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Editorial Board Member of *World Journal of Clinical Cases*, Marilia Carabotti, MD, PhD, Academic Research, Medical-Surgical Department of Clinical Sciences and Translational Medicine, University Sapienza Rome, Rome 00189, Italy. mariliacarabotti@gmail.com

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MINIREVIEWS

Examined lymph node count for gastric cancer patients after curative surgery

Yi Zeng, Lu-Chuan Chen, Zai-Sheng Ye, Jing-Yu Deng

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Yi Zeng, Lu-Chuan Chen, Zai-Sheng Ye, Department of Gastrointestinal Surgical Oncology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou 350014, Fujian Province, China

Jing-Yu Deng, Department of Gastric Surgery, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin 300202, China

Corresponding author: Jing-Yu Deng, MD, PhD, Chief Doctor, Professor, Department of Gastric Surgery, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Huanhu West Road, Tianjin 300202, China. dengery@126.com

Abstract

Lymph node (LN) metastasis is the most common form of metastasis in gastric cancer (GC). The status and stage of LN metastasis are important indicators that reflect the progress of GC. The number of LN metastases is still the most effective index to evaluate the prognosis of patients in all stages of LN metastasis. Examined LN (ELN) count refers to the number of LNs harvested from specimens by curative gastrectomy for pathological examination. This review summarizes the factors that influence ELN count, including individual and tumor factors, intraoperative dissection factors, postoperative sorting factors, and pathological examination factors. Different ELN counts will lead to prognosis-related stage migration. Fine LN sorting and regional LN sorting are the two most important LN sorting technologies. The most direct and effective way to harvest a large number of LNs is for surgeons to perform *in vitro* fine LN sorting.

Key Words: Stomach; Neoplasm; Lymph node; Metastasis; Prognosis

Core Tip: Examined lymph node (ELN) count refers to the number of lymph nodes harvested from specimens by curative gastrectomy for pathological examination. We herein discussed the factors influencing ELN count and their roles in stage migration and sorting methods.

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INTRODUCTION

Metastasis is one of the lethal biological characteristics of malignant tumor cells. Lymph node (LN) metastasis is the most common form of metastasis in gastric cancer (GC). The proportion of LN metastasis can reach more than 50% in GC with deep submucosal invasion[1]. The status and stage of LN metastasis are important indicators that reflect the progress of GC. LN metastasis can remarkably affect therapeutic effect and clinical prognosis[2]. LN metastasis staging methods that are used to evaluate the prognosis of patients with GC after radical resection include the range of LN metastasis, the number of LN metastases, LN ratio, the maximum diameter of LN metastasis, and the log odds of positive LNs[3-6]. A number of clinical analysis and research results for prognosis evaluation have shown that the number of LN metastases is still the most effective index for the evaluation of the prognosis of patients in all stages of LN metastasis[7-9]. The criteria of LN metastasis (pN) staging of GC in the Union for International Cancer Control and American Joint Commission for Cancer (AJCC) are constantly changing and updating. Therefore, how to accurately evaluate the number of LN metastases is still the focus of clinical attention. The examined LNs (ELNs) used to determine the number of LN metastases are from dissected LNs (DLNs). ELN count refers to the number of LNs harvested from specimens by curative gastrectomy for pathological examination.

This article summarizes the implication of ELN count for patients with GC after curative surgery.

INFLUENCING FACTORS OF ELN COUNT AFTER CURATIVE GASTRECTOMY

The accuracy of the evaluation of LN metastasis depends on standardized LN harvesting and subsequent detailed pathological examination. Therefore, ELN count is affected by the following factors (Table 1).

Individual and tumor factors

Individual differences in immune status, disease stage, and the biological behavior of tumor cells in different patients can lead to a certain difference in the number of perigastric LNs. LNs are derived from the differentiation and development of endothelial cells in lymphatic vessels or lymphatic sac and their surrounding mesenchymal cells in the embryonic period; that is, in theory, LNs can be formed in areas where lymphatic vessels are located. This localization can also be considered a potential reason for the recurrence of local LN metastasis after standardized LN dissection for GC. A variety of tumor-derived driving factors, including multiple antigens, cytokine growth factors and exosomes, can be drained to tumor regional LNs through the lymphatic duct system and then regulate the immune response, remodel lymphatic vessels, and induce microenvironment adaptation and the metastasis and colonization of cancer cells[10]. Dikken *et al*[11] showed that ELN count in female patients with GC after surgery is higher than that in male patients. The difference between the two sexes may be related to the difference in their immune system status. They also showed that ELN count in young patients is higher than that in elderly patients because elderly patients have a weak immune response to tumor; thus, the elderly may be subjected to a more conservative strategy of intraoperative dissection. Kodera *et al*[12] showed that obesity can affect ELN count in patients with GC. ELN count was considerably reduced in surgical patients with body mass index (BMI) ≥ 27 kg/m^2 compared with male patients with BMI < 25 kg/m^2 and female patients with BMI < 22 kg/m^2. Obesity may have a negative impact on ELN count by increasing the difficulty of surgical dissection and LN identification. Tumor stage is also one of the factors that affect the detection of LNs. The T stage of a tumor affects ELN count after surgery[13]. A higher T stage is related to more harvested LNs. Although preoperative chemotherapy can inhibit tumor cells in perigastric LNs to a certain extent and even achieve N-stage downregulation, no evidence shows that it can remarkably affect ELN count[12].

Intraoperative dissection factors

DLN refers to the number of LNs included in the surgical specimens removed from the abdominal cavity of a patient according to the radical range determined by the GC staging of the patient. DLN count is determined by the extent of LN dissection and the number of LNs around the stomach during surgery. D1+ LN dissection is currently the main choice for early GC, and D2 LN dissection should be necessary for advanced resectable GC. The number of LNs around the stomach in total gastrectomy is more than that in subtotal gastrectomy. Therefore, more LNs can be dissected for postoperative

Table 1 Influencing factors of examined lymph node count after curative gastrectomy

Classifications	Factors	Specific
Lymph node harvesting	Individual and tumor factors	Immune status (active/inhibited)[10], sex (female/male)[11], age (young/elderly)[11], body mass index (emaciation/obesity)[12], disease stage (early/advanced)[13], *etc*
	Intraoperative dissection factors	Extent of lymph node dissection (D1/D2)[14], scope of gastrectomy (total/subtotal/partial)[14], operation mode (laparoscopic/open)[15-16], qualification of the surgeons[17-19], *etc*
Examination detail	Postoperative sorting factors	Omission of small lymph nodes[21-22], persons (surgeons/pathologists)[23-24], lymph node sorting methods (fine/regional)[55-56], *etc*
	Pathological examination factors	Special metastasis (extranodal soft tissue/skip metastasis)[25-28], fat clearance technology (alcohol/coniferous oil/formaldehyde)[30-35], dye marker (methylene blue, nanocarbon)[36-38], *etc*

pathological examination. Lu *et al*[14] reported that the average number of LNs removed by subtotal gastrectomy and total gastrectomy are 26 ± 9.6 and 29 ± 10.7 ($P < 0.01$), respectively. In the same way, the total number of LNs dissected in patients with early GC who underwent partial gastrectomy and with preserved function may be decreased because parts of the perigastric LNs do not need to be dissected. With the development of minimally invasive technology, laparoscopic gastrectomy can reduce intraoperative blood loss, accelerate postoperative recovery, and shorten hospital stay. Bouras *et al*[15] showed that the number of LNs detected in laparoscopic surgery is less than that in open surgery (26.7 *vs* 31.4; $P < 0.05$) at the same tumor-node-metastasis (TNM) stage possibly because the extent of LN dissection in laparoscopic surgery is often less than that in open surgery. However, a meta-analysis of 12 studies comparing minimally invasive surgery with open surgery showed that laparoscopic surgery does not reduce the number of LNs detected compared with open surgery[16]. Therefore, the effect of laparoscopic surgery on DLN count needs to be further studied. In addition, qualification of the surgeon has a direct impact on DLN count[17-19].

Postoperative sorting factors

Theoretically, ELN count should not exceed DLN count. A trained person needs to sort the LNs from each group in the perigastric region one by one from the surgical specimens of GC and make corresponding records before sending the harvested LNs for examination. Different sorting methods may lead to different LN counts. Almost all oncologists agree that postoperative factors can directly affect the follow-up diagnosis and treatment of cancer[20]. In the postoperative sample processing, the omission of small LNs will likely cause an error in metastatic LN count, which will directly lead to the downgrading of TNM staging based on the number of metastatic LNs and cannot objectively reflect the actual situation. Noda *et al*[21] showed that 37.9% of LNs with metastasis have a maximum diameter of less than 5 mm; hence, 37.9% of metastatic LNs in GC specimens may be missed if 5 mm LNs are not found. Downstaging will occur in 14.9% and 4.2% of the cases if all nodes less than 6 and 4 mm, respectively, are ignored. Hanna *et al*[22] pointed out that the proportion of smaller LNs in ELNs showed an upward trend with the increase in ELN count. Different countries have differences regarding whether surgeons or pathologists carry out the sorting work after surgery. This work is done by pathologists in most European and American countries, whereas the procedure is done by surgeons in Japan. Bunt *et al*[23] compared the differences in LN detection in Europe, America, and Japan and suggested that the sorting of LNs should be done by surgeons immediately after surgery. The average number of LNs harvested by surgeons after D2 gastrectomy is 60 ± 24.1, which is significantly higher than that (31 ± 16.4) harvested by pathologists ($P < 0.001$). In Japan, the LNs of different groups in the perigastric region are sorted by experienced surgeons immediately after curative resection; therefore, the number of LNs harvested for GC surgery in Japan has always been in the leading position in the world with an average of 39.4[24]. By contrast, some Western pathologists object to post-operative LN sorting because it will destroy the edge of the tumor[22].

Pathological examination factors

LNs are fixed in neutral formaldehyde solution, embedded in paraffin, and sectioned in the pathology department prior to the assessment of LN metastasis. This routine postoperative procedure can directly affect ELN count. The discovery of extranodal soft tissue and skip metastases has led to some controversy on the pathological diagnosis of LN metastasis. Some studies suggest that extranodal soft tissue nodule is a risk factor for the prognosis of patients with GC, and the postoperative survival rate of patients decreases considerably with the increase in the number of extranodal-positive soft tissue nodule[25,26]. Several extranodal soft tissue nodules can be found microscopically. In fact, the structure of LNs is partially or completely destroyed by the proliferation of metastatic GC cells, which makes it impossible to identify them correctly. Therefore, pathologists can only judge them as soft tissue nodules. A similar situation can also be seen in the destruction of LN structure after multiple preoperative radiotherapy. Although the impact of skip metastasis on the prognosis of GC remains controversial, it is still a negative factor affecting the survival of patients. The occurrence of skip metastasis is related to

low DLN count; hence, the number of LNs in a pathological section is difficult to determine[27]. In theory, LNs have occult tumor cells (including micrometastases and isolated tumor cells), but serial sections of LNs are difficult to carried out[28]. Many clinical reports still support that LN micrometastasis should be considered an unfavorable factor affecting the prognosis of patients[29].

In addition, fat clearance technology can also improve the detection rate of pathological LNs[30-33]. Candela *et al*[34] reported a fat clearance technique applied to the treatment of GC specimens after operation. The average ELN count was increased from 20 to 36 by using different concentrations of alcohol and coniferous oil as pretreatment before staining, which improved the accuracy of staging. The ELN count by this method is higher than that reported by Japanese scholars in the same period, and this method has obvious advantages in detecting smaller LNs. Aoyama *et al*[35] treated samples with 10% formaldehyde aqueous solution containing methylene blue for 48 h. The LNs and lymphatic network were clearly displayed; therefore, the ELN count was increased (43.4 *vs* 33.6; $P = 0.005$), and the efficiency of LN detection was improved (1.49/min *vs* 1.12/min; $P = 0.010$). A meta-analysis included 27 studies on the application of fat clearance and methylene blue staining in the detection of LNs in gastrointestinal tumor samples[36]. The results showed that compared with the traditional manual method, the two techniques could increase ELN count, harvest more metastatic-positive LNs and improve the identification of small LNs. Carbon nanoparticles can be selectively absorbed by lymphatic vessels. Li *et al*[37] applied nanocarbon to the surgery of advanced GC, which could increase ELN count (38.33 in the nanocarbon group and 28.27 in the control group, $P = 0.041$) and identify smaller LNs (the maximum diameters of LNs in the nanocarbon and control groups were 3.32 and 4.30 mm, respectively [$P = 0.023$]). In addition, indocyanine green can be used as a tracer for LNs in GC[38]. However, indocyanine green depends on special laparoscopic equipment during the surgery and cannot develop color in pathological sorting.

ELN COUNT AND LN STAGE MIGRATION

The depth of primary invasion (pT) and distant metastasis (M) can be directly determined by pathologists under a high-power microscope in the current AJCC postoperative pathological staging (pTNM) system. The final pathological report of LN metastasis stage may have errors, such as the Will–Roger phenomenon, due to the existence of LN dissection range, ELN count, disease stage, patient individuality, and other factors[39]. Will–Roger phenomenon refers to the positive correlation between the number of LN metastases and the range of LN dissection. LN stage migration can be gradually reduced or avoided through an increase in LN dissection range. Therefore, ELN count for curative gastrectomy is closely related to LN stage migration. The clinical data of a large sample of patients undergoing radical gastrectomy in a single center in China showed that the number of metastatic LNs is positively correlated with an increase in ELN count[40]. The survival data of 7620 patients with GC from three centers in China suggest a substantial migration of postoperative LN stage (pN stage), especially in early-stage patients with less than 15 LNs (pT1NanyM0 stage) and advanced-stage patients with less than 35 LNs (pT2–4NanyM0 stage); hence, the 5-year survival rate of patients with different stages in China is obviously lower than that in Japan, South Korea, and other medical centers[7]. Sano *et al*[24] found that the proportion of patients with pN3b (8.7%) from East Asian countries except Japan and South Korea (including 979 patients in China) with a low number of LNs (24.8 per case) is almost twice as high as those in Japan and South Korea. Some studies have shown that the survival rate of patients with positive LN metastasis whose ELN count is more than 30 is the highest in the same subgroup of patients with pN stage; this prognosis-related stage migration is also caused by difference in ELN count[41].

In 2005, Smith used the Surveillance, Epidemiology and End Results database to analyze 3814 patients with GC with equal staging of T1–2N0, T1–2N1, T3N0, and T3N1[42]. The survival time of patients with more than 15 LNs detected was better than that of patients with less than 15 LNs detected at the same stage. The 5-year survival rate increased by 5.7%–10.9% for every 10 additional LNs. Volpe *et al*[43] analyzed 114 patients who underwent proximal gastrectomy (including D1, D1+, D2, and D2+) and found no remarkable relationship between ELN count and overall survival. However, for patients who underwent extended radical gastrectomy (D2 or D2+), the median survival time of patients with more than 15 LNs detected increased from 25 to 42 mo. In 2009, the authors also found that according to the 6th edition of TNM staging of GC, patients with no less than 15 LNs have remarkably longer postoperative overall survival time, disease-free survival time, or survival time than patients with less than 15 LNs after recurrence[44]. We also found that increased ELN count is an independent factor affecting the survival time of patients with GC who only have perigastric LN metastasis (only LN metastasis on the greater curvature and lesser curvature side)[45]. Therefore, in the 7th edition of the TNM staging of GC, the recommended number of LNs was changed to no less than 16. The reason is that patients with pN3b stage need at least 16 LN metastases confirmed by pathology.

However, 16 LNs are not the ultimate limit. Kim *et al*[46] pointed out that for patients with advanced differentiated GC, the prognosis when 25 and 40 LNs were used as the cut-off values of ELN count was also different. The study group with more ELN count had a longer average survival time compared

with patients with less than 25 and 40 LNs detected. Chen *et al*[47] analyzed 1363 patients with curative gastrectomy and found that ELN count and N stage are independent prognostic factors. The 5-year survival rates of N2 and N3 patients with more than 25 LNs detected are 58.59% and 32.77%, respectively, which are remarkably better than 52.48% and 21.67% of patients, respectively, with 15–24 LNs detected in the same period. The clinical data of 7620 patients with GC undergoing curative gastrectomy in three medical centers in China showed that for the same pN stage (except pN0 stage), the 5-year survival rate of patients with GC who have more than 30 LNs is 8%–15% higher than that of patients with less than 30 LNs[7].

For patients with negative LNs, we demonstrated that insufficient ELN count may be a potential risk factor for the postoperative recurrence of GC[48]. An ELN count less than 16 means higher local recurrence rate and peritoneal metastasis rate[49]. Several studies have confirmed that ELN count can affect the prognosis of patients with pN0[49-51]. ELN count is an independent prognostic factor particularly for patients with stage III pN0 GC[52,53]. In 2017, authors compared the clinicopathological data of pN0 patients in Tianjin Medical University Cancer Institute and Hospital (TJMUCH) and Tokyo Medical University Hospital (TMUH) in the past 10 years and found that ELN count in patients with pN0 GC in TMUH reached 34.84, which was much higher than that in TJMUCH, and the postoperative survival rate of patients was also significantly higher than that in TJMUCH ($P < 0.001$)[8]. Further analysis showed that the postoperative survival rate of patients with pN0 GC in TMUH, also increased by 57% with the increase of ELN count. In addition, we also confirmed that increased ELN count can reduce or prevent stage migration in pN0 patients[41].

LN SORTING TECHNOLOGY

LNs need to be sorted out from the whole specimen obtained by radical gastrectomy according to the location of LN regions in each group for postoperative pathological examination, which can provide fine information for the number and location of LN metastases. The most important factor that can reflect ELN count is the operation of LN sorting. Sorting LNs from fresh specimens during or immediately after surgery requires a detailed understanding and affirmation of the whole scope of surgical dissection. Detailed records of LNs after sorting can provide clear information for postoperative pathology to detect the location of LN metastasis. In addition, perigastric LNs are easier to harvest from fresh samples, especially in fat and soft tissue specimens, than LNs isolated after neutral formaldehyde immersion.

The two main sorting methods are fine LN sorting and regional LN sorting. ELN count in the fine LN sorting group is much higher than that in the regional LN sorting group with the same pT, pN, or pTNM stage ($P < 0.001$). The number of metastatic LNs in the fine LN sorting group was significantly higher than that in the regional LN sorting group ($P < 0.001$)[54].

Fine LN sorting

Japanese scholars have been following "fine sorting," that is, LNs are separated from GC samples and then separated from the soft tissue one by one according to the location of each group of LNs around the stomach and the surrounding soft tissue. This method can harvest a larger number of LNs, which helps in judging the extent of the local invasion of the disease and also provides objective evidence for postoperative pathology report to evaluate the quality of surgery. Schmidt *et al*[55] pointed out that on the basis of D2 LN dissection, the fine sorting of LNs from postoperative *ex vivo* specimens can make the average ELN count in each GC patient reach 40; thus, accurate LN staging can be obtained for the prognosis evaluation of patients. According to the latest research results of the Sloan Caitlin Memorial Cancer Centre, ELN count by the fine LN sorting of *ex vivo* specimens by surgeons can be significantly increased (30 *vs* 21; $P < 0.0001$) compared with regional sorting or sorting by pathologists[56]. Many scholars have explored a series of methods, including fat clearance and intraoperative marker staining, to achieve more precise LN sorting[34,57-61]. These methods provide more comprehensive information for the postoperative evaluation of patients with LN metastasis; however, they take a long time, may require toxic reagents, and need to be completed in the fume hood and could be difficult for beginners. In general, the most direct and effective way to harvest a large number of LNs is for surgeons to perform *in vitro* fine LN sorting.

Regional LN sorting

Some scholars in other countries directly separate and label each group of LNs around the stomach from the GC samples together with the surrounding soft tissues instead of separating each group of LNs from the soft tissues one by one. This method saves time. However, the pathologist needs to separate the LNs one by one. Theoretically, a certain stage migration occurs in postoperative LNs metastasis. Hanna *et al* [22] reported a systematic fat blocking and microscopic search method for regional LN sorting to improve the number of regional LNs. In this method, the pathologist obtains all the perigastric, periesophageal, and periduodenal fat from the specimen (the fat in the greater omentum is not treated); removes the larger LNs; divides the remaining fat into blocks and obtains single stained hematoxylin

and eosin slices from each block to examine the LNs under a light microscope. This method can detect more LNs compared with the ordinary manual LN sorting method (66 ± 21 *vs* 50 ± 20; $P < 0.05$), but it also has obvious disadvantages. It increases the cost of pathological examination and cannot determine the number of LNs in each group; therefore, its popularization and application are limited.

CONCLUSION

At present, the number of LN metastases is still the most effective index to evaluate the prognosis of patients. Accuracy of the evaluation of LN metastasis depends on the standardized harvesting of LNs and subsequent detailed pathological analysis. Different ELN counts will lead to prognosis-related stage migration. Fine LN sorting and regional LN sorting are the two most important LN sorting technologies. Although ELN count is affected by many factors, the most direct and effective way to harvest a large number of LNs is for surgeons to perform *in vitro* fine LN sorting.

FOOTNOTES

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ORCID number: Yi Zeng 0000-0001-9144-8414; Lu-Chuan Chen 0000-0003-3362-447X; Zai-Sheng Ye 0000-0001-9881-6400; Jing-Yu Deng 0000-0003-4299-1327.

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REFERENCES

1 **Wang J**, Dang P, Raut CP, Pandalai PK, Maduekwe UN, Rattner DW, Lauwers GY, Yoon SS. Comparison of a lymph node ratio-based staging system with the 7th AJCC system for gastric cancer: analysis of 18,043 patients from the SEER database. *Ann Surg* 2012; **255**: 478-485 [PMID: 22330040 DOI: 10.1097/SLA.0b013e31824857e2]
2 **Nitti D**, Marchet A, Olivieri M, Ambrosi A, Mencarelli R, Belluco C, Lise M. Ratio between metastatic and examined lymph nodes is an independent prognostic factor after D2 resection for gastric cancer: analysis of a large European monoinstitutional experience. *Ann Surg Oncol* 2003; **10**: 1077-1085 [PMID: 14597447 DOI: 10.1245/aso.2003.03.520]
3 **Cheong O**, Oh ST, Kim BS, Yook JH, Kim JH, Im JT, Park GC. Large metastatic lymph node size, especially more than 2 cm: independent predictor of poor prognosis in node-positive gastric carcinoma. *World J Surg* 2008; **32**: 262-266 [PMID: 18064519 DOI: 10.1007/s00268-007-9158-4]
4 **Deng J**, Liang H. Discussion of the applicability of positive lymph node ratio as a proper N-staging for predication the prognosis of gastric cancer after curative surgery plus extended lymphadenectomy. *Ann Surg* 2012; **256**: e35-6; author reply e37 [PMID: 23154399 DOI: 10.1097/SLA.0b013e3182769545]
5 **Deng J**, Liang H, Sun D, Pan Y. The prognostic analysis of lymph node-positive gastric cancer patients following curative resection. *J Surg Res* 2010; **161**: 47-53 [PMID: 19783008 DOI: 10.1016/j.jss.2008.12.019]
6 **Liu H**, Deng J, Zhang R, Hao X, Jiao X, Liang H. The RML of lymph node metastasis was superior to the LODDS for evaluating the prognosis of gastric cancer. *Int J Surg* 2013; **11**: 419-424 [PMID: 23541652 DOI: 10.1016/j.ijsu.2013.03.009]
7 **Deng J**, Liu J, Wang W, Sun Z, Wang Z, Zhou Z, Xu H, Liang H. Validation of clinical significance of examined lymph node count for accurate prognostic evaluation of gastric cancer for the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system. *Chin J Cancer Res* 2018; **30**: 477-491 [PMID: 30510359 DOI: 10.21147/j.issn.1000-9604.2018.05.01]
8 **Deng J**, Yamashita H, Seto Y, Liang H. Increasing the Number of Examined Lymph Nodes is a Prerequisite for Improvement in the Accurate Evaluation of Overall Survival of Node-Negative Gastric Cancer Patients. *Ann Surg Oncol* 2017; **24**: 745-753 [PMID: 27770340 DOI: 10.1245/s10434-016-5513-8]
9 **Dong Y**, Qiu Y, Deng J, Wang W, Sun Z, Wang Z, Zhou Z, Xu H, Liang H. Insufficient examined lymph node count

underestimates staging in pN3a patients after curative gastrectomy: a multicenter study with external validation. *J Cancer Res Clin Oncol* 2020; **146**: 515-528 [PMID: 31813005 DOI: 10.1007/s00432-019-03081-0]

10 **Sleeman JP**. The lymph node pre-metastatic niche. *J Mol Med (Berl)* 2015; **93**: 1173-1184 [PMID: 26489604 DOI: 10.1007/s00109-015-1351-6]

11 **Dikken JL**, van Grieken NC, Krijnen P, Gönen M, Tang LH, Cats A, Verheij M, Brennan MF, van de Velde CJ, Coit DG. Preoperative chemotherapy does not influence the number of evaluable lymph nodes in resected gastric cancer. *Eur J Surg Oncol* 2012; **38**: 319-325 [PMID: 22261085 DOI: 10.1016/j.ejso.2011.12.016]

12 **Kodera Y**, Ito S, Yamamura Y, Mochizuki Y, Fujiwara M, Hibi K, Ito K, Akiyama S, Nakao A. Obesity and outcome of distal gastrectomy with D2 lymphadenectomy for carcinoma. *Hepatogastroenterology* 2004; **51**: 1225-1228 [PMID: 15239284]

13 **Cunningham D**, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; **355**: 11-20 [PMID: 16822992 DOI: 10.1056/NEJMoa055531]

14 **Lu J**, Wang W, Zheng CH, Fang C, Li P, Xie JW, Wang JB, Lin JX, Chen QY, Cao LL, Lin M, Huang CM, Zhou ZW. Influence of Total Lymph Node Count on Staging and Survival After Gastrectomy for Gastric Cancer: An Analysis From a Two-Institution Database in China. *Ann Surg Oncol* 2017; **24**: 486-493 [PMID: 27619942 DOI: 10.1245/s10434-016-5494-7]

15 **Bouras G**, Lee SW, Nomura E, Tokuhara T, Tsunemi S, Tanigawa N. Comparative analysis of station-specific lymph node yield in laparoscopic and open distal gastrectomy for early gastric cancer. *Surg Laparosc Endosc Percutan Tech* 2011; **21**: 424-428 [PMID: 22146165 DOI: 10.1097/SLE.0b013e3182367dee]

16 **Straatman J**, van der Wielen N, Cuesta MA, de Lange-de Klerk ES, Jansma EP, van der Peet DL. Minimally Invasive Versus Open Total Gastrectomy for Gastric Cancer: A Systematic Review and Meta-analysis of Short-Term Outcomes and Completeness of Resection : Surgical Techniques in Gastric Cancer. *World J Surg* 2016; **40**: 148-157 [PMID: 26350821 DOI: 10.1007/s00268-015-3223-1]

17 **Kang SY**, Lee SY, Kim CY, Yang DH. Comparison of Learning Curves and Clinical Outcomes between Laparoscopy-assisted Distal Gastrectomy and Open Distal Gastrectomy. *J Gastric Cancer* 2010; **10**: 247-253 [PMID: 22076193 DOI: 10.5230/jgc.2010.10.4.247]

18 **Zhao LY**, Zhang WH, Sun Y, Chen XZ, Yang K, Liu K, Chen XL, Wang YG, Song XH, Xue L, Zhou ZG, Hu JK. Learning curve for gastric cancer patients with laparoscopy-assisted distal gastrectomy: 6-year experience from a single institution in western China. *Medicine (Baltimore)* 2016; **95**: e4875 [PMID: 27631257 DOI: 10.1097/MD.0000000000004875]

19 **Zhou D**, Quan Z, Wang J, Zhao M, Yang Y. Laparoscopic-assisted versus open distal gastrectomy with D2 lymph node resection for advanced gastric cancer: effect of learning curve on short-term outcomes. a meta-analysis. *J Laparoendosc Adv Surg Tech A* 2014; **24**: 139-150 [PMID: 24625347 DOI: 10.1089/lap.2013.0481]

20 **Ajani JA**. Operate on my stomach cancer? *J Clin Oncol* 2004; **22**: 1763-4; author reply 1764 [PMID: 15118003 DOI: 10.1200/JCO.2004.99.277]

21 **Noda N**, Sasako M, Yamaguchi N, Nakanishi Y. Ignoring small lymph nodes can be a major cause of staging error in gastric cancer. *Br J Surg* 1998; **85**: 831-834 [PMID: 9667718 DOI: 10.1046/j.1365-2168.1998.00691.x]

22 **Hanna GB**, Amygdalos I, Ni M, Boshier PR, Mikhail S, Lloyd J, Goldin R. Improving the standard of lymph node retrieval after gastric cancer surgery. *Histopathology* 2013; **63**: 316-324 [PMID: 23837447 DOI: 10.1111/his.12167]

23 **Bunt AM**, Hermans J, van de Velde CJ, Sasako M, Hoefsloot FA, Fleuren G, Bruijn JA. Lymph node retrieval in a randomized trial on western-type versus Japanese-type surgery in gastric cancer. *J Clin Oncol* 1996; **14**: 2289-2294 [PMID: 8708719 DOI: 10.1200/JCO.1996.14.8.2289]

24 **Sano T**, Coit DG, Kim HH, Roviello F, Kassab P, Wittekind C, Yamamoto Y, Ohashi Y. Proposal of a new stage grouping of gastric cancer for TNM classification: International Gastric Cancer Association staging project. *Gastric Cancer* 2017; **20**: 217-225 [PMID: 26897166 DOI: 10.1007/s10120-016-0601-9]

25 **Guo J**, Pan Y, Guo X, Sun C, Jin J, Zhang N, Liang H, Deng J. Effect of the number of positive niduses in extranodal soft tissues on the overall survival of gastric cancer patients. *Int J Clin Exp Pathol* 2017; **10**: 11090-11097 [PMID: 31966457]

26 **Jiang N**, Deng JY, Ding XW, Ke B, Liu N, Liang H. Node-extranodal soft tissue stage based on extranodal metastasis is associated with poor prognosis of patients with gastric cancer. *J Surg Res* 2014; **192**: 90-97 [PMID: 24953988 DOI: 10.1016/j.jss.2014.05.053]

27 **Choi YY**, An JY, Guner A, Kang DR, Cho I, Kwon IG, Shin HB, Hyung WJ, Noh SH. Skip lymph node metastasis in gastric cancer: is it skipping or skipped? *Gastric Cancer* 2016; **19**: 206-215 [PMID: 25708370 DOI: 10.1007/s10120-015-0472-5]

28 **Tavares A**, Monteiro-Soares M, Viveiros F, Maciel Barbosa J, Dinis-Ribeiro M. Occult Tumor Cells in Lymph Nodes of Patients with Gastric Cancer: A Systematic Review on Their Prevalence and Predictive Role. *Oncology* 2015; **89**: 245-254 [PMID: 26160338 DOI: 10.1159/000433543]

29 **Lee CM**, Cho JM, Jang YJ, Park SS, Park SH, Kim SJ, Mok YJ, Kim CS, Kim JH. Should lymph node micrometastasis be considered in node staging for gastric cancer? *Ann Surg Oncol* 2015; **22**: 765-771 [PMID: 25201506 DOI: 10.1245/s10434-014-4073-z]

30 **Cohen SM**, Wexner SD, Schmitt SL, Nogueras JJ, Lucas FV. Effect of xylene clearance of mesenteric fat on harvest of lymph nodes after colonic resection. *Eur J Surg* 1994; **160**: 693-697 [PMID: 7888471]

31 **Koren R**, Paz A, Konichezsky M, Sadikov E, Klein B, Livne P, Gal R. Lymph node revealing solution: a rapid method for the fixation of cystectomy specimens. *Pathol Res Pract* 1999; **195**: 77-80 [PMID: 10093825 DOI: 10.1016/S0344-0338(99)80074-0]

32 **Prabhudesai AG**, Dalton R, Kumar D, Finlayson CJ. Mechanised one-day fat clearance method to increase the lymph node yield in rectal cancer specimens. *Br J Biomed Sci* 2005; **62**: 120-123 [PMID: 16196457 DOI: 10.1080/09674845.2005.11732697]

33 **Scott KW**, Grace RH. Detection of lymph node metastases in colorectal carcinoma before and after fat clearance. *Br J Surg* 1989; **76**: 1165-1167 [PMID: 2688803 DOI: 10.1002/bjs.1800761118]

34 **Candela FC**, Urmacher C, Brennan MF. Comparison of the conventional method of lymph node staging with a comprehensive fat-clearing method for gastric adenocarcinoma. *Cancer* 1990; **66**: 1828-1832 [PMID: 2208038 DOI: 10.1002/1097-0142(19901015)66:8<1828::aid-cncr2820660830>3.0.co;2-z]

35 **Aoyama T**, Fujikawa H, Cho H, Ogata T, Shirai J, Hayashi T, Rino Y, Masuda M, Oba MS, Morita S, Yoshikawa T. A methylene blue-assisted technique for harvesting lymph nodes after radical surgery for gastric cancer: a prospective, randomized, controlled study. *Am J Surg Pathol* 2015; **39**: 266-273 [PMID: 25356528 DOI: 10.1097/PAS.0000000000000336]

36 **Abbassi-Ghadi N**, Boshier PR, Goldin R, Hanna GB. Techniques to increase lymph node harvest from gastrointestinal cancer specimens: a systematic review and meta-analysis. *Histopathology* 2012; **61**: 531-542 [PMID: 23551433 DOI: 10.1111/j.1365-2559.2012.04357.x]

37 **Li Z**, Ao S, Bu Z, Wu A, Wu X, Shan F, Ji X, Zhang Y, Xing Z, Ji J. Clinical study of harvesting lymph nodes with carbon nanoparticles in advanced gastric cancer: a prospective randomized trial. *World J Surg Oncol* 2016; **14**: 88 [PMID: 27009101 DOI: 10.1186/s12957-016-0835-3]

38 **Takahashi N**, Nimura H, Fujita T, Yamashita S, Mitsumori N, Yanaga K. Quantitative assessment of visual estimation of the infrared indocyanine green imaging of lymph nodes retrieved at sentinel node navigation surgery for gastric cancer. *BMC Surg* 2016; **16**: 35 [PMID: 27245664 DOI: 10.1186/s12893-016-0152-3]

39 **de Manzoni G**, Verlato G, Roviello F, Morgagni P, Di Leo A, Saragoni L, Marrelli D, Kurihara H, Pasini F. The new TNM classification of lymph node metastasis minimises stage migration problems in gastric cancer patients. *Br J Cancer* 2002; **87**: 171-174 [PMID: 12107838 DOI: 10.1038/sj.bjc.6600432]

40 **Deng J**, Liang H, Sun D, Wang D, Pan Y. Suitability of 7th UICC N stage for predicting the overall survival of gastric cancer patients after curative resection in China. *Ann Surg Oncol* 2010; **17**: 1259-1266 [PMID: 20217252 DOI: 10.1245/s10434-010-0939-x]

41 **Gu P**, Deng J, Wang W, Wang Z, Zhou Z, Xu H, Liang H. Impact of the number of examined lymph nodes on stage migration in node-negative gastric cancer patients: a Chinese multi-institutional analysis with propensity score matching. *Ann Transl Med* 2020; **8**: 938 [PMID: 32953738 DOI: 10.21037/atm-19-4727]

42 **Smith DD**, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. *J Clin Oncol* 2005; **23**: 7114-7124 [PMID: 16192595 DOI: 10.1200/JCO.2005.14.621]

43 **Volpe CM**, Driscoll DL, Douglass HO Jr. Outcome of patients with proximal gastric cancer depends on extent of resection and number of resected lymph nodes. *Ann Surg Oncol* 2000; **7**: 139-144 [PMID: 10761793 DOI: 10.1007/s10434-000-0139-1]

44 **Deng JY**, Liang H, Sun D, Pan Y, Zhang RP, Wang BG, Zhan HJ. Outcome in relation to numbers of nodes harvested in lymph node-positive gastric cancer. *Eur J Surg Oncol* 2009; **35**: 814-819 [PMID: 19111430 DOI: 10.1016/j.ejso.2008.11.007]

45 **Deng J**, Liang H, Sun D, Pan Y, Liu Y, Wang D. Extended lymphadenectomy improvement of overall survival of gastric cancer patients with perigastric node metastasis. *Langenbecks Arch Surg* 2011; **396**: 615-623 [PMID: 21380618 DOI: 10.1007/s00423-011-0753-3]

46 **Kim YI**. Does the retrieval of at least 15 lymph nodes confer an improved survival in patients with advanced gastric cancer? *J Gastric Cancer* 2014; **14**: 111-116 [PMID: 25061538 DOI: 10.5230/jgc.2014.14.2.111]

47 **Chen HN**, Chen XZ, Zhang WH, Chen XL, Yang K, Liu JP, Zhang B, Chen ZX, Chen JP, Zhou ZG, Hu JK. Necessity of harvesting at least 25 lymph nodes in patients with stage N2-N3 resectable gastric cancer: a 10-year, single-institution cohort study. *Medicine (Baltimore)* 2015; **94**: e620 [PMID: 25761190 DOI: 10.1097/MD.0000000000000620]

48 **Deng J**, Liang H, Sun D, Zhang R, Zhan H, Wang X. Prognosis of gastric cancer patients with node-negative metastasis following curative resection: outcomes of the survival and recurrence. *Can J Gastroenterol* 2008; **22**: 835-839 [PMID: 18925308 DOI: 10.1155/2008/761821]

49 **Jiao XG**, Deng JY, Zhang RP, Wu LL, Wang L, Liu HG, Hao XS, Liang H. Prognostic value of number of examined lymph nodes in patients with node-negative gastric cancer. *World J Gastroenterol* 2014; **20**: 3640-3648 [PMID: 24707149 DOI: 10.3748/wjg.v20.i13.3640]

50 **Baiocchi GL**, Tiberio GA, Minicozzi AM, Morgagni P, Marrelli D, Bruno L, Rosa F, Marchet A, Coniglio A, Saragoni L, Veltri M, Pacelli F, Roviello F, Nitti D, Giulini SM, De Manzoni G. A multicentric Western analysis of prognostic factors in advanced, node-negative gastric cancer patients. *Ann Surg* 2010; **252**: 70-73 [PMID: 20562605 DOI: 10.1097/SLA.0b013e3181e4585e]

51 **Xu D**, Huang Y, Geng Q, Guan Y, Li Y, Wang W, Yuan S, Sun X, Chen Y, Li W, Zhou Z, Zhan Y. Effect of lymph node number on survival of patients with lymph node-negative gastric cancer according to the 7th edition UICC TNM system. *PLoS One* 2012; **7**: e38681 [PMID: 22723875 DOI: 10.1371/journal.pone.0038681]

52 **Zhang N**, Bai H, Deng J, Wang W, Sun Z, Wang Z, Xu H, Zhou Z, Liang H. 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 [PMID: 33145294 DOI: 10.21037/atm-20-1358a]

53 **Zhang N**, Deng J, Wang W, Sun Z, Wang Z, Xu H, Zhou Z, Liang H. Negative lymph node count as an independent prognostic factor in stage III patients after curative gastrectomy: A retrospective cohort study based on a multicenter database. *Int J Surg* 2020; **74**: 44-52 [PMID: 31874262 DOI: 10.1016/j.ijsu.2019.12.018]

54 **Zhang N**, Deng J, He W, Liu Y, Wang X, Ding X, Zhang R, Liang H. Clinical value of standardized procedures of fine lymph node sorting from gastric cancer samples after curative resection: a study of 727 cases. *Chin J Clin Oncol* 2019; **46**: 22-27 [DOI: 10.3969/j.issn.1000-8179.2019.01.911]

55 **Schmidt B**, Chang KK, Maduekwe UN, Look-Hong N, Rattner DW, Lauwers GY, Mullen JT, Yang HK, Yoon SS. D2 lymphadenectomy with surgical ex vivo dissection into node stations for gastric adenocarcinoma can be performed safely in

Western patients and ensures optimal staging. *Ann Surg Oncol* 2013; **20**: 2991-2999 [PMID: 23760588 DOI: 10.1245/s10434-013-3019-1]

56 **Afaneh C**, Levy A, Selby L, Ku G, Tang L, Yoon SS, Coit D, Strong VE. Ex Vivo Lymphadenectomy During Gastrectomy for Adenocarcinoma Optimizes Lymph Node Yield. *J Gastrointest Surg* 2016; **20**: 165-71; discussion 171 [PMID: 26403717 DOI: 10.1007/s11605-015-2948-3]

57 **Iversen LH**, Laurberg S, Hagemann-Madsen R, Dybdahl H. Increased lymph node harvest from colorectal cancer resections using GEWF solution: a randomised study. *J Clin Pathol* 2008; **61**: 1203-1208 [PMID: 18755719 DOI: 10.1136/jcp.2008.060210]

58 **Kerwel TG**, Spatz J, Anthuber M, Wünsch K, Arnholdt H, Märkl B. Injecting methylene blue into the inferior mesenteric artery assures an adequate lymph node harvest and eliminates pathologist variability in nodal staging for rectal cancer. *Dis Colon Rectum* 2009; **52**: 935-941 [PMID: 19502859 DOI: 10.1007/DCR.0b013e31819f28c9]

59 **Märkl B**, Moldovan AI, Jähnig H, Cacchi C, Spatz H, Anthuber M, Oruzio DV, Kretsinger H, Arnholdt HM. Combination of ex vivo sentinel lymph node mapping and methylene blue-assisted lymph node dissection in gastric cancer: a prospective and randomized study. *Ann Surg Oncol* 2011; **18**: 1860-1868 [PMID: 21503792 DOI: 10.1245/s10434-011-1713-4]

60 **Märkl B**, Wünsch K, Hebick KU, Anthuber M, Probst A, Arnholdt HM, Spatz H. Methylene blue-assisted lymph node dissection in combination with ex vivo sentinel lymph node mapping in gastric cancer. *Histopathology* 2009; **54**: 433-441 [PMID: 19309395 DOI: 10.1111/j.1365-2559.2009.03243.x]

61 **Wilkinson EJ**, Hause L. Probability in lymph node sectioning. *Cancer* 1974; **33**: 1269-1274 [PMID: 4823479 DOI: 10.1002/1097-0142(197405)33:5<1269::aid-cncr2820330512>3.0.co;2-x]

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