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Tumor Location on the Vertical Section of the Anterior Wall Is Related to Favorable Prognosis and Low Incidence of Lymph Node Metastasis in Lower-third Gastric Cancer

YUSUKE TAKASHIMA*, SHUHEI KOMATSU*, MASATAKA KASUGA, TAKUMA OHASHI, HIROTAKA KONISHI, ATSUSHI SHIOZAKI, TAKESHI KUBOTA, HITOSHI FUJIWARA, KAZUMA OKAMOTO and EIGO OTSUJI

Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine, Kyoto, Japan

Abstract. *Background/Aim: This retrospective study investigated the clinical significance of vertical location in gastric cancer (GC) and the optimal treatment strategy according to the vertical location. Patients and Methods: Between 1997 and 2018, 1,304 consecutive patients with GC who underwent curative surgical resection with lymph-adenectomy were analyzed retrospectively. Results: Patients with GC in the anterior wall (AW) had a significantly better prognosis compared to those in other sites of the lower third stomach (p=0.040). Multivariate analysis showed that tumor location in the AW was an independent prognostic factor and was associated with a lower incidence of lymph node metastasis (LNM) (p=0.023). The frequency of LNM in the area of D2 was lower in patients with AW GC than those with GC in other locations. Conclusion: Patients with AW GC had a favorable prognosis, with a lower incidence of LNM in lower-third GC.*

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of death worldwide (1). The concept of cancer stage was established according to the Tumor-Node-Metastasis (TNM) classification by the Union for International Cancer Control (UICC) (2) and American Joint Committee on Cancer (AJCC) (3) to evaluate prognosis and determine treatment strategy (4, 5). As the staging system shows, lymph node metastasis (LNM) is one of the strongest prognostic factors (6, 7), and the optimal range of lymph node dissection has been reported according to preoperative diagnosis of cancer progression (8, 9).

An adequate extent of lymph node dissection is necessary to prevent the lymphatic progression of GC. Therefore, based on the results of research on lymphatic flow in GC, Japanese guidelines recommend the optimal lymphatic dissection area for radical GC surgery according to the horizontal location of GC (4). However, although there are several reports about the correlation between vertical tumor location and GC prognosis, the clinical effects of vertical tumor location on LNM have not been fully elucidated, except for the recent definition of combined splenectomy, which has not been recommended to avoid upper-third advanced GC that does not invade the greater curvature (10, 11).

In the present study, we hypothesized that tumor location in the vertical section of GC would be associated with prognosis and LNM based on a previous report suggesting that the vertical distance of the tumor from the main extramural lymphatic flow affects lymphatic metastasis and prognosis in esophageal cancer (12). To verify these hypotheses, we evaluated the prognosis according to the vertical location and incidence of LNM. Our results suggested that GC location on the anterior wall might serve as a favorable prognostic factor and result in lower LNM frequency in GC.

Patients and Methods

Patients. This study was approved by the Kyoto Prefectural University of Medicine and was performed under the ethical standards described in an appropriate version of the Declaration of Helsinki. A total of 1,721 consecutive patients underwent curative gastrectomy with lymphadenectomy for GC at our institute between January 1997 and December 2018. Of these 1,721 patients, 417 were excluded from the study because of multiple carcinomas (n=204), insufficient clinical data (n=60), remnant GC (n=49), circumferential involvement (n=66), or other reasons (n=38). Therefore, we investigated 1,304 consecutive patients (Figure 1A). The median follow-up period was 5.3 years (interquartile range=3.0-7.3 years). The resected specimens were examined by pathologists and

*These Authors contributed equally to this work.

Correspondence to: Shuhei Komatsu, MD, Ph.D., FACS, Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachihirokoji, Kamigyo-ku, Kyoto 602-8566, Japan. Tel: +81 752515527, Fax: +81 752515522, e-mail: skomatsu@koto.kpu-m.ac.jp

Key Words: Vertical location, anterior wall, lymph node metastasis, gastric cancer.

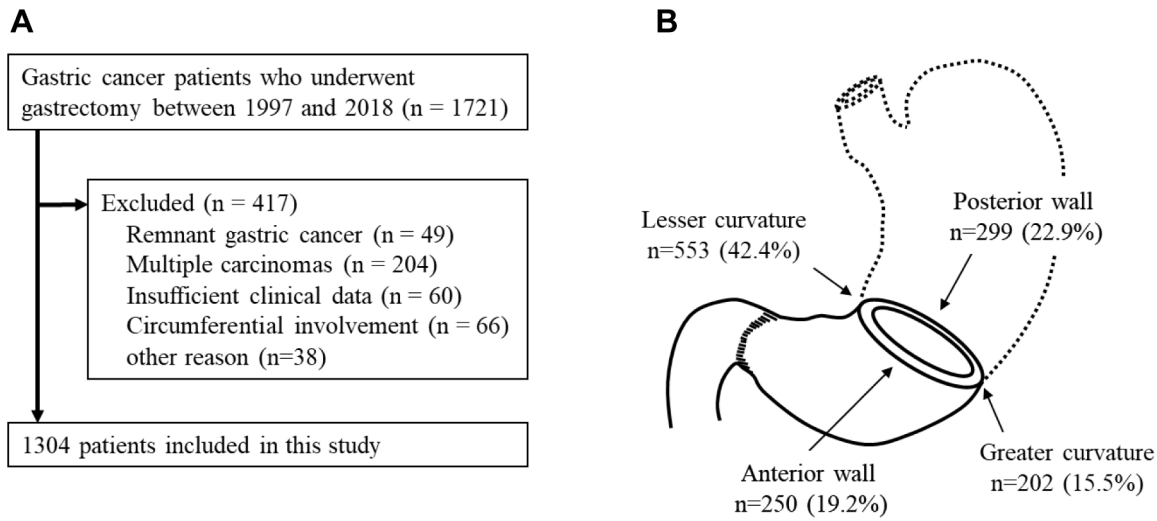

Figure 1. *Enrolled patients and definition of tumor laterality. (A) A total of 1,721 patients underwent curative gastrectomy with lymphadenectomy between January 1997 and December 2018. Of these, 417 patients were excluded from the study. Thus, data from 1,304 consecutive patients were obtained from their hospital records and retrospectively analyzed. (B) Of the 1,304 patients, 250 had gastric cancer in the anterior wall (19.2%), 299 in the posterior wall (22.9%), 553 in the lesser curvature (42.4%), and 202 in the greater curvature (15.5%).*

evaluated based on the Japanese Classification of GC. All dissected lymph nodes were fixed in buffered formalin, embedded in paraffin, and subjected to pathological examination. Pathologists in our institution examined the lymph nodes by sectioning slices in the plane of the largest node dimension to confirm the presence of metastasis. The clinicopathological findings of these patients were retrospectively obtained based on their medical records.

Definitions of vertical and horizontal locations and regional lymph nodes. The stomach was divided into three portions; namely, the upper third part (U), middle third (M), and lower third (L), while the cross-sectional circumference of the stomach was divided into four parts – the lesser curvature (LC), greater curvature, anterior wall (AW), and posterior wall (PW) – according to the Japanese Classification of GC (13). The tumor location was determined according to its main position. Of the 1,304 patients, 250 had GC in the AW (19.2%), 299 in the PW (22.9%), 553 in the LC (42.4%), and 202 patients in the greater curvature (15.5%) (Figure 1B). The differences in surgical outcomes and clinicopathological factors were compared between patients with GC in the AW and the other vertical locations. The differences in the locations of LNM were estimated according to a previous Japanese classification system (14), in which the regional lymph nodes were classified depending on the location of the primary tumor.

Statistical analysis. Statistical analyses were conducted using JMP version 16 (SAS Institute Inc., Cary, NC, USA). Mann–Whitney *U*-tests for unpaired data of continuous variables were used to compare clinicopathological variables. For survival analysis, Kaplan–Meier survival curves were constructed for groups based on univariate predictors, and differences between the groups were tested using generalized Wilcoxon tests. A Cox proportional hazards model was used for further evaluation of the multivariate survival analysis. Statistical significance was set at $p<0.05$.

Results

Anterior wall location showed favorable prognosis in lower-third GC. Figure 2 shows the 5-year overall survival (5yr-OS) curves for each of the three stomach sites. For lower-third gastric cancer, patients with GC in the AW had a significantly better prognosis compared to those in the other sites ($p=0.040$), and the 5yr-OS was 90.2% for AW, 85.3% for PW, 80.0% for GC, and 77.0% for LC, respectively. Regarding the upper and middle third gastric locations, there was no difference in the 5-yr OS rate between the AW and the other locations. Therefore, we focused on lower-third gastric cancer in our further analyses.

Univariate and multivariate analysis using Cox's proportional hazard model. Univariate and multivariate analyses using Cox's proportional hazard model were performed to elucidate the prognostic factors for OS in patients with lower-third gastric cancer. As shown in Table I, the clinical variables included sex, age, pT stage, pN stage, tumor size, histological type, venous invasion, lymphatic invasion, and cross-section. The results of multivariate analysis showed that AW [$p=0.040$, hazard ratio (HR)=2.30, 95% confidence interval (CI)=1.06-6.04] was an independent prognostic factor along with pT stage, pN stage, and tumor size.

Comparisons of clinicopathological factors between patients with AW GC and GC in other locations in the lower third of the stomach. Table II shows the results of the comparisons of

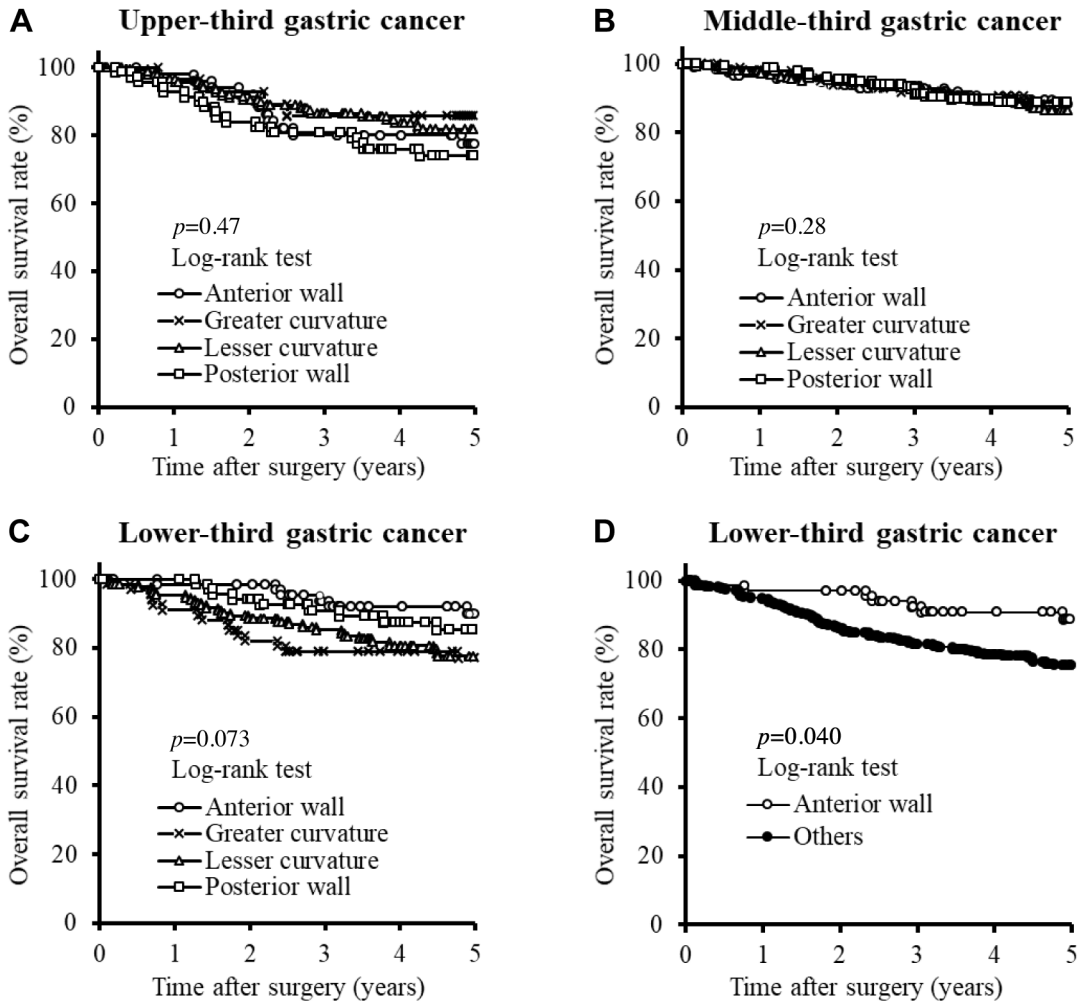

Figure 2. *Comparisons of 5-year overall survival (OS) rates according to tumor laterality. (A) Comparisons of 5-year OS rates in upper-third gastric cancer. (B) Comparisons of 5-year OS rates in middle-third gastric cancer. (C) Comparisons of 5-year OS rates in lower-third gastric cancer. (D) Comparisons of 5-year OS rates in lower-third gastric cancer located in the anterior wall and other locations.*

clinicopathological factors between AW and the other GC locations in the lower third of the stomach. GC in the AW was associated with lower incidences of lymphatic invasion (p=0.043) and LNM (p=0.023) compared to the other sites. No other significant differences in other clinicopathological factors were observed between the two groups. A logistic regression analysis of clinicopathological factors found that not-AW site was associated with LNM [p=0.016; odds ratio (OR)=2.63, 95%CI=1.19-6.41] as well as advanced pT, undifferentiated histological, lymphatic invasion, and venous invasion (Table III).

Comparisons of AW GC to GC in other locations on LNM. We next compared the region of LNM based on the Japanese Classification of Gastric Carcinoma, 3rd edition. In early GC, there were no significant differences in LNMs between vertical tumor locations in the areas of lymph node stations D1 and D2. In contrast, patients with advanced AW GC tended to have a lower incidence of LNM in the area of D1 (p=0.098) and a significantly lower incidence of LNM in the area of D2 compared to the incidences in other locations (p=0.030) (Figure 3).

Discussion

Mine *et al*. demonstrated that vertical tumor location, also known as tumor laterality, affects prognosis and systemic lymphatic metastases in esophageal cancer. Patients with esophageal tumors on the right and dorsal sides, which were near the thoracic duct, have poorer prognoses due to the high frequency of hematogenous metastasis (12). However, few reports have assessed the influence of tumor laterality on the prognosis and LNM of GC (15). The results of this study

Table I. *Results of univariate and multivariate analysis using Cox's proportional hazard model.*

Variables	Univariate[a]		Multivariate[b]	
	p-Value	HR[c]	95%CI[d]	*p*-Value
Gender				
Male *vs*. Female	0.753	1.203	0.700-2.130	0.509
Age (years)				
≥65 *vs*. <65	0.216	1.284	0.739-2.283	0.379
pT category[e]				
pT4 *vs*. pT1-3	**<0.001**	2.017	1.041-3.824	**0.038**
pN category[e]				
pN1-3 *vs*. pN0	**<0.001**	2.985	1.519-5.885	**0.002**
Tumor size (mm)				
≥30 *vs*. <30	**<0.001**	2.217	1.080-4.923	**0.029**
Histological type				
Undifferentiated *vs*. differentiated	**0.043**	1.267	0.733-2.207	0.397
Venous invasion				
3 *vs*. 0-2	0.752	0.638	0.188-1.640	0.379
Lymphatic invasion				
3 *vs*. 0-2	**<0.001**	1.090	0.566-2.029	0.791
Cross-section part				
Non-anterior *vs*. anterior	**0.040**	2.304	1.060-6.042	**0.034**

[a]Analyzed by log-rank (Mantel-Cox) test; [b]analyzed by Cox's proportional hazard model; [c]HR: hazard ratio; [d]CI: confidence interval; [e]classified according to the Japanese Classification of Gastric Carcinoma Significant; *p*-Values are shown in bold.

Table II. *Comparisons of clinicopathological factors between patients with gastric cancer located in the anterior wall and other locations in the lower third of the stomach.*

Variables	Anterior wall (n=77)	Others (n=287)	*p*-Value*
Gender			
Male	53 (68.8%)	193 (67.2%)	0.792
Female	24 (31.2%)	94 (32.8%)	
BMI (kg/m^2)			
<21	26 (33.8%)	100 (34.8%)	0.860
≥21	51 (66.2%)	187 (65.2%)	
Age (years)			
<65	37 (48.1%)	124 (43.2%)	0.447
≥65	40 (51.9%)	163 (56.8%)	
Tumor major axis(mm)			
<30	34 (44.2%)	122 (42.5%)	0.795
≥30	43 (55.8%)	165 (57.5%)	
pT-stage			
T1–3	70 (90.9%)	257 (89.5%)	0.725
T4	7 (9.1%)	30 (10.5%)	
pN-stage			
N0	63 (81.8%)	197 (68.6%)	**0.023**
N1–3	14 (18.2%)	90 (31.4%)	
Histopathological type			
Differentiated	44 (57.1%)	163 (56.8%)	0.956
Undifferentiated	33 (42.9%)	124 (43.2%)	
Venous invasion			
Absent	59 (76.6%)	196 (68.3%)	0.156
Present	18 (23.4%)	91 (31.7%)	
Lymphatic invasion			
Absent	52 (67.5%)	157 (54.7%)	**0.043**
Present	25 (32.5%)	130 (45.3%)	

**p*-Values are from the chi-square test. Significant *p*-Values are shown in bold.

Table III. *Risk factors for lymph node metastasis in lower-third gastric cancer.*

Variables		Univariate[a]		Multivariate[b]	
		p-Value	OR[c]	95%CI[d]	*p*-Value
pT category	pT4 *vs*. pT1-3	**<0.001**	33.70	12.10-120.40	**<0.001**
Histological type	Undiff.[f] *vs*. Diff.[g]	**0.001**	1.84	1.03-3.33	**0.039**
Venous invasion	3 *vs*. 0-2	**0.003**	5.55	1.84-17.24	**0.004**
Lymphatic invasion	3 *vs*. 0-2	**<0.001**	10.03	4.87-21.56	**<0.001**
Cross-sectional part	Non-anterior *vs*. anterior	**0.017**	2.63	1.19-6.41	**0.016**

[a]Analyzed by chi-square test; [b]analyzed by multiple logistic regression analysis; [c]OR: odds ratio; [d]CI: confidence interval; [f]Undiff; undifferentiated type; [g]Diff: differentiated type. Significant *p*-Values are shown in bold.

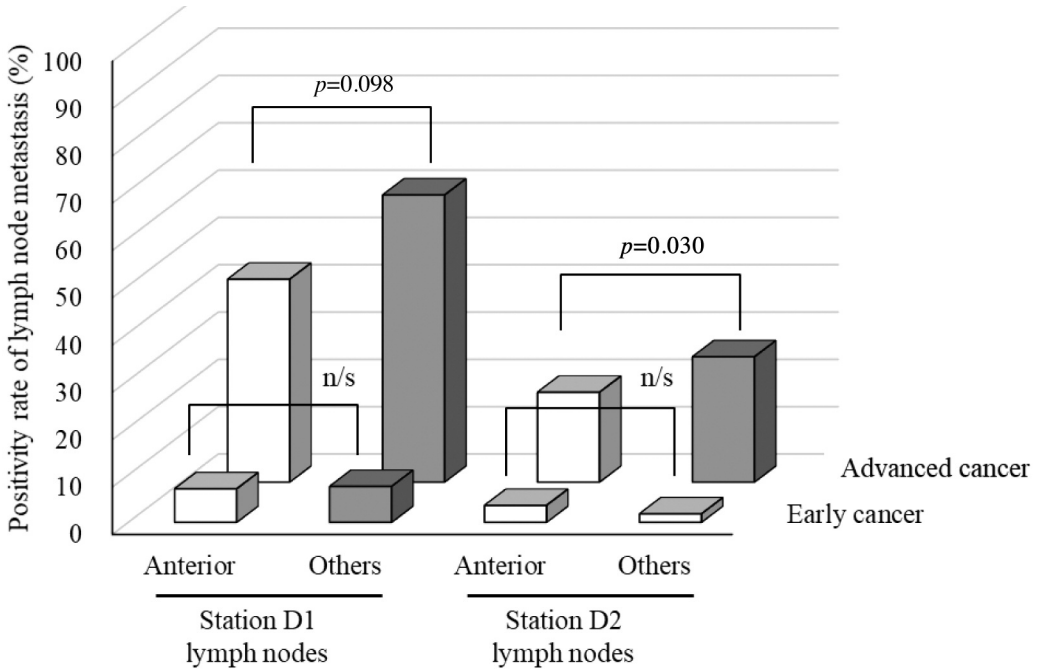

Figure 3. *Comparisons of the incidence of lymph node metastasis (LNM) between patients with gastric cancer (GC) on the anterior wall (AW) and other locations. In advanced GC, there was a lower incidence of LNM in the area of D2 resection in the AW compared to those in the other locations. However, in early GC, there was no difference in LNM between locations in the areas of D1 and D2 resection. The LNM area was based on the Japanese Classification of Gastric Carcinoma, 3rd edition. GC: Gastric cancer; LNM: lymph node metastasis; AW: anterior wall.*

demonstrated that AW position was an independent prognostic factor in third-lower GC (p=0.040, HR=2.30, 95%CI=1.06-6.04). Moreover, patients with AW GC tended to have fewer LNMs, especially in the D2 region. These results indicated that cancer laterality could be an important indicator of prognosis and LNM in lower-third GC, strongly suggesting that the distance from the main lymphatic flow may be closely related to LNM.

The most striking finding in the present study was that the patients with AW GC had significantly fewer LNMs in the area of station D2 lymph nodes in the lower third of the stomach. From the viewpoint of the distance from the tumor to the main lymphatic flow, presumably, GC located on the greater curvature wall is more likely to metastasize to lymph node station No.6 (16), which has lymphatic flow to stations No.14v and No.16, making lymphadenectomy difficult (17-19). Jung *et al*. reported a worse prognosis in patients with GC on the greater curvature than those in patients with GC with other locations (15). Meanwhile, GC on the lesser curvature wall might metastasize to lymph node stations No.3 and 5, which have lymphatic flow to station Nos.7, 8a, and 12a. GC of the PW also metastasizes to station No.11p due to lymphatic flow of the posterior artery.

Regarding remnant GC, tumor location in the greater curvature was reported to be an independent risk factor for LMN, especially lymph node Nos.4sb and 10 (20). The lymphatic flows of the greater curvature and splenic hilum are preserved as the main lymphatic flow after the initial gastrectomy (21). Thus, these previous reports strongly suggest that the vertical tumor location is also a pivotal indicator of prognosis and LNM as well as histological type (22, 23), lymphatic vessel invasion (24, 25), and venous invasion (26, 27) in GC.

The gastric lymphatic compartments are divided according to the five directions along the main feeding arteries, namely, the left gastric, right gastric, left gastroepiploic, right gastroepiploic, and posterior gastric arteries, based on detailed anatomical studies of the lymphatic drainage of GC (16, 28). The AW is located a comparatively longer distance from these main feeding arteries and major lymphatic flows, which may be related to the different frequencies of LNM. These results may lead to the potential for minimized gastrectomy for AW GC in elderly or high-risk patients for whom extended invasive gastrectomy might be a risk factor for postoperative complications (29, 30) and also to stratify GC patients to undergo functional preserving gastrectomy leading to favorable postoperative outcomes (31).

This study had some limitations, as the results were obtained from a retrospective evaluation of a small number of patients at a single institute. Moreover, the findings require validation in a larger prospective multicenter study using a standardized surgical approach. Nevertheless, our findings suggest the impact of tumor laterality on the prognosis of GC patients due to lymphatic flow entering the systemic circulation. Moreover, patients with GC in locations other than the AW might benefit from formal lymphadenectomy due to the higher incidence of lymph node involvement.

Conflicts of Interest

The Authors have no conflicts of interest to disclose in relation to this study.

Authors' Contributions

YT, SK designed and SK, EO reviewed the research; YT, SK drafted the manuscript; SK, MK, TO, HK, AS, TK, HF, KO and EO provided clinical data and performed analyses. All Authors read and approved the final manuscript.

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