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# Therapeutic Value of Lymph Node Dissection Along the Superior Mesenteric Vein and the Posterior Surface of the Pancreatic Head in Gastric Cancer Located in the Lower Third of the Stomach

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## ABSTRACT

**Background** Therapeutic value of lymph node dissection along the superior mesenteric vein (14v) and the posterior surface of the pancreatic head (13) remains unclear in gastric cancer patients.

**Methods** We reviewed 355 patients with advanced gastric cancer in the lower third of the stomach who had undergone gastrectomy at our hospital.

**Results** The frequency of lymph node (LN) metastasis was 10.2% and 7.4% in stations 13 and 14v, respectively. The frequency of station 13 metastasis was 26.8% for T3/T4 tumors with group 2 LNs metastasis and 1.4% for all other tumors. The frequency of station 14v metastasis was 22.2% for T3/T4 tumors with group 2 LNs metastasis and 1.8% for all other tumors. The therapeutic values for dissecting LN stations 13 and 14v were 1.9 and 0.9, respectively, similar to the therapeutic value for group 2 LN dissection.

**Conclusion** Because metastasis to stations 13 and 14v occurs frequently in patients with T3/T4 gastric cancer located in the lower third of the stomach who also have metastasis to group 2 LNs, stations 13 and 14v should be dissected in these patients.

**Key words** gastric cancer; lymph node dissection; prognosis

Gastric cancer is one of the most common cancers in Asia, and its mortality still ranks second among all cancer deaths worldwide.<sup>1</sup> In Japan, gastrectomy with D2 lymph node (LN) dissection is performed safely and is widely accepted as a standard treatment for locally advanced gastric cancer.<sup>2,3</sup> According to the Gastric Cancer Treatment Guidelines, the extent of dissection required for D2 LN dissection varies according to the type of gastrectomy.<sup>4</sup> Because distal gastrectomy is usu-

ally performed for lower-third gastric cancer, required LNs stations are 1, 3a, 3b, 4sb, 4d, 5, 6, 7, 8a, 9, 11p, and 12a to achieve D2 LN dissection. However, the suitable extent of LN dissection is still controversial. The LNs along the superior mesenteric vein are referred to as station 14v according to the 2nd English edition of the Japanese Classification of Gastric Carcinoma (JCGC).<sup>5</sup> These nodes receive the majority of lymphatic drainage from the lower third of the stomach and used to be conventionally included in the N2 group according to the previous Japanese classification.<sup>5</sup> In the past, the need for 14v dissection has been assessed based on anatomical location in the lymphatic drainage pathway and on the frequency of 14v metastasis as reported in several Japanese studies.<sup>6,7</sup> However, some papers have demonstrated that 14v dissection does not contribute to the prognosis of gastric cancer patients.<sup>8</sup> Therefore, the latest version of the Gastric Cancer Treatment Guidelines excludes station 14v from the nodes required for D2 LN dissection in gastric cancer located in the lower third of the stomach.<sup>4</sup>

The LNs on the posterior surface of the pancreatic head are referred to as station 13 according to the second English edition of the Japanese Classification of Gastric Carcinoma.<sup>5</sup> Because of its anatomical location, gastric cancer in the lower third of the stomach preferentially metastasizes to station 13 LNs.<sup>9,10</sup> However, the clinical significance and prognostic value of station 13 LN dissection remain controversial as well. The aim of this study was to evaluate therapeutic value of lymph node dissection of 13 and 14v LNs in gastric cancer located in the lower third of the stomach.

## MATERIALS AND METHODS

### Patients

From 1980 to 2010, 2262 patients underwent gastrectomy for gastric cancer at Tottori University Hospital, and 1210 patients were pathologically diagnosed with advanced gastric cancer. Among the patients with advanced gastric cancer, 355 patients had gastric cancer restricted to the lower third of the stomach and the

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Abbreviations: LN, lymph node; JCGC, Japanese Classification of Gastric Carcinoma; RCT, randomized control trial

**Table 1. Relationships among stations 13 and 14 lymph node dissection and clinicopathological variables in patients with gastric cancer**

Variable	13 lymph node dissection		<i>P</i> value	14v lymph node dissection		<i>P</i> value
	Performed ( <i>n</i> = 157)	Not performed ( <i>n</i> = 198)		Performed ( <i>n</i> = 121)	Not performed ( <i>n</i> = 234)	
Age	60.6 ± 11.1	68.0 ± 11.2	< 0.0001	61.2 ± 12.0	66.6 ± 11.2	0.0002
Tumor size	7.1 ± 2.6	6.0 ± 2.7	0.0003	6.9 ± 2.6	6.3 ± 2.7	0.026
Sex			0.53			0.072
Male ( <i>n</i> = 228)	98 (62.4%)	130 (65.7%)		70 (62.4%)	158 (65.7%)	
Female ( <i>n</i> = 127)	59 (37.6%)	68 (34.3%)		51 (37.6%)	76 (34.3%)	
Histology <sup>a</sup>			0.17			0.47
Differentiated ( <i>n</i> = 159)	64 (40.8%)	95 (48.0%)		51 (42.1%)	108 (46.2%)	
Undifferentiated ( <i>n</i> = 196)	93 (59.2%)	103 (52.0%)		70 (57.9%)	126 (53.8%)	
Depth of invasion <sup>b</sup>			0.09			0.62
T2 / T3 ( <i>n</i> = 158)	62 (39.5%)	96 (48.5%)		52 (43.0%)	107 (45.7%)	
T4 ( <i>n</i> = 197)	95 (60.5%)	102 (51.5%)		69 (57.0%)	127 (44.3%)	
Lymph node metastasis			0.0023			0.0049
Absent ( <i>n</i> = 104)	33 (21.0%)	71 (35.9%)		24 (19.8%)	80 (34.2%)	
Present ( <i>n</i> = 251)	124 (79.0%)	127 (64.1%)		97 (90.2%)	154 (65.8%)	
Lymphatic invasion			0.35			0.29
Absent ( <i>n</i> = 76)	30 (19.1%)	46 (23.2%)		22 (18.2%)	54 (23.1%)	
Present ( <i>n</i> = 279)	127 (80.9%)	152 (76.8%)		99 (81.8%)	180 (76.9%)	
Venous invasion			0.99			0.021
Absent ( <i>n</i> = 138)	61 (38.9%)	77 (38.9%)		37 (30.6%)	101 (43.2%)	
Present ( <i>n</i> = 217)	96 (61.1%)	121 (61.1%)		84 (69.4%)	133 (56.8%)	
Stage of disease			0.013			0.14
I / II ( <i>n</i> = 148)	54 (34.4%)	94 (47.5%)		44 (36.4%)	104 (44.4%)	
III / IV ( <i>n</i> = 207)	103 (65.6%)	104 (52.5%)		77 (63.6%)	130 (55.6%)	

All results are expressed as the mean ± SD.

<sup>a</sup>Differentiated, papillary, or tubular adenocarcinoma; undifferentiated, poorly differentiated, mucinous adenocarcinoma, and signet-ring cell carcinoma.

<sup>b</sup>Depth of invasion: T2, tumor invasion of the muscularis propria; T3, tumor invasion of the subserosa; T4, tumor penetration of the serosa or tumor invasion of adjacent organs

duodenum; these patients were recruited for analysis in this study. Patients with invasion involving the middle or upper third of the stomach were excluded from the present study. All patients underwent open gastrectomy with regional LN dissection. The clinicopathological findings were determined according to the JCGC.<sup>5</sup> Pathological diagnosis was made by single pathologist in our hospital. Clinicopathological features were retrospectively collected from the institute's database. This study was approved by our institutional review board (1608A086), and informed consent requirement was waived for this retrospective study.

### Therapeutic value of lymph node dissection

The therapeutic value of LN dissection was evaluated by multiplying the frequency of metastasis to the station by the 5-year survival rate of patients with metastasis in that station as proposed by Sasako et al.<sup>9</sup>

### Statistical analysis

Associations among factors were evaluated by the chi-squared test. Five-year survival rates were calculated according to the Kaplan–Meier method. Survival data shown in the current study are for cancer-specific survival. To this end, patients who died from causes other than gastric cancer were considered lost to follow-up as of the time of death. The accepted level of significance was *P* < 0.05. Stat View software (Abacus Concepts; Berkeley, CA) was used for all statistical analyses.

### RESULTS

Among 355 patients included in this study, station 13 and 14v LN dissection was performed in 157 and 121 patients, respectively. Table 1 shows the relationships among 13 and 14 lymph node dissection and clinicopathological variables in gastric cancer patients. Patients who underwent station 13 LN dissection were significantly younger than those who did not undergo station 13 LN dissection (*P* < 0.0001). Tumor size was

**Table 2. Relationship between the presence of stations 13 and 14 lymph node metastasis and clinicopathological variables in patients with gastric cancer**

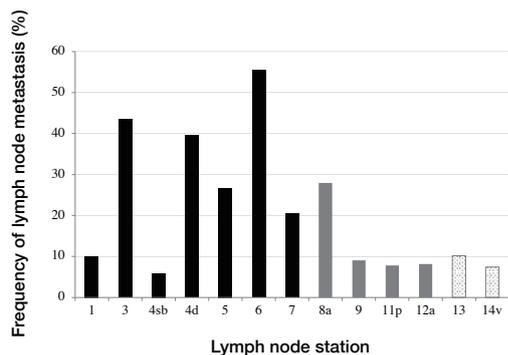
Variable	13 lymph node metastasis			P value	14v lymph node metastasis			P value
	n	Absent (n = 141)	Present (n = 16)		n	Absent (n = 112)	Present (n = 9)	
Age		60.3 ± 11.4	62.8 ± 8.1	0.59		61.3 ± 12.3	59.4 ± 5.3	0.32
Tumor size		7.0 ± 2.7	7.2 ± 1.7	0.51		6.9 ± 2.6	7.4 ± 1.8	0.35
Sex				0.11				1
Male	98	84 (59.6%)	13 (81.2%)		70	65 (62.4%)	5 (55.5%)	
Female	59	57 (40.4%)	3 (18.8%)		51	47 (37.6%)	4 (44.5%)	
Histology				0.066				0.077
Differentiated	74	61 (43.3%)	3 (18.8%)		51	50 (40.8%)	1 (11.1%)	
Undifferentiated	83	80 (56.7%)	13 (81.2%)		70	62 (59.2%)	8 (88.9%)	
Depth of invasion				0.1				0.09
T2 / T3	62	59 (41.8%)	3 (18.8%)		52	51 (45.5%)	1 (11.1%)	
T4	95	82 (58.2%)	13 (81.2%)		69	61 (54.5%)	8 (88.9%)	
Lymph node metastasis				0.025				0.2
Absent	33	33 (23.4%)	0 (0%)		88	24 (21.4%)	0 (0%)	
Present	124	108 (76.6%)	16 (100%)		33	88 (78.6%)	9 (100%)	
Lymphatic involvement				0.31				0.36
Absent	30	29 (20.6%)	1 (6.3%)		22	22 (19.6%)	0 (0%)	
Present	127	112 (79.4%)	15 (93.7%)		99	90 (80.4%)	9 (100%)	
Venous involvement				0.11				1
Absent	61	58 (41.1%)	3 (18.8%)		37	34 (30.4%)	3 (33.3%)	
Present	96	83 (58.9%)	13 (81.2%)		84	78 (69.6%)	6 (66.7%)	
Stage of disease				0.013				0.026
I / II	54	54 (38.3%)	0 (0%)		44	44 (39.3%)	0 (0%)	
III / IV	103	87 (61.7%)	16 (100%)		77	68 (60.7%)	9 (100%)	

All results are expressed as the mean ± SD. See table 1 for the detail of histology and depth of invasion.

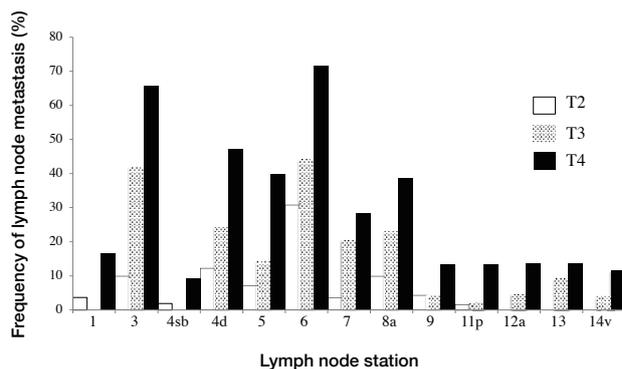
significantly larger in patients who underwent station 13 LN dissection than in those who did not undergo station 13 LN dissection ( $P = 0.0003$ ). Furthermore, the presence of LN metastasis was significantly more in patients who underwent station 13 LN dissection than in those who did not undergo station 13 LN dissection ( $P = 0.0023$ ). With regard to 14v LN dissection, patients who underwent station 14v LN dissection were significantly younger than those who did not undergo station 14v LN dissection ( $P = 0.0002$ ). Tumor size was significantly larger in patients who underwent station 14v LN dissection than in those who did not undergo station 14v LN dissection ( $P = 0.026$ ). Furthermore, the presence of LN metastasis and venous invasion was significantly more in patients who underwent station 14v LN dissection than in those who did not undergo station 14v LN dissection ( $P = 0.0049$  for LN metastasis and  $P = 0.021$  for venous invasion). We then determined the frequency of LN metastasis associated with gastric cancer located in the lower third of the stomach (Fig. 1). Station 1, 3, 4sb, 4d, 5, 6, and 7 LNs are ones that are required to be dissected to achieve D1 LN dissection in gastric cancer located in the lower third of the stomach. Station 8a, 9, 11p, and 12a LNs are ones that are required to be dissected to

achieve D2 LN dissection in gastric cancer located in the lower third of the stomach. The frequency of LN metastasis was 10.2% and 7.4% for stations 13 and 14v, respectively, similar to that for the group 2 LNs, such as stations 9, 11p, and 12a. We then determined relationship between the presence of 13 and 14 LN metastasis and clinicopathological variables in patients with gastric cancer (Table 2). Patients with LN metastasis and those with stage III / IV tumors had significantly more station 13 LN metastasis than did those without LN metastasis ( $P = 0.025$ ) and those with stage I / II tumors ( $P = 0.013$ ). Patients with stage III / IV tumors had significantly more station 14v LN metastasis than did those with stage I / II tumors ( $P = 0.026$ ). Figure 2 shows correlations between the depth of invasion and the frequency of metastasis to each LN station. Metastasis in station 1, 3, 4sb, 4d, 5, 6, 7, 8a, 9, and 11p LNs was observed for T2 tumors. However, both station 13 and station 14v LN metastasis were observed for T3 and T4 tumors, but not for T2 tumors.

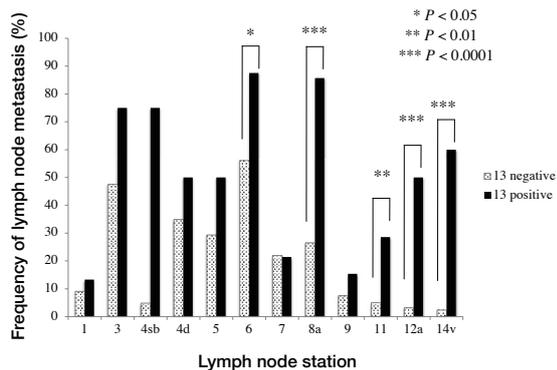
We then determined the frequency of LN metastasis to each station according to the status of station 13 LN metastasis. Tumors with station 13 metastasis metastasized significantly more often to stations 6, 8a,



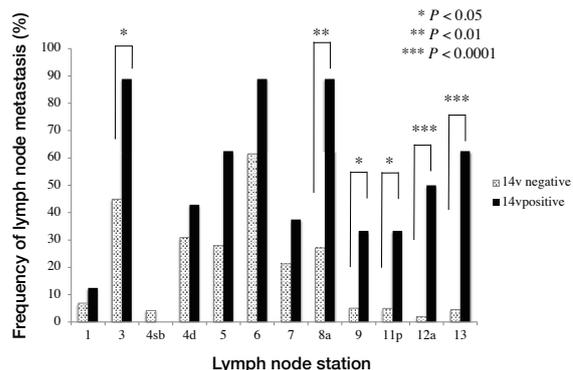
**Fig. 1.** The frequency of metastasis to each lymph node station in gastric cancer located in the lower third of the stomach.



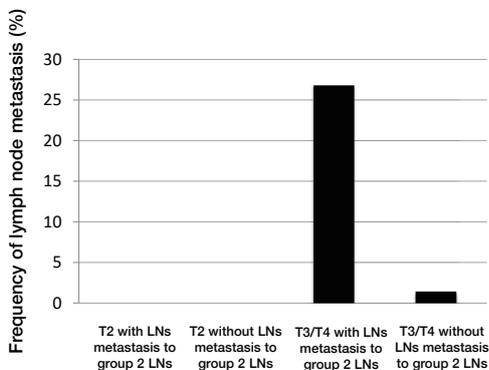
**Fig. 2.** The frequency of metastasis to each lymph node station according to the depth of invasion in gastric cancer located in the lower third of the stomach. Depth of invasion: T2, tumor invasion of the muscularis propria; T3, tumor invasion of the subserosa; T4, tumor penetration of the serosa or tumor invasion of adjacent organs.



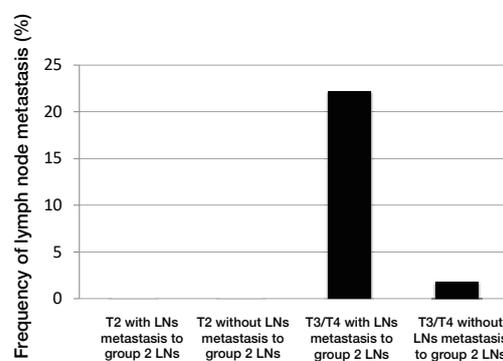
**Fig. 3.** The frequency of metastasis to each lymph node station according to the presence of station 13 lymph node metastasis in gastric cancer located in the lower third of the stomach.



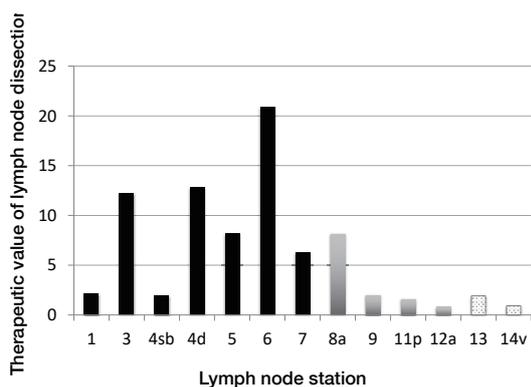
**Fig. 4.** The frequency of metastasis to each lymph node station according to the presence of station 14 lymph node metastasis in gastric cancer located in the lower third of the stomach.



**Fig. 5.** The frequency of station 13 lymph node metastasis according to the depth of invasion and the presence of metastasis to the group 2 lymph nodes in gastric cancer located in the lower third of the stomach. LN, lymph node. See Fig. 2 for the detail of depth of invasion.



**Fig. 6.** The frequency of station 14v lymph node metastasis according to the depth of invasion and the presence of metastasis to the group 2 lymph nodes in gastric cancer located in the lower third of the stomach. LN, lymph node. See Fig. 2 for the detail of depth of invasion.



**Fig. 7.** The therapeutic value of dissection at each lymph node station in gastric cancer located in the lower third of the stomach.

11, 12a, and 14v. Furthermore, this difference was more strikingly observed in the group 2 LNs, such as stations 8a, 11p, and 12a, compared with the group 1 LN such as station 6 (Fig. 3). Tumors with station 14v metastasis metastasized significantly more often to stations 3, 8a, 9, 11p, 12a, and 13. This difference was also more strikingly observed in the group 2 LNs, such as stations 8a and 12a, compared with the group 1 LN such as station 3 (Fig. 4). The frequency of station 13 LN metastasis was 26.8% for T3/T4 tumors with group 2 LN metastasis and 1.4% for all other tumors (Fig. 5). Furthermore, the frequency of station 14v LN metastasis was 22.2% for T3/T4 tumors with group 2 LN metastasis and 1.8% for all other tumors (Fig. 6). These results indicate that the presence of 13 and 14v LN metastasis could be predicted based on the depth of invasion and the presence of metastasis to the group 2 LNs.

The 5-year disease specific survival rates of patients with metastasis in each LN station were as follows: station 1, 21.9%; station 3, 28.2%; station 4sb, 33.3%; station 4d, 32.4%; station 5, 30.7%; station 6, 37.7%; station 7, 30.6%; station 8a, 29.3%; station 9, 22.7%; station 11p, 21%; station 12a, 10.5%; station 13, 18.8%; station 14v, 12.5%. Finally, we determined the therapeutic value of dissecting each LN station (Fig. 7). The therapeutic values for LN dissection of stations 13 and 14v were 1.9 and 0.9, respectively, similar to the therapeutic value for group 2 LN dissection (i.e., stations 9, 11p, and 12a).

## DISCUSSION

There is a general consensus regarding the role of regional LN dissection in gastric cancer surgery.<sup>11–13</sup> The optimal method to evaluate the therapeutic value of dissecting each LN station is randomized control trial (RCT) and some RCTs have been done in gastric cancer thus far. For instance, Songun et al. demonstrated

that D2 lymphadenectomy is associated with lower locoregional recurrence and gastric-cancer-related death rates than D1 surgery, indicating that group 2 lymph node dissection was useful in improving the prognosis of gastric cancer patients.<sup>14</sup> On the other hand, it is now accepted that prophylactic para-aortic LN dissection confers no survival advantage,<sup>15,16</sup> However, the optimal extent of LN dissection is still controversial since it is difficult to conduct RCT. Therefore, it is indispensable to develop other methods to evaluate the therapeutic value of each LN dissection. In this regard, Sasako et al. developed new method, known as therapeutic value index, to evaluate the therapeutic value of each LN dissection for gastric cancer. This index includes the prognosis of the patients with metastasis to the station, as well as the metastatic incidence and used in many studies of gastric cancer to evaluate the theoretical therapeutic impact of dissecting each LN station.<sup>10,17</sup> The high therapeutic value index of the LN station indicates that the dissection of that LN station is useful in improving the prognosis of gastric cancer patients.

The therapeutic value of station 13 LN dissection remains controversial. Tokunaga et al. showed that the frequency of station 13 LN metastasis in patients with advanced gastric cancer restricted to the lower third of the stomach and the duodenum was 23.9% in cases with duodenal invasion and 7% in cases without duodenal invasion; this difference was statistically significant.<sup>10</sup> In our study, the frequency of station 13 LN metastasis in patients with advanced gastric cancer restricted to the lower third of the stomach and the duodenum was 16.7% in cases with duodenal invasion and 9.7% in cases without duodenal invasion, which is almost identical to the previous report, indicating that metastasis to the 13 and 14v LNs occurs frequently in patients with gastric cancer located in the lower third of the stomach. Sasako et al. reported a 5-year survival rate of 0% for cases of lower-third advanced gastric cancer with station 13 LN metastasis. Therefore, these authors discounted any therapeutic value in station 13 LN dissection.<sup>9</sup> In contrast, Tokunaga et al. reported a 5-year survival rate of 17.5% in advanced gastric cancer patients with duodenal invasion and station 13 LN metastasis; the frequency of metastasis to these LNs was 23.9%. As a result, the therapeutic index for station 13 LN dissection in these advanced gastric cancer patients with duodenal invasion was 4.19, equivalent to that for most second-tier LNs. Therefore, these authors concluded that station 13 LNs should be dissected in patients with advanced gastric cancer with macroscopic duodenal invasion.<sup>10</sup> Our results demonstrated that a 5-year survival rate was 18.8% in advanced gastric cancer patients with station 13 LN

metastasis in this study. Furthermore, therapeutic index for station 13 LN dissection was almost equivalent to that for group 2 LNs such as stations 9, 11p, and 12a, indicating that station 13 LN dissection might be useful in improving the prognosis of patients with gastric cancer located in the lower third of the stomach. On the other hand, it remains unclear whether there is difference in therapeutic index for station 13 LN dissection according to the presence of duodenal invasion in the current study because of the small number of patients with duodenal invasion in the current study. Further investigations are urgently required in this regard.

With regard to the station 14v nodes, An et al. reported overall 3- and 5-year survival rates of 26% and 10%, respectively, in patients with positive 14v nodes who underwent R0 resections. Because the prognosis for patients with positive 14v nodes is poor, similar to that of patients with M1 disease, these authors concluded that exclusion of the 14v LNs from regional lymph node dissection should be considered.<sup>8</sup> In the current study, a similar 5-year survival rate of 12.5% was found in patients with positive 14v nodes. The therapeutic index for 14v LN dissection identified in our study was equivalent to that for most second-tier LNs. Therefore, 14v LN dissection has therapeutic value if R0 resection can be achieved.

Dissection of the station 13 and 14v LNs is technically demanding. Therefore, it is important to select patients who have a possibility of metastasis to these LNs. In this regard, Masuda et al. reported that the station 6 status was a useful predictive factor for 14v-negative status.<sup>18</sup> Tumors with station 13 metastasis metastasized significantly more often to stations 6, 8a, 11, and 12a in this study. Tumors with station 14v metastasis metastasized significantly more often to stations 3, 8a, 9, 11p, and 12a. These results indicate the possibility that there are lymphatic flows from these LNs to 13 and 14v LNs. In the current study, furthermore, we have demonstrated that patients who have T3/T4 tumors with metastasis to the group 2 LNs are likely to have metastasis to LN stations 13 and 14v. Therefore, stations 13 and 14v should be dissected in patients with T3/T4 gastric cancer located in the lower third of the stomach who also have possible metastasis to the group 2 LNs.

The present study has a few limitations. First, some bias was present because the study was retrospective. Particularly, the number of patients who underwent the dissection of LN stations 13 and 14v is 157 (44.2%) and 121 (34.1%), respectively, and is smaller than that of patients who underwent the dissection of group 1 and 2 LNs. Second, the number of patients included in the current study was small; therefore, a large-scale, prospec-

tive randomized controlled trial is needed to confirm the results.

In conclusion, the dissection of LN stations 13 and 14v might be beneficial for survival in patients with gastric cancer located in the lower third of the stomach. Because metastasis to the 13 and 14v LNs occurs frequently in patients with T3/T4 gastric cancer located in the lower third of the stomach who also have group 2 LN metastasis, stations 13 and 14v should be dissected in these patients.

*Human rights statement and informed consent:* All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent from patients was waived because of the retrospective design of this study.

*The authors declare no conflict of interest.*

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