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ORIGINAL ARTICLE

Proximal gastrectomy with exclusion of no. 3b lesser curvature lymph node dissection could be indicated for patients with advanced upper-third gastric cancer

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Abstract

Background Proximal gastrectomy has been introduced for early gastric cancer located in the upper third of the stomach, but expansion of its indication to advanced tumors has not been generally accepted in terms of lesser curvature lymph node dissection.

Methods We reviewed the medical records of 385 patients with tumors in the upper third of the stomach, and the incidence of metastasis and the therapeutic index related to the proximal (no. 3a) and distal (no. 3b) lymph nodes of the lesser curvature were analyzed and compared with those of tumors in the middle third ($n = 1093$) and lower third ($n = 922$) of the stomach.

Results The no. 3a rate of metastasis from advanced tumors in the upper third of the stomach was significantly higher than that from tumors in the middle third or lower third of the stomach. The no. 3b metastasis rate did not show any significant differences between the three locations, but the therapeutic index of no. 3b lymph nodes in the upper third of the stomach (1.7) was far lower than that in the middle third (7.1) or lower third (7.0). Further, the rate of metastasis from tumors with the distal border ending in the upper third of the stomach (2.2 %) was significantly ($P < 0.0001$) lower than that from tumors located in the upper third of the stomach but extending to the middle third (19.6 %), as well as from tumors located in middle third (17.1 %) or lower third (19.6 %), with the therapeutic index being only 1.1. The four no.-3b-positive tumors all measured more than 40 mm, and included one T3 tumor and three T4 tumors.

Conclusion Proximal gastrectomy with exclusion of no. 3b lymphadenectomy could be indicated for at least T2 tumors measuring less than 40 mm localized in the upper third of the stomach.

Keywords Proximal gastrectomy · Upper-third gastric cancer · Lesser curvature lymph nodes · Lymphadenectomy · Right gastric artery

Introduction

The incidence of upper-third gastric cancer including cancer of the gastroesophageal junction has been increasing steadily in Western countries, even though the incidence of gastric cancer is on the decline [1–3]. A similar trend has been observed in Japan and in Eastern countries in recent decades [4, 5]. Surgery is indispensable for curing this disease. Total gastrectomy, which entails the removal of all perigastric lymph nodes (LNs), is the standard surgery, and proximal gastrectomy is the alternative. Several reports have demonstrated that the incidence of metastasis from upper-third gastric cancer to LNs at the right gastroepiploic (no. 4d), suprapyloric (no. 5), and infrapyloric (no. 6) stations is extremely rare [6, 7]. Sasako et al. [8] reported that the surgical dissection of these LNs is not beneficial for patient survival. In contrast, the no. 3 lesser curvature LN station is the most frequent metastatic site [7, 8]. In proximal gastrectomy, insufficient dissection of the distal part of this station occurs when an attempt is

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made to secure blood flow of the remnant stomach [9]. Therefore, expansion of the indication of proximal gastrectomy to advanced upper-third gastric cancer has not been generally accepted [10].

Anatomically, the lesser curvature of the stomach is fed by two arteries: the left gastric artery (LGA) and the right gastric artery (RGA) [11, 12]. The no. 3 station consists of the proximal part, including nodes along the LGA, and the distal part, comprising nodes along the RGA. Considering the direction of lymphatic flow, lymphatics from upper-third tumors drain to the proximal lesser curvature nodes and then to the nodes alongside the root of the LGA (no. 7), rather than to the distal lesser curvature nodes [13]. In 2011, the Japanese Gastric Cancer Association (JGCA) redefined the no. 3 station by separating it into no. 3a (along the LGA) and no. 3b (along the RGA) substations [14]. This new classification appears to be useful for clarifying the extent of LN dissection when proximal gastrectomy is performed.

In the present study, we reviewed a clinical database containing information on 2400 gastric cancer patients who underwent radical gastrectomy with complete no. 3 dissection over a 20-year period and analyzed the metastasis rates and individual therapeutic benefits of the dissection of no. 3a and no. 3b substations according to tumor location and depth of invasion. On the basis of these results, we discuss whether proximal gastrectomy with exclusion of no. 3b lesser curvature LN dissection could be indicated for patients with advanced upper-third gastric cancer.

Patients and methods

Inclusion criteria and data collection

Since 1994, we have explored the no. 3 station in a manner similar to the current rule stipulated by the JGCA [15]. The base population for this study was 3921 patients who underwent gastrectomy for primary adenocarcinoma of the stomach from January 1994 through August 2014 at Toranomon Hospital, Tokyo, Japan. Patients who underwent incomplete no. 3 LN dissection in proximal gastrectomy performed for early upper-third gastric cancer ($n = 204$), pylorus-preserving gastrectomy ($n = 197$), palliative surgery ($n = 297$), or surgery for stump tumor ($n = 105$) were excluded. Patients with tumors invading more than 3 cm of the distal part of the esophagus ($n = 57$), tumors extending to two thirds of the stomach ($n = 226$), and/or multiple tumors in the stomach ($n = 465$) were also excluded. A total of 2400 patients who fulfilled these criteria were included in the study. The median follow-up period for all eligible patients was 44 months.

Description of tumor location and depth of invasion

Tumor location was described by the regions that were mainly involved, as the upper third of the stomach (U), middle third of the stomach (M), lower third of the stomach (L), duodenum (D), and esophagus (E), as per the JGCA [14]. That is, tumors located in the upper third of the stomach extending into the esophagus (UE), in the upper third of the stomach (U), and in the upper third of the stomach extending into the middle third (UM) were categorized as U; tumors located in middle third of the stomach extending into the upper third (MU), in the middle third of the stomach (M), and in the middle third of the stomach extending into the lower third (ML) were categorized as M; and tumors located in the lower third of the stomach extending into the middle third (LM), in the lower third of the stomach (L), and in the lower third of the stomach extending into the duodenum (LD) were categorized as L. The depth of invasion was categorized into four groups: T1 (mucosal or submucosal), T2 (muscularis propria), T3 (subserosal), and T4 (serosa or invading adjacent structures).

Preparation for LN examination

All regional LNs were retrieved from the adipose connective tissue of the surgical specimen immediately after surgery, and node numbers and locations were recorded in accordance with the JGCA guidelines [14]. Nodes found at substations no. 3a and no. 3b were individually labeled and sent for histological examination together with other dissected LNs.

Therapeutic index of estimated benefit from LN dissection

We calculated the incidence of metastasis to each no. 3 substation by dividing the number of patients with metastasis at that station by the number of patients in whom the station was dissected. The cumulative 5-year survival rates of patients with LN metastasis were calculated for each substation by the life-table method [16]. An index of the benefit gained by dissection of each station (therapeutic index, TI) was calculated by multiplication of the frequency of metastasis to the station and the 5-year survival rate of patients with metastasis to that station.

Investigation of no. 3 vasculature in the surgical specimens

Surgical specimens from the most recent 90 patients were submitted for investigation of the morphometric anatomy of the vasculature of the lesser curvature. The length of the lesser curvature, the distance from the pyloric ring to the

entry point of the first and final gastric branches of the RGA in the lesser curvature, and the distance from the gastric cardia to the entry point of the final gastric branch of the LGA were measured. Values are expressed as the means with the standard deviation in parentheses.

Statistical analysis

Associations between the incidence of LN metastasis and tumor location were analyzed by Pearson's chi-squared test. Cumulative survival rates were calculated by the Kaplan–Meier method, and statistical significance was evaluated by the log-rank test. Quantitative variables were compared by the Student *t* test. IBM SPSS Statistics for Windows (version 19; IBM Armonk, NY, USA) was used for all analyses. $P < 0.05$ was considered to be statistically significant.

Results

Incidence of no. 3 metastasis depending on tumor location and depth of invasion

The characteristics of 2400 patients (1683 men and 717 women) included in this study are shown in Table 1. The middle third of the stomach was the commonest location ($n = 1093$), followed by the lower third ($n = 922$) and the upper third ($n = 385$). Total gastrectomy was performed in 682 patients, including most of the 378 patients with tumors located in the upper third of the stomach, and distal gastrectomy was performed in the remaining 1718 patients. The rates of metastasis to the no. 3a and no. 3b substations depending on tumor location and depth of invasion are shown in Fig. 1. The rate of metastasis to the no. 3a substation from early gastric cancer did not show any significant differences between the three tumor locations. In contrast, the rate of metastasis from advanced tumors located in the upper third of the stomach (57.1 %) was significantly higher than that from tumors located in the middle third (49.8 %, $P = 0.043$) or lower third (38.3 %, $P < 0.0001$). Metastasis to no. 3b was infrequent compared with that to no. 3a for all tumor locations and depths. No early tumors located in the upper third of the stomach showed no. 3b metastasis. There were no

Table 1 Characteristics of the patients included in this study

	U ($n = 385$)	M ($n = 1093$)	L ($n = 922$)
Sex			
Male	295 (76.6 %)	726 (66.4 %)	658 (71.4 %)
Female	90 (23.4 %)	367 (33.6 %)	264 (28.6 %)
Depth of tumor invasion			
T1	96 (25.0 %)	653 (59.7 %)	559 (60.6 %)
T2	45 (11.7 %)	108 (9.9 %)	108 (11.7 %)
T3	98 (25.5 %)	113 (10.3 %)	100 (10.8 %)
T4	146 (37.9 %)	219 (20.0 %)	155 (16.8 %)
Nodal involvement			
N0	161 (41.8 %)	738 (67.5 %)	597 (64.8 %)
N1	62 (16.1 %)	97 (8.9 %)	105 (11.4 %)
N2	71 (18.4 %)	105 (9.6 %)	97 (10.5 %)
N3	91 (23.6 %)	153 (14.0 %)	123 (13.3 %)
Final stage			
I	118 (30.6 %)	688 (62.9 %)	590 (64.0 %)
II	87 (22.6 %)	162 (14.8 %)	133 (14.4 %)
III	180 (46.8 %)	243 (22.2 %)	199 (21.6 %)
Type of gastrectomy			
Total	378 (98.2 %)	274 (25.1 %)	30 (3.3 %)
Distal	7 (1.8 %)	819 (74.9 %)	892 (96.7 %)

L tumors located in the lower third of the stomach, *M* tumors located in the middle third of the stomach, *U* tumors located in the upper third of the stomach

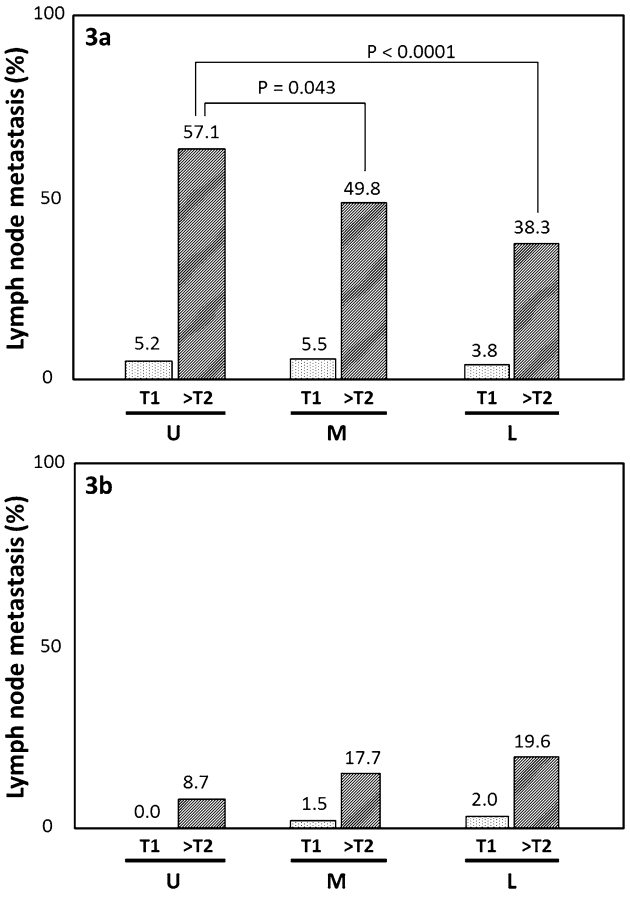


Fig. 1 Rates of nodal metastasis at the no. *3a* and no. *3b* substations according to the tumor location. *L* tumors located in the lower third of the stomach, M tumors located in the middle third of the stomach, *U* tumors located in the upper third of the stomach

Table 2 Five-year survival rate and index of estimated benefit from no. 3 lymph node dissection according to the tumor location and depth of invasion

	U		M		L	
	SR (%)	TI	SR (%)	TI	SR (%)	TI
T1						
3a	80.0	4.2	93.8	5.2	85.9	3.2
3b	No case	0.0	100	1.5	88.9	1.7
T2-T4						
3a	43.6	24.9	43.2	21.5	41.6	15.9
3b	20.0	1.7	40.1	7.1	35.9	7.0

L tumors located in the lower third of the stomach, *M* tumors located in the middle third of the stomach, *SR* 5-year survival rate, *TI* therapeutic index, *U* tumors located in the upper third of the stomach

significant differences in the rates of no. 3b metastasis from advanced cancer between the three locations; the rates were 8.7, 17.7, and 19.6 % for U, M, and L tumors respectively.

Therapeutic benefit of dissection of no. 3 LNs

The 5-year survival rates of patients with nodal metastases and the TIs of the no. 3a and no. 3b substations are given in Table 2. In early tumors located in the upper third of the stomach, the TI of no. 3b was 0.0 since there were no patients with no. 3b metastasis. In advanced tumors located in the upper third of the stomach, the TI of no. 3a was higher than that of other tumor locations. In contrast, the TI of no. 3b was far lower than that of other tumor locations, and the values were 1.7, 7.1, and 7.0 for U, M, and L tumors respectively.

Characteristics of upper-third gastric cancer patients with no. 3b metastasis

For further analysis, we classified advanced upper-third gastric cancer patients as those in whom the distal tumor border ended in the upper third of the stomach (UE/U, $n = 253$) wherein the resection margin could be adequately secured by proximal gastrectomy and those in whom the distal tumor border extended to the middle third of the stomach (UM, $n = 132$). These results are summarized in Table 3. The rate of no. 3a metastasis showed no significant difference between the two groups. In contrast, only 4 of 182 advanced UE/U tumor patients had no. 3b metastasis: this metastasis rate of 2.2 % was significantly ($P < 0.0001$) lower than that in patients with UM tumors (19.6 %) as well as in patients with M tumors (17.7 %) or L tumors (19.6 %) . Further, the TI in patients with advanced UE/U tumors was only 1.1.

Characteristics of UE/U tumors with no. 3b metastasis

Figure 2 shows the detailed clinicopathological features of no.-3b-positive UE/U tumor patients. All four tumors measured more than 40 mm in diameter, were T3 ($n = 1$) or T4 ($n = 3$) in depth, were located on the lesser gastric curvature, and had concomitant no. 3a metastasis. One patient (case 1) had no. 5 metastasis but none of the patients had no. 12a metastasis. All patients were treated by total gastrectomy with D2 lymphadenectomy, and two patients including one with no. 5 metastasis remained alive after surgery. The cause of death in the two patients was peritoneal recurrence.

Metastasis to no. 4d, no. 5, no. 6, and no. 12a LNs from advanced UE/U tumors

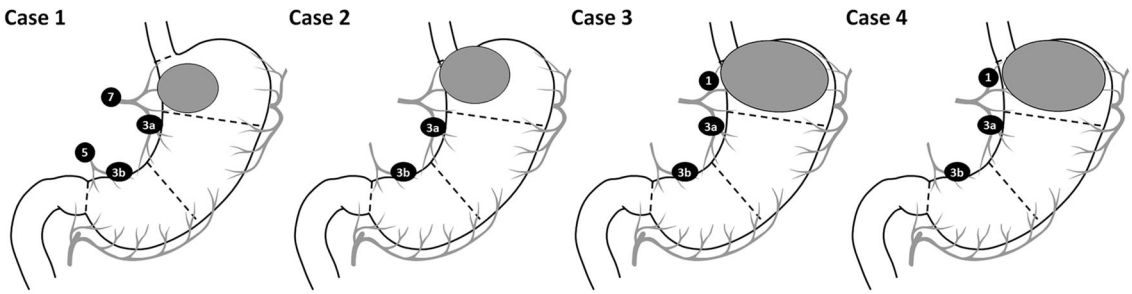
To further clarify the characteristics of UE/U cancer for which the radicality of proximal gastrectomy might be inferior to that of total gastrectomy, we investigated the incidence of metastasis to the other nodal stations on the distal side of the stomach (Table 4). None of the no.-3b-negative patients had lesser curvature LN (no. 5 and no. 12a) metastasis. The metastasis rates at no. 4d and no. 6 were 3.3 and 1.6 % respectively. All of the no.-4d-positive and/or no.-6-positive tumors were T4 in depth and were more than 60 mm in diameter. However, the TIs of no. 4d, no. 5, no. 6, and no. 12a calculated as 0.6, 0.6, 0.0, and 0.0 respectively, were extremely low.

Table 3 Metastasis rate and therapeutic benefit of dissection of no. 3 lymph nodes in advanced upper-third gastric cancer by subclassification of the tumor location

	UE/U ($n = 182$)			UM ($n = 107$)		
	Node-positive cases	SR (%)	TI	Node-positive cases	SR (%)	TI
3a	100 (54.9 %)	45.2	24.8	63 (60.7 %)	41.5	25.2
3b	4 (2.2 %*)	50.0	1.1	21 (19.6 %)	14.3	2.8

SR 5-year survival rate, *TI* therapeutic index, *UE/U* upper-third gastric cancer with the distal tumor border ending in the upper third, *UM* upper-third gastric cancer with the distal tumor border extending to the middle third

*$P < 0.0001$ compared with no. 3a lymph nodes.



	Case 1	Case 2	Case 3	Case 4
Diameter (mm)	45	55	65	65
Macroscopic Type	3	3	3	3
Histological classification	por2	por2	tub2	tub2
Depth of tumor invasion	T4	T3	T4	T4
Nodal involvement	N3	N2	N2	N2
Prognosis (months)	Alive (60)	Alive (210)	Peritoneal (15)	Peritoneal (8)

Fig. 2 Clinicopathological features of no.-3b-positive advanced gastric cancer patients in whom the distal tumor border ended in the upper third of the stomach. Numbers in *black circles* indicate metastasis-positive lymph node stations. *por2* poorly differentiated adenocarcinoma of nonsolid type, *tub2* moderately differentiated tubular adenocarcinoma

Table 4 Metastasis to lymph nodes located around the distal side of the stomach from 182 cases of advanced gastric cancer with the distal tumor border ending in the upper third of the stomach

Station	No. of node-positive cases (T2/T3/T4)	Metastasis rate (%)	TI
4d	0/0/6	3.3	0.6
5	0/0/1	0.5	0.6
6	0/0/3	1.6	0.0
12a	0/0/0	0.0	0.0

TI therapeutic index

Mapping of the primary tumor with solitary metastasis to no. 3a or no. 3b

To roughly reveal the lymphatic stream to the lesser curvature LNs, we constructed a map indicating the location of tumors with solitary metastasis to the no. 3a or the no. 3b substation. As shown in Fig. 3a, tumors with single-node metastasis to no. 3a were not localized to any third of the stomach, and no specific pattern was seen. In contrast, most of the tumors with single-site metastasis to no. 3b were localized in the lesser curvature, mostly in the middle third of the stomach and partly in the lower third.

Distribution of vasculature and LN count in the lesser curvature

Finally, we investigated the distribution of the LGA and RGA in the most recent 90 cases. The mean length of the lesser curvature was 153.7 (18.4) mm. As shown in Fig. 3c, the mean distance from the entry point of the descending limb to the final branch of the LGA, equivalent to the area draining to no. 3a, was 92.6 (15.2) mm. The distance from the entry point of the first gastric branch to the final gastric branch of the RGA, equivalent to the area draining to no. 3b, was 32.8 (9.0) mm, which was significantly ($P < 0.0001$) shorter than the value related to no. 3a. Overall, 1.4 (2.1) LNs were retrieved from no. 3b, which was significantly ($P < 0.0001$) fewer than the 7.7 (5.4) LNs retrieved from no. 3a.

Discussion

Proximal gastrectomy has been introduced for early gastric cancer located in the upper third of the stomach [9]. In our institution, proximal gastrectomy is a commoner choice than total gastrectomy. Among the 3921 individuals comprising the base population, 204 of 300 patients with T1 upper-third gastric cancer underwent proximal gastrectomy. Although LNs lying along the right gastric and right gastroepiploic vessels are not dissected, survival outcome after proximal gastrectomy performed for early upper-third gastric cancer is known to be comparable with that after total gastrectomy [17, 18]. Several reports have demonstrated that the occurrence of metastasis from upper-third gastric cancer to LNs at the no. 4d, no. 5, or no. 6 station is rare [6, 7]. However, to date, there is little knowledge of the rate of metastasis to the distal part of the lesser curvature LNs. These LNs were separately classified into two substations in 2010 by the JGCA [14]. Owing to the exploration of no. 3 LNs in our institute, we could analyze data from 2400 patients over a 20-year period. Among 96

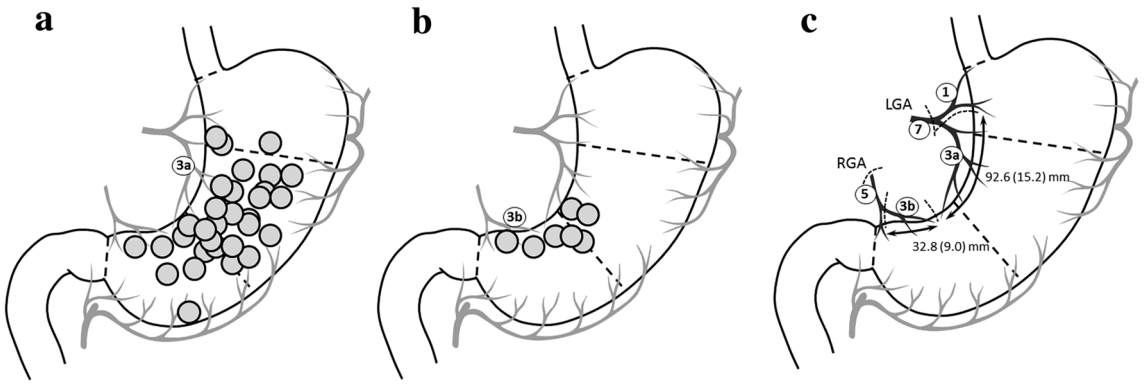


Fig. 3 **a**, **b** Mapping of the primary tumors with single-site metastasis to the no. 3a substation (**a**, $n = 31$) or the no. 3b substation (**b**, $n = 7$). **c** Distribution of the left gastric artery (*LGA*) and the right gastric artery (*RGA*) at the lesser curvature of the stomach

early upper-third gastric cancer patients, no tumors showed no. 3b metastasis. These results strongly support the current indication of proximal gastrectomy for early upper-third gastric cancer.

In the present study, we analyzed the metastasis rate and the therapeutic benefit of dissection of no. 3 LNs in advanced gastric cancer. When we classified the tumor location simply as U, M, and L, the rate of no. 3a metastasis from advanced tumors located in the upper third of the stomach was higher than that from tumors located in the middle third or lower third, and the no. 3b metastasis rate did not show any differences between the three locations. These results are consistent with previous data, indicating that the lesser curvature LN station is the most frequent metastatic site from upper-third gastric cancer [7, 8]; this is also the reason why expanding the indication of proximal gastrectomy to advanced tumors has not been generally accepted. However, when we subdivided the upper-third tumor location, the rate of no. 3b metastasis from tumors with a distal border ending in the upper third (UE/U) was extremely low and the TI was only 1.1. These results imply that the exclusion of no. 3b LN dissection from radical surgery would be oncologically acceptable when the distal resection margin is secured. All no.-3b-positive UE/U tumors measured more than 40 mm in diameter and were classified as T3 or T4 in depth. Therefore, proximal gastrectomy can be applicable for advanced gastric cancer localized in the upper third of the stomach except in T3/T4 tumors larger than 40 mm.

Metastasis to the distal nodal station in the greater curvature LNs should also be considered when proximal gastrectomy is performed for advanced upper-third tumors. In the present series, the rates of metastasis at no. 4d and no. 6 LNs from advanced UE/U tumors were very low and only a low therapeutic benefit was noted, indicating that the surgical dissection of these LNs is not beneficial for patient survival. In addition, all tumors with no. 4d and/or no. 6 metastasis were T4 in depth and huge (more than 60 mm). These results were as we expected and are consistent with data from previous reports [6–8]. Further, metastasis to the suprapyloric (no. 5 and no. 12a) LNs was not found from no.-3b-negative UE/U tumors. These results imply that, under the tumor conditions described above, the radicality of proximal gastrectomy is not inferior to that of total gastrectomy.

In the gastrointestinal tract, the lymphatic channels pass within the organ-associated mesenteries along with the vasculature toward the terminal LNs situated around the root of the central vasculature [19]. Thus, the number of LNs is roughly correlated with the size of the mesenteries. Our morphometric analyses using 90 surgical specimens revealed that the length of the lesser gastric curvature supplied by the RGA branches was shorter than that supplied by the descending limb of the LGA in a 1:3 ratio, indicating that the size of the mesentery for no. 3b was one third of that for no. 3a. On average, 7.7 LNs were retrieved from the no. 3a substation. However, the mean number of LNs (1.4) retrieved from the no. 3b substation was far fewer than the estimated "one-third" value, suggesting that the lymphatics along the RGA may provide only a minor lymphatic stream from the stomach. Such speculation is also supported by our results that demonstrated tumors with solitary metastasis to no. 3a were not localized to any part of the stomach, whereas those with metastasis to no. 3b were localized to the lesser curvature of the lower stomach. This may be due to the embryological characteristics of the origin of the LGA from the celiac artery, which is derived from the dorsal mesogastrium connected to the aorta, whereas the RGA arises in the ventral mesogastrium connected to the abdominal wall [20].

Although proximal gastrectomy is generally thought to offer advantages over conventional total gastrectomy in terms of maintenance of food intake volume [21–23] and postoperative nutrition status [17], reflux esophagitis or

gastric stasis that mainly depends on esophagogastric anastomosis remains a potential disadvantage [24]. Several reconstruction methods, such as jejunal interposition [9, 16] or the double tract method [25], are used to prevent regurgitation of the gastric contents, but these procedures are slightly complicated and no general agreement exists regarding the optimal reconstruction procedures. The reasons why on -third of patients with a T1 U tumor received total gastrectomy in our institute may be related to this problem. Recently, we and others developed novel methods for modified esophagogastrostomy by creating a reliable angle of His using a stapler [26, 27]. These techniques may become a feasible choice for simple reconstruction after proximal gastrectomy.

More importantly, the resection margin from the cancer tissue poses a problem for performing proximal gastrectomy. The Japanese gastric cancer treatment guidelines recommend proximal gastrectomy for tumors where more than half of the distal part of the stomach can be preserved, and also recommend that a gross distance of 2 cm for T1 tumors and 3 cm or more for T2 or deeper tumors should be obtained [10]. In the present study, we showed that the mean length of the lesser curvature was 153.7 mm. That is, when an advanced tumor is located in the lowest part of the U region, we need to remove the stomach 8 cm away from the esophagogastric junction to ensure a safe resection margin, wherein less than half of the distal stomach can be preserved. We consider that cancer with a distal border ending in the U region, especially cancer of the esophagogastric junction, would be a good indication for proximal gastrectomy.

In conclusion, the metastasis rate of no. 3b LNs and the therapeutic benefits of the dissection of no. 3b LNs were extremely low when the distal tumor border ended in the upper third of the stomach. Proximal gastrectomy with the exclusion of no. 3b lymphadenectomy could be indicated for at least T2 tumors measuring less than 40 mm localized in the upper third of the stomach.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval and patient consent All patients gave their informed consent before all the procedures were performed, and the experimental protocol was approved by the Ethics Committee of Toranomon Hospital (no. 1019).

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