

## 2016 Gastric Cancer: Global view

**Clinical significance of lymphadenectomy in patients with gastric cancer**

Dezső Tóth, János Plósz, Miklós Török

Dezső Tóth, Department of General Surgery, Kenézy Teaching Hospital, 4043 Debrecen, Hungary

János Plósz, Department of Internal Medicine, Kenézy Teaching Hospital, 4043 Debrecen, Hungary

Miklós Török, Department of Pathology, Kenézy Teaching Hospital, 4043 Debrecen, Hungary

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Correspondence to: Dezső Tóth, MD, PhD, Associate Professor, Department of General Surgery, Kenézy Teaching Hospital, 2-26 Bartók Street, 4043 Debrecen, Hungary. [detoth@gmail.com](mailto:detoth@gmail.com)  
Telephone: +36-30-9388867  
Fax: +36-52-511797

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**Abstract**

Approximately thirty percent of patients with gastric

cancer undergo an avoidable lymph node dissection with a higher rate of postoperative complication. Comparing the D1 and D2 dissections, it was found that there is a significant difference in morbidity, favoured D1 dissection without any difference in overall survival. Subgroup analysis of patients with T3 tumor shows a survival difference favoring D2 lymphadenectomy, and there is a better gastric cancer-related death and non-statistically significant improvement of survival for node-positive disease in patients with D2 dissection. However, the extended lymphadenectomy could improve stage-specific survival owing to the stage migration phenomenon. The deployment of centralization and application of national guidelines could improve the surgical outcomes. The Japanese and European guidelines enclose the D2 lymphadenectomy as the gold standard in R0 resection. In the individualized, stage-adapted gastric cancer surgery the Maruyama computer program (MCP) can estimate lymph node involvement preoperatively with high accuracy and in addition the Maruyama Index less than 5 has a better impact on survival, than D-level guided surgery. For these reasons, the preoperative application of MCP is recommended routinely, with an aim to perform "low Maruyama Index surgery". The sentinel lymph node biopsy (SNB) may decrease the number of redundant lymphadenectomy intraoperatively with a high detection rate (93.7%) and an accuracy of 92%. More accurate stage-adapted surgery could be performed using the MCP and SNB in parallel fashion in gastric cancer.

**Key words:** Gastric cancer; Surgery; Lymphadenectomy; Sentinel node biopsy; Maruyama computer program

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**Core tip:** Comparing the D1 and D2 dissections, it was found that there is a significant difference in postoperative morbidity and mortality, favoured D1

dissection without any difference in overall survival. The implementation of centralization and application of national guidelines could improve the surgical outcomes. More accurate stage-adapted surgery could be performed using the Maruyama computer program and sentinel lymph node biopsy in parallel fashion in gastric cancer.

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## INTRODUCTION

In most cases, modern, optimal treatment of patients with different neoplasms can be achieved with a stage adapted, combined modality therapy according to international protocols. In case of solid tumors, the lymph node (LN) involvement and its exact number is the most important prognostic factor. Adjuvant chemotherapy, as well as the oncological outcome is terminated by the tumor-node-metastasis stage. Preoperative imaging techniques provide a much more accurate determination of the T and M stage than that of the N stage. The correct status of LN metastases can be obtained only by histology following an optimally extended node dissection. The removal of further LNs on the other hand, increases operative time, the rate of complications, and if negative may be considered unnecessary.

Almost three hundred thousand patients with gastric adenocarcinoma do not have LN metastasis in the one million new cases each year<sup>[1,2]</sup>. The depth of tumor invasion<sup>[3,4]</sup>, the metastatic LN status and R0 resection are the most important independent prognostic factors for overall and disease free survival (OS, DFS)<sup>[5-7]</sup>. Moreover, a lot of study proved that LN metastasis is an independent risk factor for local recurrence as well as the time interval between radical gastrectomy and hepatic metastasis in patients after R0 resection<sup>[8-10]</sup>.

The aim of this review is to report the latest issues from 2014 according to lymphadenectomy in gastric cancer and compare these results with earlier studies.

## LN INVOLVEMENT

Successful estimation of LN involvement may help to define which patients would or would not benefit from an extended LN dissection in association with gastrectomy<sup>[11]</sup>. However, preoperative diagnostic tools have a low sensitivity and specificity for defining these patient subpopulations. Sensitivity, specificity and accuracy of spiral computer tomography for detection of pathologic LN involvement are 73.1%, 50.0% and 84.2%, respectively<sup>[11,12]</sup>. Endoscopic ultrasonography has an accuracy of 68.6%, with a sensitivity and specificity of 66.7%

and 73.7%, respectively<sup>[11,13]</sup>. The real problem of these imaging procedures is that exclusion of endoscopic ultrasonography, only the size of the LNs is taken into account.

In association with T stage, LN involvement can be found in 15% of patients with carcinoma confined to the mucosa, whereas LN metastases were detected in 23.4%, 48.2%, and 69.8% of patients with carcinoma invading the submucosa, muscularis propria and serous layer, respectively<sup>[14]</sup>. Gertler *et al.*<sup>[15]</sup> showed that not only infiltration of the submucosa but also lymphatic vessel invasion, multifocal tumor growth, younger patient age and poor tumor differentiation were associated with nodal disease. Besides T stage, LN involvement can also be influenced by tumor size. The overall accuracy of tumor size for preoperative N staging was 82.13%<sup>[16]</sup>. The incidence of LN metastasis in patients with a cancer size of 3-5 cm is 64.9%, 80% in patients with a cancer size of 5-7 cm and 84.3% in patients with a cancer size of > 7 cm<sup>[14]</sup>. Additionally, early gastric cancer (EGC) has nodal metastases in 38.9% in poorly differentiated or undifferentiated types of tumor, in 41.7% with Lauren diffuse type and in 33.3% with a size larger than 3 cm<sup>[17]</sup>. Yang *et al.*<sup>[18]</sup> found that venous invasion, submucosal invasion or antral tumor location were independent predictors for LN metastasis in multivariate analysis. The rates of LN metastasis were 1.1% for patients with one or no predictor and 17.8% for those with two or more predictors<sup>[18]</sup>.

While the prognostic significance of macrometastasis in the LNs is obvious, the role of lymphovascular invasion (LVI) or micrometastasis (MM) is controversial. Lee *et al.*<sup>[19]</sup> confirmed that the recurrence-free survival is lower in N0/LVI(+) patients than in N0/LVI(-) patients, however they did not find any effect of LVI+ on overall survival. The incidence of LN MM is lower than 10% in patients with node negative EGC<sup>[20]</sup> but it is higher in histologically diffuse type tumors<sup>[21]</sup>. The presence of MM influenced DFS, although the OS analysis revealed no significant difference between MM-positive and MM-negative patients<sup>[19]</sup>. The reverse transcriptase polymerase chain reaction proved to be the most sensitive method in the detection of MM<sup>[22]</sup>.

Meanwhile, a multivariate survival analysis concluded that the number of examined LN (eLN) was an independent predictor of overall survival of patients with node-negative gastric cancer. According to the cut-point analysis, T2-T4 patients with 11-15 eLN had a significantly longer mean OS than those with 4-10 eLN or 1-3 eLN. Patients with ≤ 15 eLN were more likely to experience locoregional and peritoneal recurrence than those with > 15 eLN<sup>[23]</sup>. However, this trend was not observed when the number of examined LN exceeded 30<sup>[24]</sup>.

These results are potentially associated with the elimination of MM in negative LNs<sup>[25]</sup>. Based on these findings, LVI and MM should be considered in postoperative management of gastric cancer<sup>[19]</sup>.

**Table 1** The primary and revised results of prospective randomized trials comparing D1 to D2 dissection

Ref.	Morbidity (%)		Mortality (%)		Splenectomy (%)		Pancreatectomy (%)		RR (%)		OS (%)	
	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2	D1	D2
Dent <sup>[32]</sup>	13.6 <sup>a</sup>	38 <sup>a</sup>	0	0	0	0	0	0			81	76
British <sup>[33,36]</sup>	28 <sup>a</sup>	46 <sup>a</sup>	6.5 <sup>a</sup>	13 <sup>a</sup>	27	9	4 <sup>1</sup>	57 <sup>1</sup>	NS	NS	35	33
Dutch <sup>[34,37]</sup>	24 <sup>a</sup>	43 <sup>a</sup>	4 <sup>a</sup>	10 <sup>a</sup>	11	37	3	30	43	47	45	47
Dutch - 15 yr <sup>[38]</sup>									22 <sup>a</sup>	12 <sup>a</sup>	21	29
Taiwanese <sup>[39,44]</sup>	7.3 <sup>a</sup>	17.1 <sup>a</sup>	0	0	3	1	1 <sup>1</sup>	13 <sup>1</sup>	50.6	40.3	53.6 <sup>a</sup>	59.5 <sup>a</sup>
Italian <sup>[35,43]</sup>	12	17.9	3	2.2	6.8	9.0	1.5	1.5			66.5	64.2

<sup>a</sup> $P < 0.05$ . <sup>1</sup>Pancreato-splenectomy. RR: Relapse risk; OS: Overall survival; NS: Non-significant.

## LYMPHADENECTOMY

### D1 vs D2 lymphadenectomy

The adequate extension of lymphadenectomy differs significantly between East Asian and Western countries. Extended lymphadenectomy (D2) is the standard of care in Japan and South Korea, while for example, the majority of United States patients receive at most a limited lymphadenectomy (D1)<sup>[26,27]</sup>. This controversy may originate from different factors. First, the incidence of gastric cancer is significantly higher in Asia than in European Union, or in the United States<sup>[27,28]</sup>.

Second, centralization of treatment has not yet been solved in the latter regions; 80% of Medicare patients with gastric cancer in the United States go through surgery in centers performing less than 20 procedures per year<sup>[29]</sup> and there is a significant number of low-volume surgeons performing less than two cases annually<sup>[30,31]</sup>.

Table 1 shows the primary and revised results of prospective randomized trials (RCT) comparing D1 to D2 lymphadenectomy in association with postoperative morbidity, mortality, frequency of splenectomy and pancreatectomy and long term oncological outcomes such as relapse risk and overall survival (OS). The three earliest studies found a higher morbidity and mortality rate following extended LN dissection of patients with gastric cancer when compared to those undergoing D1 dissection only<sup>[11,32-34]</sup>. These higher rates were related mostly to splenectomy and pancreatectomy. Although Dent *et al.*<sup>[32]</sup> did not perform resection of these organs, this study should be evaluated with reservations because of the small series size. Furthermore, limited surgical experience could explain these results. The quality control of lymphadenectomy was inadequate, as the non-compliance rate (absence of LNs from more than two LN stations that were supposed to be harvested) was 51% in the D2 group in the Dutch trial<sup>[34,35]</sup> and, in the extended group of the British trial, the dissection of LN station no.7 was 63.5%, and was less than 50% in station no.8 and no.9<sup>[36]</sup>.

Moreover, extended LN dissection did not have any effect on oncological outcomes. The relapse risk and survival were similar in these studies. Only the revision of the Dutch trial showed better survival in advanced disease in the D2 group, after 11-year follow-up<sup>[37]</sup>. The 15-year follow-up results revealed that cancer-related death rates were lower (37% vs 48%) with a lower rate

of local recurrence in the D2 lymphadenectomy group (Table 1)<sup>[38]</sup>. Subgroup analysis of this trial demonstrated significantly higher survival for females (35% vs 21%) and in stage II disease (33% vs 15%) in the D2 arm. The 15-year survival in patients without pancreatico-splenectomy was significantly higher with D2 than D1 dissection (35% vs 22%)<sup>[38]</sup>.

The two latest randomized trials from the 21<sup>st</sup> century did not present significant differences in postoperative mortality between the D1 and D2 group<sup>[35,39]</sup>. The morbidity rate was higher with D2 lymphadenectomy in the Taiwanese trial (which compared D1 to D3 dissection; however their D3 lymphadenectomy is similar to the current definition of D2 dissection). The Italian study did not show this difference and proved that D2 dissection could be performed safely without splenectomy and distal pancreatectomy, with comparable mortality and morbidity to those with D1 dissection in specialized centers<sup>[39,40]</sup>. These rates are comparable to the Japan Clinical Oncology Group (JCOG) 9501 trial and the nationwide Japanese registry where the mortality was less than 2% after D2 dissection<sup>[41,42]</sup>. Neither did the latter study find any survival benefit from the extended lymphadenectomy<sup>[43]</sup>. Subgroup analyses showed a 5-year disease-specific survival benefit for patients with pathological tumor 1 (pT1) disease in the D1 group (9% vs 83% for the D2 group;  $P = 0.015$ ), and for patients with pT2-4 status and positive LNs in the D2 group (59% vs 38% for the D1 group;  $P = 0.055$ ). However, the non-compliance rate was 33.6%<sup>[43]</sup>. It was concluded that the contamination (over-extensive nodal dissection) (18%) and the higher rate of stage IA disease in the D1 group and of stage IV in the D2 arm, apparently nullified the effect of correct extended dissection<sup>[41,43]</sup>. The other randomized trial from Taiwan proved a better ( $P = 0.041$ ) survival with D2 dissection<sup>[44]</sup>.

The results of these recent studies call attention to the importance of the learning curve and the necessity of standardized procedures with routine preservation of the spleen and pancreas in experienced centers<sup>[40]</sup>.

Besides the RCT, the latest meta-analysis found significant differences in morbidity, anastomotic leakage, pancreatic leakage, reoperation rates, wound infection, pulmonary complications and postoperative mortality, all of which favoured D1 dissection. The conclusion was that there is no difference in OS when comparing the D1 and D2 arm. Subgroup analysis of patients

with T3 tumor shows a survival difference favoring D2 lymphadenectomy (25.9% vs 11.5%), and there is a trend towards a lower risk of gastric cancer-related death among patients having a D2 dissection with preservation of the spleen or pancreas and non-statistically significant improvement of survival for node-positive patients<sup>[40,45]</sup>. Unfortunately, the main problem of meta-analysis was that it was not possible to match patient groups for treatment with age, sex, type of gastrectomy, pathological stage, tumor location, co-morbidity, treatment strategies, surgeon experience, hospital case volume and extent of LN dissection, all of which affect postoperative complications and overall survival rates<sup>[40]</sup>.

Keeping this in mind, the comparison of oncological outcomes of D1 and D2 dissections in association with different T and N stages could be problematic due to the concept of stage migration. The reason for this is that a limited lymphadenectomy can not represent the adequate staging of LN involvement. Conversely, extended lymphadenectomy could improve stage-specific survival due to the stage migration phenomenon. Furthermore, Xu *et al.*<sup>[46]</sup> demonstrated that it is necessary to examine at least 16 LNs for accurate pathological examination of gastric cancer, even in node-negative gastric cancer patients<sup>[25]</sup>, and Datta *et al.*<sup>[47]</sup>, who analyzed the data of more than 22000 patients found that the examination of 15 or more LN is a reproducible prognostic factor for gastric cancer outcomes in the United States and should continue to serve as a benchmark for the quality of care.

In addition to the quality of surgery, the pathologist plays a large role in the proper identification and examination of the extracted LN<sup>[48]</sup>.

## EXTENSION OF LYMPHADENECTOMY BEYOND SUGGESTED LIMITS

The latest issue of the Japanese Gastric Cancer Association treatment guideline contains the standard lymphadenectomies regarding the type of gastric resection: Total gastrectomy with D2: D1 (Nos.: 1-7) + Nos. 8a, 9, 10, 11p, 11d, 12a; distal gastrectomy with D2: D1 (Nos. 1, 3, 4sb, 4d, 5, 6, 7) + Nos. 8a, 9, 11p, 12a; pylorus-preserving gastrectomy with D1+: D1 (Nos. 1, 3, 4sb, 4d, 6, 7) + Nos. 8a, 9; and in proximal gastrectomy with D1+: D1(Nos. 1, 2, 3a, 4sa, 4sb, 7) + Nos. 8a, 9, 11p<sup>[49]</sup>.

In the field of tumor-location specific LN involvement recent studies can be divided into 2 cohorts depend on the position of the gastric tumor (proximal vs middle and distal).

### Proximal gastric cancer

The frequency of metastasis in station no.4d, 5 and 6 LNs in patients with proximal gastric cancer is more than 10%<sup>[14,50]</sup>. The incidence of station no.10 LN metastasis is 11.82% in upper third advanced gastric cancer (AGC). The estimated OS were 46% and 37% regarding station

no.10 dissection or not, which was not statistically significant. Authors suggest high-quality studies with larger sample sizes to determine the clinical significance of no.10 LN removal<sup>[51]</sup>. Following an 18 mo follow-up of 108 patients Li *et al.*<sup>[52]</sup> concluded that routine no.10 lymphadenectomy may be unnecessary for advanced, upper third gastric cancer without serosal invasion, unless T3 tumors are located in the greater curvature.

### Middle and distal gastric cancer

LN metastasis in station no.2 LNs from distal gastric cancer is only 1.0%, while the metastasis in station no.4 LNs is more than 20%. Since station no.11p is immediately adjacent to stations no.7 and no.9, in the case of distal gastric cancer, station no.11d should be preserved; however, both no.11p and no.11d stations should be removed in cases of proximal gastric cancer<sup>[14]</sup>. According to Japanese gastric cancer treatment, as station no.14v is closely adjacent to station no.6, station no.14v LNs should also be removed if suspicion of metastasis to the LNs in station no.6 arises<sup>[14,49]</sup>.

As the LN metastasis rate in station no.7 was similar to that of perigastric LNs in 570 patients with advanced distal gastric tumor it is reasonable to include LNs in the no.7 station in the D1 LN dissection<sup>[53]</sup>. Evaluating LN involvement after total gastrectomy, Galizia found that the incidence of nodal involvement of stations no.10, no.11d, and no.12a was 5%, and the 5-year DFS rate was zero; they concluded that modified D2 lymphadenectomy confers the same oncologic adequacy as standard D2 lymphadenectomy, with a significant reduction of postoperative morbidity<sup>[54]</sup>.

During investigation of LN involvement of the hepato-duodenal ligament (HDLN) a logistic regression analysis showed that no.5 and no.12a LN metastases were associated with a 6.9 and 11.3 fold increase respectively, for risk of no.12p and no.12b LN metastases. In addition, significant differences in 5-year OS of patients with and without no.12p and no.12b LN metastases were observed<sup>[55]</sup>. However, the clinical significance of removing these LN was not evaluated. Analyzing the data of 1872 patients, LN involvement in station no.12 was 3.6% whereas HDLN metastasis was not a significant factor for survival in multivariate analysis and the 5-year survival rate of 41 patients with HDLN metastasis without distant metastasis at any other site was significantly higher than that among 120 patients with stage IV disease without HDLN metastasis. It is suggested that the inclusion of HDLN in the distant metastatic LN group in gastric cancer is inappropriate and that the seventh American Joint Committee on Cancer criteria for node grouping should be revised<sup>[56]</sup>.

The incidence of no. 14v LN metastasis was 5.0% in 1661 patients who underwent curative resection for middle or lower third gastric cancer. In clinical stages I and II, no.14v LN dissection did not affect overall survival; in contrast, no.14v LN dissection was an independent prognostic factor in patients with clinical stage III/IV





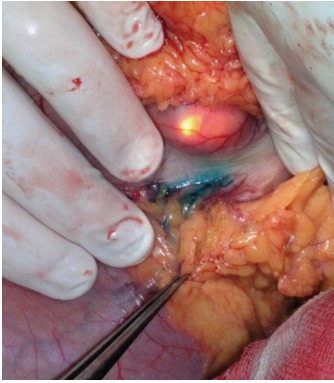


Figure 2 Sentinel lymph node mapping following submucosal marking by an endoscopist.

93%<sup>[72]</sup>.

Our study demonstrated a similar degree of reliability of MCP to those cited above, with 90.2% of sensitivity, 63.3% of specificity and 78.4% of accuracy. The rate of false negatives was 9.8%<sup>[73]</sup>. These studies demonstrate that the results of the computerized prediction of LN metastases are superior to those of the standard preoperative imaging techniques.

Another advantage of the MCP is that it can determine long term oncological results. Hundahl defined the Maruyama Index (MI) at first in 2002 as a measure of unresected regional nodal disease in gastric cancer using the data of the Intergroup 0116 trial and he proved it is an independent predictor of survival<sup>[74,75]</sup>. Peeters *et al*<sup>[76]</sup> reanalyzed the data of the Dutch D1-D2 trial using univariate and multivariate analyses and showed that the MI is an independent predictor of overall survival ( $P = 0.016$ , HR = 1.45) and relapse risk ( $P = 0.010$ , HR = 1.72). It was concluded that the MI is a quantitative yardstick for assessing the adequacy of lymphadenectomy in gastric cancer patients<sup>[75,76]</sup>. Later, Hundahl evaluated autopsy findings from the Dutch D1-D2 trial and showed that MI < 5 or a low MI for surgery is associated with enhanced regional control and survival<sup>[76,77]</sup>. Dikken *et al*<sup>[78]</sup> proved the prognostic significance of low MI in a 2-year survival rate (82% vs 59%), as did Sachdev, who demonstrated that lower MI correlated with better survival, as a continuous ( $P < 0.02$ ) and categorical ( $P < 0.04$ ) variable<sup>[79]</sup>.

Overall these results suggest that a Maruyama Index less than 5 has a better impact on survival, than D-level guided surgery. For these reasons, the preoperative application of MCP is recommended routinely, with an aim to perform "low Maruyama Index surgery". In addition, the application of MCP to predict LN involvement can influence the indication for neoadjuvant chemo-therapy, and furthermore a "high Maruyama Index" could indicate the necessity for postoperative oncological treatment.

## SENTINEL LYMPH NODE BIOPSY

While the MCP calculates the probability of LN involvement preoperatively, the concept of sentinel lymph

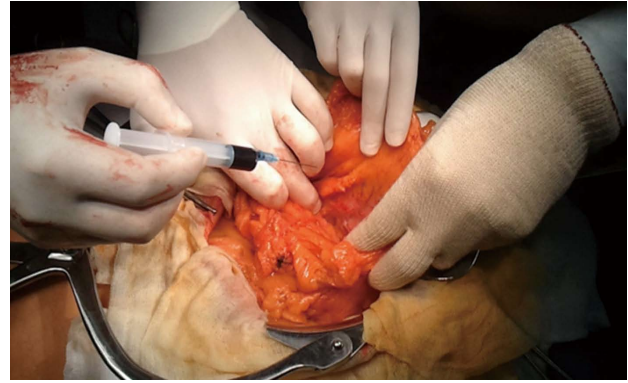


Figure 3 Subserosal marking by a surgeon.

node biopsy (SNB) can determine the existence of LN metastases intraoperatively. The first potentially affected LN, the sentinel lymph node (SLN), reliably reflects the status of the nodes in the second and third line, which is supported by data of numerous publications. If the SLN contains tumor deposit(s), extended dissection is warranted, but if findings are negative, the patient could be spared additional complications associated with extended dissection. However, the method of dye/tracer injection and the tracer's selection is controversial. Some authors use dye alone (patent blue, indocyanine green, isosulfan blue)<sup>[11,80-82]</sup>, Kitagawa *et al*<sup>[83]</sup> handle 99m Tc colloid, and Aikou *et al*<sup>[84]</sup> uses the combination of these tracers. The latest systematic review concluded that the SLN's identification rate is the same with the dual or single mapping method<sup>[85]</sup>. It is eminent that body-mass index (BMI) affects the sentinel LN detection rate<sup>[86]</sup>. The Hungarian study proved that the identification of sentinel LNs in obese patients can be difficult owing to the feathering of blue dye in the fatty tissues<sup>[11]</sup>. This was concluded as the only patient in whom marking did not occur had a BMI significantly higher than average (26.8 vs 22.8)<sup>[11]</sup>. Then again, the application of blue dye for SNB has a beneficial side effect, as it significantly increased the number of harvested LN and the ratio of the number of the harvested LN per time<sup>[87]</sup>. To avoid quick dispersal to multiple LNs Kong applied ICG/poly- $\gamma$ -glutamic acid complex, which remained longer than diluted ICG in animal models<sup>[88]</sup>.

Yaguchi, Lee and Tóth have compared the subserosal to the submucosal labeling method (Figures 2 and 3) without any significant difference and they suggest the endoscopic injection of a tracer in cases of non-palpable tumors and/or laparoscopic procedures<sup>[89-91]</sup>.

The cardinal problem in the SNB concept is the intraoperative false negative rate. The JCOG 0302 trial called attention to the importance of the learning curve and the inadequacy of the pick-up method. The demand for only five patients per institute provided an insufficient learning period which presented a 46% false negative rate<sup>[92]</sup>.

Lee *et al*<sup>[93]</sup> proved that the removal of entire nodal basins can significantly decrease this rate against the pick-up method, and Kumagai *et al*<sup>[94]</sup> called attention to the opportunity of introducing the one-step nucleic acid

amplification test for the intraoperative diagnosis of LN metastasis with similar results to postoperative 2-mm-interval histological examination.

Miyashiro *et al.*<sup>[95]</sup> demonstrated that an extensive surgical experience is necessary for application of SNB concept and standardization of SLN mapping technique, using improved tracer, and guideline to evaluate the positiveness of SLN specimen should be planned to incorporate SNB in routine practice<sup>[96]</sup>. Recent studies and the latest meta-analysis of SLN mapping have shown a high detection rate (93.7%) and an accuracy of 92%<sup>[97]</sup> and suggest that the SNB concept could be suitable for tumors following endoscopic resection<sup>[98]</sup> and could represent a new era of sentinel node navigation surgery in EGC<sup>[99,100]</sup>. Moreover, its success rate did not correlate to tumor grade<sup>[101]</sup>.

Based on the results of the largest prospective multicenter trial from Japan with an identification rate of 97.5% and an accuracy of 99%<sup>[102]</sup>, a phase III multicenter trial for individualized surgery for EGC based on SLN mapping has been commenced in the Eastern Asian countries. The long-term results of these studies will be available between 2018 and 2020.

## CONCLUSION

The latest RCT comparing D1 and D2 dissections represents a higher surgical quality (more contamination, less non-compliance, low morbidity and mortality rate) than previous trials<sup>[43]</sup>. This could lead to a trend towards the execution of the less limited D1 lymphadenectomy for more experienced and well-trained surgeons, and hopefully the results of western surgeons will achieve a level similar to those of the Asian surgical outcomes in the near future.

On the other hand, the era of multimodal treatment and the increase in elderly patients with serious comorbidities indicates the necessity of a stage- and patient-adapted, individualized surgery in gastric cancer. It was conceived at an expert panel, also: "A D2 lymphadenectomy is preferred for curative-intent resection in advanced, non-metastatic gastric cancer; in patients with EGC or substantial comorbidities, a D1 lymphadenectomy is more appropriate"<sup>[103]</sup>. The Japanese guidelines enclose that the AGC should be treated with D2 lymphadenectomy. D1 or D1+ should be recommended as a choice for EGC. D1+ can be an alternate for D2 in high-risk patients<sup>[104]</sup>. Inokuchi *et al.*<sup>[105]</sup> suggested that the presence of heart or liver disease is a significant risk factor for postoperative morbidity in patients who undergo laparoscopic gastrectomy. Although it did not reduce complications, insufficient LN dissection (for example, D1+ for advanced gastric cancer) might be permissible in high-risk patients as it had no negative impact on gastric cancer-specific survival. More accurate stage-adapted surgery could be performed using the MCP and SNB in parallel fashion.

It is generally accepted that metastases in the SLNs warrant a D2 lymphadenectomy. The authors analyzed

the relevance of MCP in sentinel node positive patients in an earlier study<sup>[73]</sup>; while the efficiency of SNB method is superior to MCP, the positive predictive value of MCP and SNB was proven equivalent in the sentinel node positive group and the accuracy of MCP in these cohort of patients was 10% higher. For these reasons it would be interesting to find the appropriate combination of these techniques in the future and we suggest using them simultaneously in the operating room.

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