well differentiated types as the control group. Following analysis, studies were removed one by one for sensitivity analysis. There was no significant change in heterogeneity and there was a significant statistical difference betweentwo groups (OR = 2.29, 95% CI = 1.80–2.92, I^2 = 25%, p < 0.01) (figure 2g).

Depth of invasion

Data regarding depth of invasion was included in 10 studies. We set T3 and T4 as the exposure group, and T1 and T2 as the control group. There was no significant heterogeneity in either group and there was

a significant statistical difference between T1-2 and T3-4 (OR = 6.39, 95% CI = 4.04–10.12, I^2 = 1%, p < 0.01) (figure 2h).

Lymph node metastases

Nine studies mentioned lymph node metastases, which included N1, N2, and N3. We grouped N1 and N2–3 separately. After the data was combined, the results showed a significant difference (OR = 6.96, 95% CI = 4.64–10.44, I^2 = 44%, p < 0.01) (figure 2i). Because of the heterogeneity, we conducted sensitivity analysis by eliminating studies one by one, and found that the heterogeneity disappeared when Huang (2009) was removed (I^2 = 0%).

Distance metastasis

Three articles containing 1272 patients included data on distant metastases. After the data were combined, there was no heterogeneity and there was a statistically significant difference (OR = 8.66, 95% CI = 5.53–13.56, I^2 = 0%, p < 0.01) (figure 2j).

Neurological, vascular, and lymphatic invasion

Because several studies combined data on blood vessels and lymphatics, we excluded these studies. Two studies included data regarding neurological invasion. After the data was combined, the results did not show a significant difference between the two groups (OR = 1.72, 95% CI = 0.98–3.03, I^2 = 16%, p < 0.01) (figure 2k). Three studies mentioned vascular invasion. After the data was combined, the results showed a significant difference between the two groups(OR = 2.57, 95% CI = 1.21–5.47, I^2 = 0%, p = 0.01) (figure l). Three articles mentioned lymphatic invasion. After the data was combined, the results showed a significant difference between the two groups(OR = 3.41, 95% CI = 1.81–6.44, I^2 = 0%, p < 0.01) (figure 2m).

TNM stage

Eight articles mentioned TNM stage. The TNM stage was divided into four types: type I, type II, type III, and type IV. We combined types I–III and compared this group with type IV. The heterogeneity of the two groups was small and there was a significant difference between types I-II and types III-IV (OR = 22.70, 95% CI = 11.57–44.56, I^2 = 0%, p < 0.01) (figure 2n).

Other groups with positive lymph node metastasis

Four studies referred to other regional lymph node metastases, which were associated with SHLNs metastasis. We collected their combined values and effects; these are listed in Table 2. The results showed that other regional lymph nodes, with the exception of No. 5 LN (p = 0.14) and No. 8a LN (p = 0.10), are associated with SHLNs metastasis. We performed sensitivity analysis by changing the effect model, and found no change.

Figure 2 Forest plot analysis of risk factors.

1. **age, b. sex, c. tumor size, d. tumor location. e. Lauren's type, f. Borrman type, g. histological differentiation, h. depth of invasion, i. lymph node metastases, j. distance metastasis, k. neurological invasion, l. vascular invasion, m. lymphatic invasion, n. TNM stage.**

Publication bias

Publication bias was assessed only when more than 10 studies were included in the risk factor analysis. There was no obvious asymmetry in the funnel plot of histological differentiation (figure 3). Similarly, other aggregated data was not found to exhibit publication bias.

Figure 3 Funnel plot of histological differentiation.

Discussion

Gastric cancer has a high mortality rate. The presence of lymph node metastasis in the splenic hilum indicates poor prognosis.[23] Risk factors for SHLNs metastasis have been assessed in other studies, but the impact of other regional lymph nodes on splenic hilum metastasis has not been assessed. In this study, we identified 11 risk factors for SHLNs metastasis. Among the clinicopathological features, T stage (OR = 6.39), N stage (OR = 6.96), M stage (OR = 8.66), and TNM stage (OR = 22.70) were strongly associated with No. 10 lymph node metastasis. Joeng *et al* reported that when SHLNs metastasis occurred, all patients were in stage 3 or 4. When lymph node metastasis of the splenic hilum had not occurred, patients were in stage 1 or 2.[9] Lymph from the stomach wall flows into the submucosal lymphatic network, eventually flowing into the peri-gastric lymphatic system.[24]Therefore, the deeper the tumor invades, the easier it is to invade the lymphatic vessels, leading to a high rate of lymph node metastasis.

Generally, cancer located in the upper part or greater curvature of the stomach tends to metastasize to the splenic hilum, which may be related to the lymphatic reflux pathway in the region.[25-27] It has been reported that gastric adenocarcinoma located in the upper one-third of the greater curvature is drained to SHLNs through lymphatic vessels of the posterior gastric artery (4sa).[24,28] In addition, Toshio *et al*, who injected activated carbon particles under serosa, pointed out that when the tumour is located in the middle one-third of the greater curvature of the stomach, lymph flowed to the upper or lower part of the peri-gastric lymph nodes (4sb, 4d).[29] Yura's results showed that the rate of lymph node metastasis of

Nos. 4sa, 4sb, 4d, and 10 was significantly higher than that of tumors located in the non-greater curvature side.[27] This is also consistent with our results that No. 4sa (OR = 17.71), 4sb (OR = 6.91), and 4d (OR = 4.54) LN metastasis was strongly associated with No. 10 LN metastasis. Meanwhile, in the normal lymphatic reflux pathway, the metastasis of some higher lymph node stations, such as No. 11 (OR = 3.92) and 16 (OR = 4.34), may also indicate SHLNs metastasis. However, no statistically significant difference between No. 16-positive and No. 10-positive has been reported in the literature.[30,31]

One report indicated that the survival rate of patients with lymph node dissection was worse than that of non-dissected patients when SHLNs metastasis has occurred. Most of the cases in this study were advanced GC patients, which may lead to the risk of bias.[3] A randomized controlled trial showed that there was no significant difference in 5-year survival rates between patients who received total gastrectomy compared with patients who received total gastrectomy with splenectomy.[4] Thus, the survival benefit of lymph node dissection for proximal GC remains controversial.

Because of the complexity of the anatomical location of the splenic hilum, it is still debated whether SHLNs should be dissected or whether splenectomy or spleen-preserving lymph node dissection should be performed.[6,32-35] In the past, splenectomy has been considered to allow for complete resection of lymph nodes in the splenic hilum. However, some subsequent experiments have shown that there is no significant difference in the 5-year survival rate between patients who undergo splenectomy compared with those who do not.[6,33] There are still some reports that splenectomy has limited benefits.[34,35] Recently, the results of a large-scale randomized controlled trial in Japan showed that splenectomy resulted in more morbidity and complications, and did not increase the survival benefits of patients. However, GC patients with splenic hilum lymph node metastasis were rare, so there has been a lack of relevant randomized controlled trials. It is still unknown whether surgical removal of the spleen provides survival benefits.[4]

In terms of surgical treatment, reasonable and individual surgery considering safety and quality of life is a new trend in Japan.[36] It is becoming increasingly necessary to implement individualized treatment for each patient. When the tumor is in a late stage, or the tumor is located in the greater curvature of the stomach with No. 4sa, 4sb, or 4d lymph node metastasis, or the tumor is located in the lesser curvature of the stomach with No. 3, 7, or 11 lymph node metastasis, it is recommended to perform splenic hilum lymph node dissection. When other risk factors are present, spleen-preserving splenic hilum lymph node dissection could be considered.

There are some limitations of our study. (1) Because all of the included studies are retrospective, there is a risk of bias. (2) There are no clear definitions of certain indicators in the included studies, which are likely to be heterogeneous. (3) There are large heterogeneities in the parameters between some studies, which may be related to factors such as surgical operations and statistical analysis. (4) In some cases, complete data could not be obtained, which may result in deviation of results. (5) Some of the analyses, such as neurological invasion and No. 2, 6, and 16, resulted in p-values around 0.05. Although we have

made a conclusion based on these results, further verification using large-scale prospective experiments will be necessary in the future.

Conclusions

We identified 11 risk factors for SHLNs metastasis. According to ORs, we have determined that tumor size, tumor location, Lauren's type, Borrman's type, histological differentiation, depth of invasion, lymph node metastases, distance metastasis, vessel invasion, TNM stage, and No. 1-, 2-, 3-, 4sa-, 4sb-, 4d-, 6-, 7-, 9-, 11-, and 16-positive have a strong association with SHLNs metastasis. Understanding these clinicopathological features can help clinicians assess patients' conditions and develop individualized surgical plans.

Abbreviations

SHLNs: Splenic hilum lymph nodes; GC: gastric cancer; NOS: Newcastle-Ottawa quality assessment scale.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All the data analyzed in this study are obtained from the original articles.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributors

DJ planned the study and wrote the manuscript. SYC and YWW extracted data and performed quality evaluation. WJG resolved the dispute and supervised the study. All authors screened and approved the final manuscript.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2018;68:394-424.
2. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). J Gastric Cancer 2017;20:1-19.
3. Lin JX, Huang CM, Zheng CH, Li P, Xie JW, Wang JB, Lu J, Chen QY, Cao LL, Lin M. Is it necessary to dissect the posterior lymph nodes along the splenic vessels during total gastrectomy with D2 lymphadenectomy for advanced gastric cancer? Eur J Surg Oncol 2017;43:2357-2365.
4. Sano T, Sasako M, Mizusawa J, Yamamoto S, Katai H, Yoshikawa T, Nashimoto A, Ito S, Kaji M, Imamura H, Fukushima N, Fujitani K. Randomized Controlled Trial to Evaluate Splenectomy in Total Gastrectomy for Proximal Gastric Carcinoma. Ann Surg 2017;265:277-283.
5. Chen XL, Yang K, Zhang WH, Chen XZ, Zhang B, Chen ZX, Chen JP, Zhou ZG, Hu JK. Metastasis, risk factors and prognostic significance of splenic hilar lymph nodes in gastric adenocarcinoma. PLoS One 2013;9:e99650.
6. 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.
7. Reeves BC, Deeks JJ, Higgins JPT, Wells GA. Chapter 13: Including non-randomized studies. In: Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration 2009:399-400.
8. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. http://ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed 20 July 2019.
9. 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.
10. Chen GX, Sun ZQ, Wang HJ. Risk factors and prognostic impact of No.10 lymph nodes metastasis for patients with advanced gastric cancer in the upper and/or the middle third of the stomach. Zhong Liu Fang Zhi Za Zhi 2016;23:530-534.
11. Bian S, Xi H, Wu X, Cui J, Ma L, Chen R, Wei B, Chen L. The Role of No. 10 Lymphadenectomy for Advanced Proximal Gastric Cancer Patients Without Metastasis to No. 4sa and No. 4sb Lymph Nodes. J Gastrointest Surg 2016;20:1295-1304.

12. Huang CM, Zhang JR, Zheng CH, Li P, Xie JW, Wang JB, Lin JX, Lu J, Chen QY. A 346 Case Analysis for Laparoscopic Spleen-Preserving No.10 Lymph Node Dissection for Proximal Gastric Cancer: A Single Center Study. PLoS ONE 2014;9:e108480-.
13. Zhu GL, Sun Z, Wang ZN, Xu YY, Huang BJ, Xu Y, Zhu Z, Xu HM. 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.
14. Zhang CH, Wu AW, Zhang LH, Bu ZD, Wu XJ, Zong XL, Shan F, Ji JF. Analysis of splenic hilar lymph node metastasis in advanced gastric cancer and dissection techniques. Zhonghua Wei Chang Wai Ke Za Zhi 2011;14:589-592.
15. Kosuga T, Ichikawa D, Okamoto K, Komatsu S, Shiozaki A, Fujiwara H, Otsuji E. Survival benefits from splenic hilar lymph node dissection by splenectomy in gastric cancer patients: relative comparison of the benefits in subgroups of patients. J Gastric Cancer 2011;14:172-177.
16. Aoyagi K, Kouhuji 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.
17. Shin SH, Jung H, Choi SH, An JY, Choi MG, Noh JH, Sohn TS, Bae JM, Kim S. Clinical Significance of Splenic Hilar Lymph Node Metastasis in Proximal Gastric Cancer. Ann Surg Oncol 2009;16:1304-1309.
18. Sasada S, Ninomiya M, Nishizaki M, Harano M, Ojima Y, Matsukawa H, Aoki H, Shiozaki S, Ohno S, Takakura N. Frequency of lymph node metastasis to the splenic hilus and effect of splenectomy in proximal gastric cancer. Anticancer Res 2009;29:3347-3351.
19. Huang CM, Wang JB, Lu HS, Zheng CH, Li P, Xie JW, Zhang XF. Prognostic analysis of splenectomy in patients with advanced proximal gastric cancer. Zhonghua Wai Ke Za Zhi 2009;47:1483-1486.
20. Kunisaki C, Makino H, Suwa H, Sato T, Oshima T, Nagano Y, Fujii S, Akiyama H, Nomura M, Otsuka Y, Ono HA, Kosaka T, Takagawa R, Ichikawa Y, Shimada H. Impact of Splenectomy in Patients with Gastric Adenocarcinoma of the Cardia. J Gastrointest Surg 2007;11:1039-1044.
21. Ikeguchi M, Kaibara N. Lymph node metastasis at the splenic hilum in proximal gastric cancer. Am Surg 2004;70:645-648.
22. Stefan P, Mönig SP, Collet PH, Baldus SE, Schmackpfeffer K, Schröder W, Thiele J, Dienes HP, Hölscher AH. Splenectomy in proximal gastric cancer: Frequency of lymph node metastasis to the splenic hilus. J Gastrointest Surg 2001;76:89-92.
23. Hong ZL, Chen QY, Zheng CH, Li P, Xie JW, Wang JB, Lin JX, Lu J, Cao LL, Lin M, Tu RH, Huang CM. 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.
24. Lirosi MC, Biondi A, Ricci R. Surgical anatomy of gastric lymphatic drainage. Transl Gastroenterol Hepatol 2017;2:14.
25. Maezawa Y, Aoyama T, Yamada T, Kano K, Hayash T, Sato T, Oshima T, Rino Y, Masuda M, Togata T, Cho H. Priority of lymph node dissection for proximal gastric cancer invading the greater curvature.

J Gastric Cancer 2017;21:569-572.
26. 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.
27. Yura M, Yoshikawa T, Otsuki S, Yamagata Y, Morita S, Katai H, Nishida T. 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.
28. Manzoni GD, Roviello F, Leo AD, Verlato G. And Levels Of Lymphatic Dissection In Gastric Cancer. Surgery in the Multimodal Management of Gastric Cancer 2013:15-23.
29. 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.
30. Nomura E, Sasako M, Yamamoto S, Sano T, Tsujinaka T, Kinoshita T, Furukawa H, Shimizu T, Hiratsuka M, Kobayashi O, Kurokawa Y, Tanigawa N. Risk Factors for Para-aortic Lymph Node Metastasis of Gastric Cancer from a Randomized Controlled Trial of JCOG9501. Jpn J Clin Oncol 2007;37:429-433.
31. Wang L, Liang H, Wang X, Li F, Ding X, Deng J. Risk factors for metastasis to para-aortic lymph nodes in gastric cancer: A single institution study in China. J Surg Res 2013;179:54-59.
32. Luigi M, Fabio R, Alberto B, Mario T, Giampaolo C, Graziano C. Oncologic Effectiveness and Safety of Splenectomy in Total Gastrectomy for Proximal Gastric Carcinoma: Meta-analysis of Randomized Controlled Trials. Anticancer Res 2018;38:3609-3617.
33. 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.
34. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, van Elk P, Obertop H, Gouma DJ, Taat CW. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet 1995;345:745–748.
35. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, Cook P. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. Lancet 1996;347:995–999.
36. Maruyama K, Katai H. Surgical treatment of gastric cancer in Japan, trend from standardization to individualization. Chirurgia (Bucur) 2014;109:722-7.

Tables

Table 1. General characteristics of the included studies

Author	Year	Country	Number	Method	Risk factors	Quality
Jeong O [9]	2018	Korea	665	Retrospective	2,4,5,6,8,9,10,14	High/8
Chen GX [10]	2016	China	243	Retrospective	1,2,3,4,5,6,7,8,9,11,14	High/8
Bian S [11]	2016	China	380	Retrospective	15	High/9
Chen XL [5]	2014	China	205	Retrospective	1,2,3,4,5,6,8,9,11,14	High/8
Huang CM [12]	2014	China	346	Retrospective	1,2,4,5,8,9,14,15	High/9
Zhu GL [13]	2012	China	265	Retrospective	2,5,6,7,8,9,10	High/8
Zhang CH [14]	2011	China	590	Retrospective	1,2,3,4,5,6,15	High/8
Kosuga T [15]	2011	Japan	280	Retrospective	1,2,3,4,5,8	High/8
Aoyagi K [16]	2010	Japan	191	Retrospective	1,2,3,4,5,6,8,9,12,13,14,15	Moderate/7
Shin SH [17]	2009	Korea	319	Retrospective	1,2,3,4,5,6,7,8,9,11,12,13,14	Moderate/7
Sasada S [18]	2009	Japan	201	Retrospective	2,8	Moderate/7
Huang CM [19]	2009	China	237	Retrospective	2,4,5,6,8,9	Moderate/6
Kunisaki C [20]	2007	Japan	118	Retrospective	2,3,4,5,8,12,13,14,15	High/9
Ikeguchi M [21]	2004	Japan	225	Retrospective	9	Moderate/6
Stefan P [22]	2001	Germany	112	Retrospective	2,4,6,7,8,14	Moderate/7

1, Age 2, Gender 3, Tumor size 4, Tumor location 5, Depth of invasion 6, Borrman type 7, Lauren type 8, Differentiation 9, Lymph node metastasis 10,Distance metastasis 11, Neurological invasion 12, Vascular invasion 13, lymphatic invasion 14, TNM stage 15, Positive lymph node metastasis in other groups. High, NOS score> 7 points; Low, NOS score< 6 points; Moderate, 6~ 7 points.

Table 2. Other groups with positive lymph node metastasis.

Regional LN stations (+)	Studies	Effect model	Pooled OR	95% CI	I²	*p value*
No.1	3	Fixed	1.76	1.19- 2.60	0%	<0.01
No.2	4	Random	2.38	1.06- 5.32	80%	0.04
No.3	4	Random	3.65	1.74- 7.67	58%	<0.01
No.4sa	2	Fixed	17.71	10.35- 30.30	0%	<0.01
No.4sb	3	Fixed	6.91	4.50- 10.62	0%	<0.01
No.4d	2	Fixed	4.54	2.32- 8.87	0%	<0.01
No.5	3	Fixed	1.77	0.90- 3.46	0%	0.14
No.6	3	Fixed	1.74	1.03- 2.94	31%	0.04
No.7	4	Random	3.05	1.62- 5.73	64%	<0.01
No.8a	2	Fixed	1.61	0.92- 2.81	0%	0.10
No.9	4	Random	2.83	1.22- 6.56	76%	0.02
No.11	4	Fixed	3.92	2.81- 5.49	47%	<0.01
No.16	2	Fixed	4.34	1.08- 17.39	44%	0.04

Figures

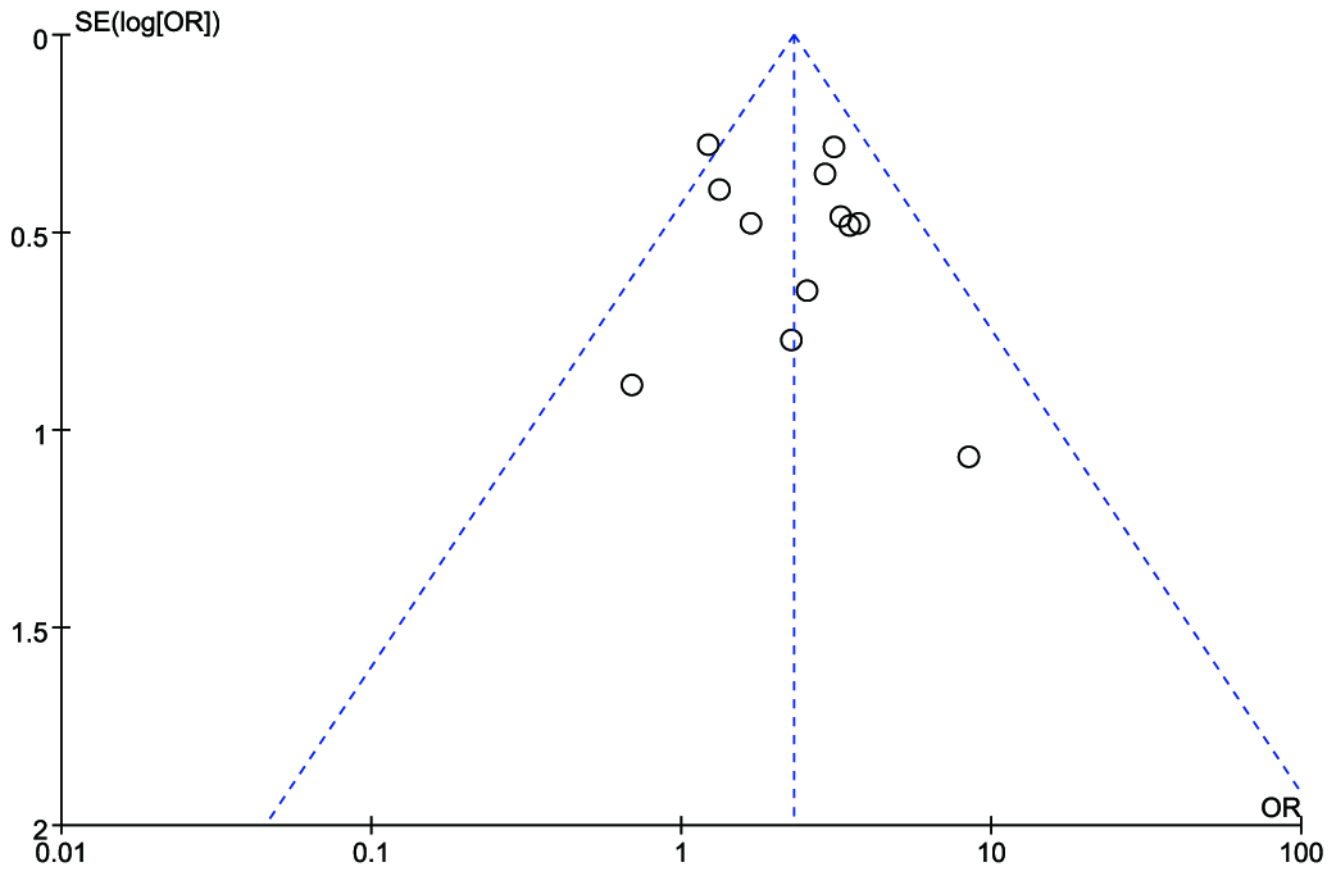

Figure 1

Funnel plot of histological differentiation.

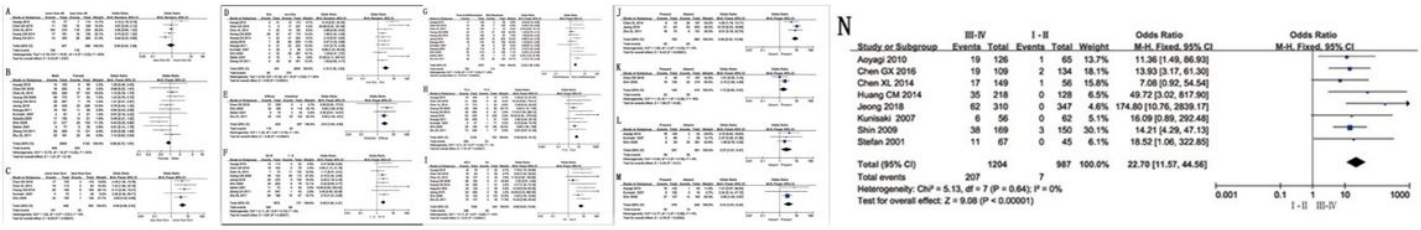

Figure 2

Forest plot analysis of A. age, B. sex, C. tumor size, D. tumor location. E. Lauren's type, F. Borrman type, G. histological differentiation, H. depth of invasion, I. lymph node metastases, J. distance metastasis, K. neurological invasion, L. vascular invasion, M. lymphatic invasion, N. TNM stage.

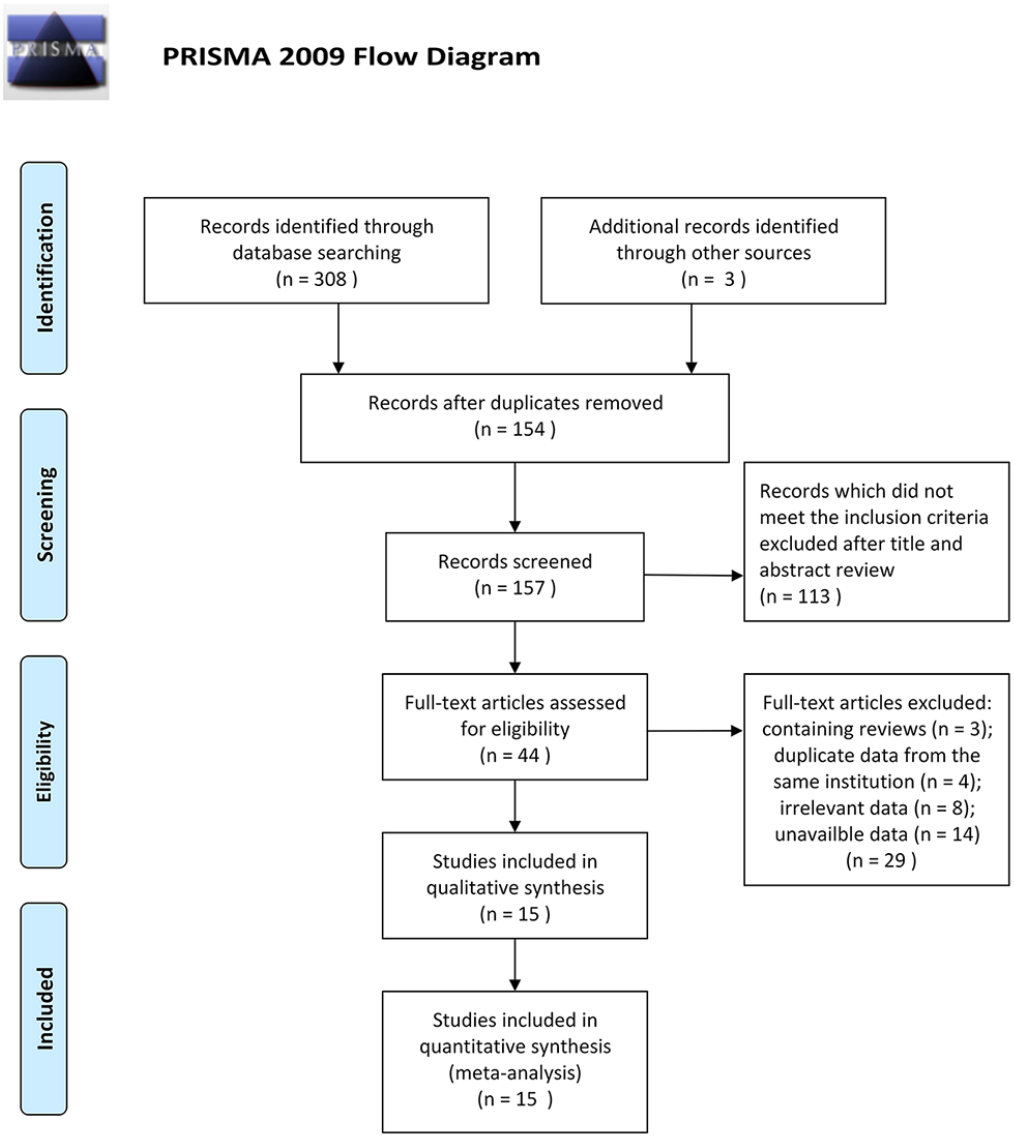

Figure 3

Flow diagram of the search and selection process.