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Misclassification of nodal stage in gastric cancer: 16 lymph nodes is not enough

Sorin Miftode[1] and Helge Bruns[1,2*]

Abstract

Background: In gastric cancer, nodal stage plays an important role. Insufficient lymph node harvesting or incomplete examination may lead to misclassification and affect postoperative strategy and group survival. This study's objective was to determine the minimum number of examined lymph nodes needed in gastric cancer and compare this to the minimum lymph node count according to the current Union for International Cancer Control (UICC) classification using real world data.

Methods: Based on anatomical data, expected mean lymph node counts and their 95% confidence intervals for complete D2 lymphadenectomy were calculated. Using stochastic analysis, a threshold for correct classification in 95% of cases was determined. Survival data of nodal negative gastric cancer patients was extracted from the Surveillance, Epidemiology, and End Results (SEER)-Database for 2010–2017. Patients reaching at least the calculated theoretical threshold were compared to the minimum threshold according to the current UICC classification.

Results: The expected lymph node count was 30 (95% CI: 28–32; range 17–52), corresponding to a 27 lymph nodes. In nodal negative patients with exactly 16 and at least 27 examined lymph nodes, relative 5 year survival was 79 and 89% in T1/T2 and 39 and 64% T3/T4 gastric cancer, respectively. Theoretically, when only 16 lymph nodes are analyzed, nodal negative staging may be incorrect in up to 47% of cases.

Conclusions: A minimum threshold of 16 examined lymph nodes cannot be justified. Retrospective analysis confirmed systematic misclassification of patients with insufficient lymphadenectomy in nodal negative gastric cancer patients. Correct lymphadenectomy and thorough examination of the surgical specimen is mandatory.

Keywords: Gastric cancer, Lymphadenectomy, Surgical oncology

Introduction

In gastric cancer, cancer-specific mortality is decreased in nodal negative patients (Deng and Liang 2014; Huang et al. 2013; Siewert et al. 1998). Consequently, both preoperative and postoperative lymph node stage determines whether a perioperative or adjuvant chemotherapy will be applied (Moehler et al. 2019; Smyth et al. 2016). While preoperative lymph node staging is based on imaging, the postoperative classification depends on surgical technique and adequate pathological examination of the surgical specimen. The current Union for International Cancer Control (UICC) classification recommends a minimum of 16 or more lymph nodes for accurate pathological staging in gastric cancer (Amin et al. 2017).

The true number of lymph nodes that exist in an individual patient is unknown and variable. Anatomical studies provide guidance for what is to be expected. Almost 30 years ago, Wagner et al. published a cadaver-based study and found a mean number of 27 lymph nodes for D2 lymphadenectomy (Wagner et al. 1991). Recently, Sharma et al. have performed a comparable study and found 35 lymph nodes (Sharma et al.

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2005). Herballa et al. identified a mean of 34 lymph nodes in D2-lymphadenectomy in gastric cancer-free individuals (Herbella et al. 2019). Since these studies have been performed in patients without gastric cancer, small lymph nodes may not have been counted. The true number of lymph nodes present in the D2-stations may be higher; due to reactive hyperplasia more lymph nodes may be identifiable in gastric cancer patients (Noguchi et al. 1989). The fact that the real lymph node count may be a lot higher than the minimum number of lymph nodes demanded for Tumor, Nodes and Metastases (TNM)-staging is reflected in the current German guideline (Moehler et al. 2019; Siewert et al. 1998; Wagner et al. 1991). Consequently, the guideline mentions the removal and pathological examination of 25 lymph nodes as a benchmark for an adequate D2-lymphadenectomy (Moehler et al. 2019).

In theory, performing a lymphadenectomy in nodal negative gastric cancer patients is of no oncological use. Nonetheless, a decreased survival has been shown in groups of nodal negative patients with a low number of examined lymph nodes (Martinez-Ramos et al. 2014; MingHua et al. 2020; Zhao et al. 2016). While this may also be due to biological differences between tumors, the most likely cause for most patients in these groups is misclassification. The consequences are dramatic: patients who clearly would benefit from adjuvant chemotherapy might be denied an important and life-prolonging therapy.

To wipe out this uncertainty, all lymph nodes would need to be harvested and examined. This clearly neglects that not all lymph nodes are equally prone to harbor tumor cells. Sentinel lymph nodes and sentinel lymph node stations may indeed justify a limited lymphadenectomy (Hiramatsu et al. 2019; Ohdaira et al. 2009). Based on Japanese registry data, differences in the likelihood of metastases in different lymph node stations have been demonstrated decades ago (Kampschöer et al. 1989). Limited gastric resections and limited lymphadenectomies may be justified in selected patients (Hiramatsu et al. 2019; Ohdaira et al. 2009). In patients with early gastric cancer, the probability of positive lymph nodes is very low and endoscopic resections have shown a cancer-specific mortality comparable to surgical resection (Pourmousavi et al. 2020).

This study's objective was to determine the theoretical threshold needed for pathological examination after D2-lymphadenectomy in gastric cancer based on anatomical findings and to compare these findings to real patient data extracted from the Surveillance, Epidemiology, and End Results (SEER) database.

Methods

Identification of anatomical studies

To determine the total amount of lymph nodes present, relevant anatomical studies were identified using a systematic medline search using the search terms *("lymph node counts" OR "lymph node" OR lymphnode OR lymphadenectomy) AND cadaver AND (gastric OR stomach)*. Only anatomical studies describing lymph node yields from D2-lymphadenectomy according to the Japanese Gastric Cancer Association (JGCA) were included. After data extraction, mean lymph node counts and their respective 95% confidence intervals were calculated for D2 lymphadenectomy in gastric cancer.

Calculation of theoretical thresholds

A hypergeometric distribution was assumed and thresholds for lymph node counts were calculated to identify single positive lymphnodes with a 5% probability of misclassification of nodal negative patients. Moreover, the probability of misclassification was calculated for patients with only 16 examined lymph nodes.

Correlation to real patient data

Data from patients diagnosed with and operated for gastric cancer from 2007 to 2014 was extracted from the SEER database. Relative 5-year survival was calculated for nodal negative patients for stages T1/2 and T3/4 for patients with lymph node counts above the calculated threshold and patients matching the UICC/TNM-criterium of 16 lymph nodes.

Results

Using the search phrase described above, 15 publications were identified. After screening of titles and abstracts, three studies reporting numbers of lymph nodes according to the JGCA classification referring to gastric cancer were identified (Herbella et al. 2019; Sharma et al. 2005; Wagner et al. 1991). In total, data from 66 cadavers was included in the present analysis. The calculated mean number of lymph nodes expected for a complete D2 lymphadenectomy was 30 (95% CI: 28–32; range: 17–52), corresponding to a threshold of at least 29 (95% CI: 27–31) lymph nodes for pathological examination (Fig. 1). Based on the lower range of the confidence interval, a number of 27 lymph nodes was set as threshold for correct nodal negative classification in 95% of patients. When 16 of a total number of 30 lymph nodes are examined, the probability of misclassification is up to 47% (Fig. 2). When lymphadenectomy is seen as part of the surgical therapy, the number of lymph nodes to be resected depends on the probability of metastasation (Fig. 3).

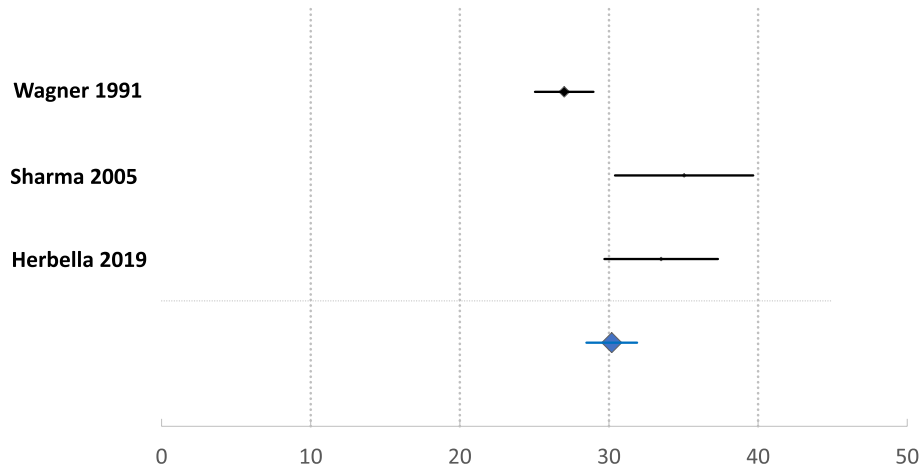

Fig. 1 Lymph node counts for D2 lymphadenectomy. Mean numbers of lymph nodes (individual studies and pooled) and their 95% confidence intervals. Size of dots represents number of cadavers examined

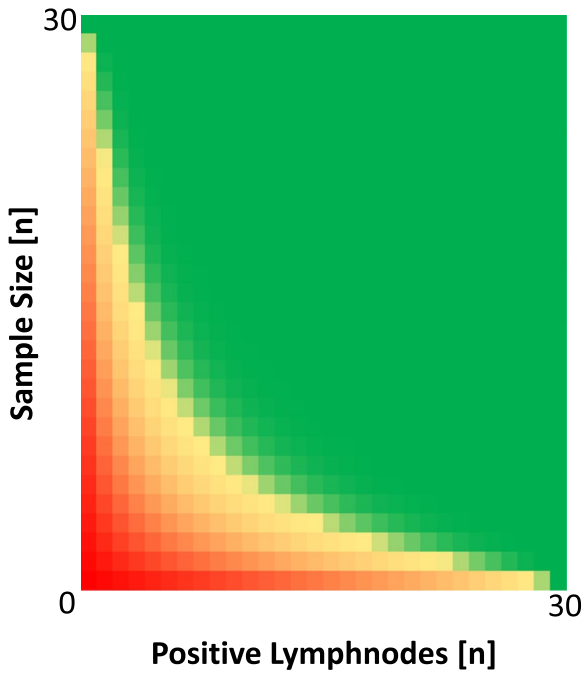

Fig. 2 Probability of misclassification. Under the assumption of equal distribution of positive lymph nodes in the sample, the probability for nodal negative classification is shown for any given number of positive lymph nodes and any given sample size. Green color: 0% probability; red color: 100% misclassification

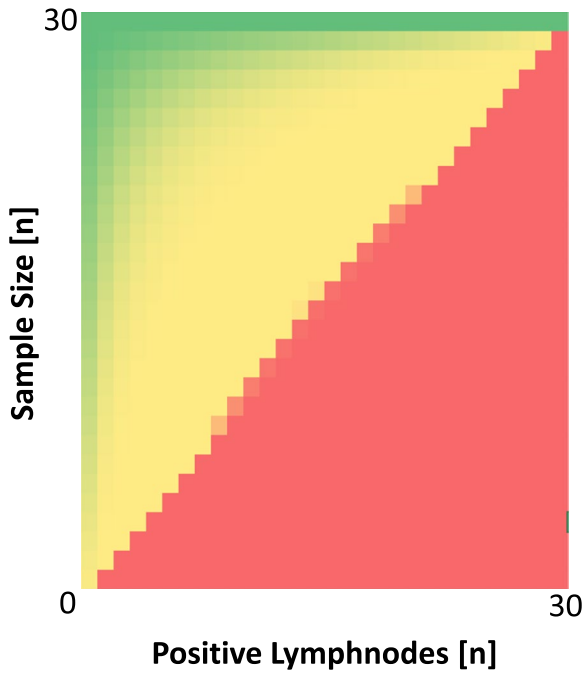

Fig. 3 Extent of Lymphadenectomy needed in a therapeutic context. Extent of D2-lymphadenectomy for complete resection of positive lymph nodes in dependence from number of positive lymph nodes. Green color: 95% probability or more; red color: 0% probability

The analysis of SEER-data of nodal negative patients confirmed the suspected survival difference. While 5 year relative survival in patients with 27 or more examined lymph nodes was 89 and 64% (T1–2 and T3–4), relative survival was 79 and 39% in patients with 16 examined lymph nodes (Table 1, Fig. 4; $p < 0.001$). The proportions of patients with or without neoadjuvant or adjuvant chemotherapy were not different between nodal-negative groups with low and high numbers of lymph nodes.

Table 1 Relative survival in nodal negative patients with different lymph node counts

T-Stage	lymph node count	patients [n]	Median survival [months]	5-year survival [%]
T1/2	16	368	not reached	79
	≥ 27	758	not reached	89
T3/4	16	49	36	39
	≥ 27	105	not reached	64

Discussion

Lymph node stage is an important prognostic factor in gastric cancer (Zhou et al. 2015). A single positive lymph node can make a huge difference in survival probability and affects the choice for perioperative and adjuvant chemotherapy. The extent of lymphadenectomy in gastric cancer has been subject to an ongoing discussion. In today's gastric cancer surgery, D2 lymphadenectomy is considered state of the art (Degiuli et al. 2016). Long term follow-up of the Dutch D1D2 trial demonstrated a decreased locoregional recurrence for patients and decreased gastric cancer related death after D2 lymphadenectomy in comparison to D1 lymphadenectomy (Songun et al. 2010). In nodal negative patients, the extent of lymphadenectomy should not matter since there is no harm to be expected from a negative lymph node, but retrospective analyses and meta analyses have shown an increased survival in nodal negative patients with increased numbers of lymph node counts in the surgical specimen (MingHua et al. 2020; Zhang et al. 2020; Zhou et al. 2015). This is a clear hint to misclassification of patients. In their retrospective analysis, Martinez-Ramos et al. demonstrated equal survival for nodal negative patients with 9 or less examined lymph nodes and nodal positive patients (Martinez-Ramos et al. 2014). Our analysis represents a different approach: since the real number of existing lymph nodes in the D2-stations is not totally clear, we have analyzed data from anatomical studies and used these findings to stratify patients from the SEER-database. We found increased median and longterm survival in nodal negative patients with higher lymph node counts (Table 1, Fig. 4). Our findings are in line with other studies that demonstrated decreased survival in nodal negative patients with low numbers of examined lymph nodes (Erstad et al. 2021; Zhang et al. 2020; Zhao et al. 2021). While the findings are not entirely novel, our approach was quite different. We calculated expected lymph nodes from anatomical data and tested our findings against real-world data from the SEER-database, while e.g. Erstad et al. started from clinical data and employed a ROC analysis (Erstad et al. 2021). Zhao et al. also used clinical data to examine patients at stage T3 and T4 (Zhao et al. 2021). They were also able to show improved disease free survival for patients with 30 or more lymph nodes examined. There is one important pitfall in our study's logic: We have assumed an equal probability of any lymph node to be positive. In the end, any study comparing lymph node counts in nodal negative patients is based on this simplification, which indeed may not be true. Decades ago, Maruyama et al. have already shown different probabilities of metastases for different lymphatic sites depending on preoperative findings in gastric cancer (Kampschöer et al. 1989). Sentinel lymph node biopsies and limited lymphadenectomies represent a Bayesian approach to oncologic surgery and might be an alternative to complete D2-lymphadenectomy (Symeonidis and Tepetes 2018). In breast cancer and in malignant melanoma, decision making based on sentinel lymph node biopsies is considered common sense (Esposito et al. 2017; Gonzalez 2018). While extensive lymphadectomy can be harmful, limited lymphadenectomy can be justified if certainty of a patient being nodal negative can be reached. Quite obviously, an extensive lymphadenectomy in completely nodal negative patients is not necessary. Limited lymphadenectomy could even

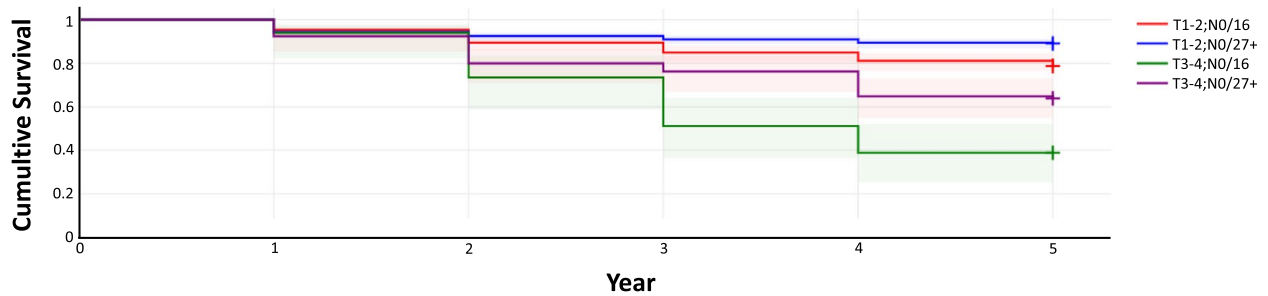

Fig. 4 Relative cumulative survival in nodal negative patients with different lymph node count. Survival function and confidence intervals for T1/2 and T3/4 nodal negative patients with exactly 16 or 27 or more harvested and evaluated lymphnodes

be justified in selected nodal positive patients, given that there is certainty that further lymphadenectomy has no benefit or no positive lymph node is left behind. When not all lymph nodes and lymph node stations are equally likely to harbor metastases, drawing lymph nodes like marbles from an urn with an unknown number of blue and yellow marbles representing positive and negative lymph nodes is a simplification of tumor biology. Surgery does not blindly draw marbles but harvests lymph nodes from selected stations. It seems reasonable to adjust the extent of lymphadenectomy to the T stage. Our data shows a median survival of 36 months in the T3/4 group, when only 16 lymph nodes were examined (Table 1). In all other groups, median survival was not reached. Since influence on the median survival is independent from the patients' T stage, this can be seen as a clear indication that there is a higher probability of positive lymph nodes at a higher T stage. Similar findings have been published more than a decade ago in relation to colon cancer by Gönen et al. who demonstrated that the probability of missing a positive node increased with T-stage and a higher lymph node count was needed to adequately stage a patient to be nodal negative in higher T-stages (Gönen et al. 2009). Thus, a Bayesian approach to lymphadenectomy should be preferred. Extensive or complete regional lymphadenectomy is needed when the probability of skipped lymph nodes is high and therefore sentinel lymph node sites have no consequence. If sentinel sites are not respected for decision making or are not meaningful, a high certainty for a patient being nodal negative can only be achieved when a sufficient number of lymph nodes is being harvested.

Tumor and host biology may also have an impact on the number of lymph nodes harvested and examined. Patients who show a stronger immune response to their tumor disease might have larger lymph node yields. Especially in these patients, tumor biology is more favorable in terms of better survival. To what extent this applies to the patients included in the SEER database and thus has led to a possible bias of the data is unclear. As far as a therapeutic effect of lymphadenectomy is concerned, the number of lymph nodes that need to be resected depends on the number of positive lymph nodes. We have calculated theoretical thresholds for the minimum numbers of lymph nodes in specimens from nodal positive patients (Fig. 3). Quite clearly, the limitation of an equal distribution of metastases between all lymph nodes in the D2-stations still holds true. Under this assumption, a complete D2 lymphadenectomy would be needed when there are 2 or more positive nodes to be sure in 95% of cases to resect all positive nodes. Moreover, the probability to resect all positive lymph nodes when only 16 lymph nodes are taken is below 5% when there are more than 4 positive nodes.

The hard outcome parameters of oncologic surgery are survival and quality of life. Consequently, certainty of lymph node stage does need to be good enough as long as this has implications for therapy and prognosis. "Good enough" certainly is not equal to 100% and may be different depending on tumor biology, life expectancy, risk inherent to surgery, individual anatomical variations, and probability of lymph node metastases.

Taken together, a 16-lymph node threshold is not acceptable because it both neglects stochastic realities and individual variations based on anatomy and probability of metastasation. Future guidelines need to respect these two aspects. It seems important to examine lymph nodes according to their respective stations, leading to an adaptive, Bayesian threshold for the number of lymph nodes demanded.

With a strict focus on the current UICC/TNM guideline and its requirement for examination of at least 16 lymph nodes without respect to different probabilities of metastasation, our study clearly demands a much higher number of lymph nodes to be examined.

Conclusions

In general, all harvested lymph nodes should undergo pathological examination. Quite clearly, this has an impact on group survival and is related to individual prognosis. Lymph node stage has an impact on the choice of adjuvant therapy. Moreover, the number of lymph nodes is the lymphadenectomy's quality control and therefore needed to reach and keep a high standard in surgical technique. While the lymph node counts demanded in most guidelines are insufficient and need to be adjusted, demanding a fixed minimum number of lymph nodes is a simplification of tumor biology and differences in metastatic probability in different stations. A Bayesian approach to lymphadenectomy seems to be promising and realistic.

Abbreviations

CI: Confidence Interval; JGCA: Japanese Gastric Cancer Association; SEER: Surveillance, Epidemiology, and End Results; TNM: Tumor, Nodes and Metastases; UICC: Union for International Cancer Control.

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Authors' contributions

Both authors contributed equally to this manuscript. HB: wrote research protocol, performed analysis of anatomical study data, wrote manuscript; MS: performed analysis of SEER-data, wrote manuscript. The author(s) read and approved the final manuscript.

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Availability of data and materials
The patient data studied are freely available in the Surveillance, Epidemiology, and End Results (SEER) database.

Declarations

Ethics approval and consent to participate
In accordance with the institutional guidelines of the University of Oldenburg, an ethics consultation was conducted by the Medical Ethics Committee. As this is a study on anonymized data, no ethics vote was required and the conduct of the study was approved in its present form.

Consent for publication
According to institutional guidelines, no consent by subjects was needed.

Competing interests
No competing interests.

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References

Amin MB, Edge S, Greene F, et al. AJCC Cancer staging manual, 8. Aufl: Springer International Publishing; 2017.
Degiuli M, De Manzoni G, Di Leo A, et al. Gastric cancer: current status of lymph node dissection. World J Gastroenterol. 2016;22:2875–93. https://doi.org/10.3748/wjg.v22.i10.2875.
Deng J-Y, Liang H. Clinical significance of lymph node metastasis in gastric cancer. World J Gastroenterol. 2014;20:3967–75. https://doi.org/10.3748/wjg.v20.i14.3967.
Erstad DJ, Blum M, Estrella JS, et al. Navigating nodal metrics for node-positive gastric Cancer in the United States: an NCDB-based study and validation of AJCC guidelines. J Natl Compr Cancer Netw. 2021:1–12. https://doi.org/10.6004/jnccn.2021.7038.
Esposito E, Di Micco R, Gentilini OD. Sentinel node biopsy in early breast cancer. A review on recent and ongoing randomized trials. Breast. 2017;36:14–9. https://doi.org/10.1016/j.breast.2017.08.006.
Gönen M, Schrag D, Weiser MR. Nodal staging score: a tool to assess adequate staging of node-negative colon cancer. J Clin Oncol. 2009;27:6166–71. https://doi.org/10.1200/JCO.2009.23.7958.
Gonzalez A. Sentinel lymph node biopsy: past and present implications for the Management of Cutaneous Melanoma with nodal metastasis. Am J Clin Dermatol. 2018;19:24–30. https://doi.org/10.1007/s40257-018-0379-0.
Herbella FAM, Lourenço LG, Bonini AL, et al. Anatomical analysis of gastric lymph nodes in cancer-free individuals. Clin Anat. 2019;32:9–12. https://doi.org/10.1002/ca.23241.
Hiramatsu Y, Takeuchi H, Goto O, et al. Minimally invasive function-preserving Gastrectomy with sentinel node biopsy for early gastric Cancer. Digestion. 2019;99:14–20. https://doi.org/10.1159/000494407.
Huang J, Xu Y, Li M, et al. The prognostic impact of occult lymph node metastasis in node-negative gastric cancer: a systematic review and meta-analysis. Ann Surg Oncol. 2013;20:3927–34. https://doi.org/10.1245/s10434-013-3021-7.
Kampschöer GH, Maruyama K, van de Velde CJ, et al. Computer analysis in making preoperative decisions: a rational approach to lymph node dissection in gastric cancer patients. Br J Surg. 1989;76:905–8. https://doi.org/10.1002/bjs.1800760910.
Martinez-Ramos D, Calero A, Escrig-Sos J, et al. Prognosis for gastric carcinomas with an insufficient number of examined negative lymph nodes. Eur J Surg Oncol. 2014;40:358–65. https://doi.org/10.1016/j.ejso.2013.08.027.
MingHua Z, KeCheng Z, ZhenYu C, et al. Impact of lymph nodes examined on survival in ypN0 gastric Cancer patients: a population-based study. J Gastrointest Surg. 2020. https://doi.org/10.1007/s11605-020-04579-6.
Moehler M, Al-Batran S-E, Andus T, et al. S3-Leitlinie Magenkarzinom – Diagnostik und Therapie der Adenokarzinome des Magens und des ösophagogastralen Übergangs – Langversion 2.0 – August 2019. AWMF-Registernummer: 032/009OL. Z Gastroenterol. 2019;57:1517–632. https://doi.org/10.1055/a-1018-2516.
Noguchi Y, Imada T, Matsumoto A, et al. Radical surgery for gastric cancer. A review of the Japanese experience. Cancer. 1989;64:2053–62 https://doi.org/10.1002/1097-0142(19891115)64:10<2053::aid-cncr2820641014>3.0.co;2-j.
Ohdaira H, Nimura H, Takahashi N, et al. The possibility of performing a limited resection and a lymphadenectomy for proximal gastric carcinoma based on sentinel node navigation. Surg Today. 2009;39:1026–31. https://doi.org/10.1007/s00595-009-3993-x.
Pourmousavi MK, Wang R, Kerdsirichairat T, et al. Comparable Cancer-specific mortality of patients with early gastric Cancer treated with endoscopic therapy Vs surgical resection. Clin Gastroenterol Hepatol. 2020. https://doi.org/10.1016/j.cgh.2020.04.085.
Sharma D, Thakur A, Toppo S, Chandrakar SK. Lymph node counts in indians in relation to lymphadenectomy for carcinoma of the oesophagus and stomach. Asian J Surg. 2005;28:116–20. https://doi.org/10.1016/S1015-9584(09)60274-8.
Siewert JR, Böttcher K, Stein HJ, Roder JD. Relevant prognostic factors in gastric cancer: ten-year results of the German gastric Cancer study. Ann Surg. 1998;228:449–61. https://doi.org/10.1097/00000658-199810000-00002.
Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27:v38–49. https://doi.org/10.1093/annonc/mdw350.
Songun I, Putter H, Kranenbarg EM-K, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol. 2010;11:439–49. https://doi.org/10.1016/S1470-2045(10)70070-X.
Symeonidis D, Tepetes K. Techniques and current role of sentinel lymph node (SLN) concept in gastric Cancer surgery. Front Surg. 2018;5:77. https://doi.org/10.3389/fsurg.2018.00077.
Wagner PK, Ramaswamy A, Rüschoff J, et al. Lymph node counts in the upper abdomen: anatomical basis for lymphadenectomy in gastric cancer. Br J Surg. 1991;78:825–7. https://doi.org/10.1002/bjs.1800780719.
Zhang N, Bai H, Deng J, et al. Impact of examined lymph node count on staging and long-term survival of patients with node-negative stage III gastric cancer: a retrospective study using a Chinese multi-institutional registry with surveillance, epidemiology, and end results (SEER) data validation. Ann Transl Med. 2020;8:1075. https://doi.org/10.21037/atm-20-1358a.
Zhao J, Du F, Zhang Y, et al. Impact on long-term survival of the number of lymph nodes resected in patients with pT1N0 gastric cancer after R0 resection: a multicenter study in China. Medicine (Baltimore). 2016;95:e4420. https://doi.org/10.1097/MD.0000000000004420.
Zhao L, Han W, Yang X, et al. Exceeding 30 ELNs is strongly recommended for pT3-4N0 patients with gastric cancer: a multicenter study of survival, recurrence, and prediction model. Cancer Sci. 2021;112:3266–77. https://doi.org/10.1111/cas.15003.
Zhou Y, Yu F, Wu L, et al. Survival after Gastrectomy in node-negative gastric Cancer: a review and Meta-analysis of prognostic factors. Med Sci Monit. 2015;21:1911–9. https://doi.org/10.12659/MSM.893856.

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