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Clinical Implication of Tumor-invasive Status into the Muscularis Propria in T2 Gastric Cancer

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Abstract. *Background/Aim: Several studies have investigated prognostic factors in patients with T2 gastric cancer, but no consensus has been reached to date. The aim was to investigate the clinicopathological significance of the status of tumor invasion into the muscularis propria (MP) in T2 gastric cancer patients. Patients and Methods: A total of 113 patients with T2 cancer were enrolled. The status of caner invasion was analyzed according to width (extent of horizontal invasion) and depth (extent of vertical invasion). Results: The prognosis of the group with wide width of invasion (≥1.5 cm) was significantly poorer than that of the group with narrow width of invasion (<1.5 cm) (p=0.001). Multivariate analysis identified the width, and not the depth, as an independent prognostic factor. The analysis according to AJCC N stage showed that the width, and not the nodal status, was an independent prognostic factor in the N2-N3 patients (p=0.005). Conclusion: Measurement of the width of tumor invasion into the MP was useful to understand the malignant potential of T2 gastric cancer.*

Advanced gastric cancer confined to the muscularis propria (T2 gastric cancer) is as an intermediate-stage carcinoma, between early and advanced cancer (1, 2). Therefore, it is considered to have a better prognosis than more advanced cancer, and recently minimally-invasive surgical procedures, such as laparoscopic gastrectomy, have been actively adopted (3, 4). However, although at a low frequency, recurrences do occur, and it is clinically important to investigate prognostic factors for T2 gastric cancer.

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Key Words: Gastric cancer, muscularis propria, prognosis, tumor invasion.

Several studies have investigated prognostic factors in patients with T2 gastric cancer. While studies have been conducted to determine the influence of age (5, 6), tumor diameter (7, 8), lymph node metastasis (9, 10) and macroscopic type (11) on the prognosis, no consensus has been reached yet. Therefore, in this study, we investigated the clinicopathological significance of the status of tumor invasion at the invasive front, namely, in the muscularis propria (MP), in patients with T2 gastric cancer.

Patients and methods

Patients. Between January 2006 and December 2016, 980 consecutive patients with gastric cancer underwent curative gastrectomy at the Department of Gastroenterological Surgery of Tokai University School of Medicine. Of these patients, the data of 113 patients with tumor invasion into the MP were analyzed in this retrospective study. The gross classification and histopathological classification were based on the Japanese Classification of Gastric Carcinoma (JCGC) published by the Japanese Gastric Cancer Association (12). Staging was performed according to the American Joint Committee on Cancer (AJCC) staging manual, eighth edition (13). Patients were mainly followed-up on an outpatient basis at our hospital; however, those who had moved to other institutions were asked relevant questions over telephone. Follow-up was continued until December 2018, with a median duration of follow-up of 2129 days (range=205-4787). Diagnosis of tumor recurrence was suspected on clinical grounds and confirmed by further investigations. In some patients, the initial recurrence was diagnosed at two or more sites, and in such patients, all of the sites were counted as sites of initial recurrence.

The research was conducted in accordance with the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki and its later amendments. This study was approved by the institutional review board of Tokai University Hospital (registration number 18R-150).

Assessment of the status of tumor invasion into the MP. The resected stomach was opened and placed on a flat board with the mucosal side up, and fixed in 10% formalin. After fixation, the neoplasm was sectioned along the maximum cross-sectional plane parallel to the lesser curvature, based on the general rules of the JCGC (12). Several additional sections parallel to the maximum cross-sectional plane and one section perpendicular to this plane were prepared to

identify the area with the deepest invasion. The status of caner invasion into the MP was analyzed according to width (extent of horizontal invasion) and depth (extent of vertical invasion). The method that we have previously used to measure the horizontal width of tumor invasion in gastric cancer patients with tumor invasion of the subserosa was applied to the present study (14). Specifically, the width of invasion was defined as the horizontal length of cancerous invasion measured along the upper rim of the MP layer in these cross-sectional planes. The depth was defined as the distance from the upper rim of the MP to the point of deepest tumor penetration. In the patients that a tumor invaded the MP at two or more sites, the maximum width and depth were defined as the width and depth of tumor invasion.

Statistical analysis. The chi-squared test was used to compare categorical data, and the Mann-Whitney *U*-test to compare continuous variables. The cumulative relapse-free survival rates were calculated by the Kaplan-Meier method, and compared by the log-rank test. Multivariate analyses were performed to identify independent prognostic factors. All significant factors from the univariate analyses were entered in the multivariate analysis. The Cox proportional hazards regression model was used to determine the optimal cutoff threshold for the width and depth of invasion of the MP. A p-value <0.05 was considered as indicative of statistical significance. All the statistical analyses were performed with SPSS, version 25.0J (IBM Corp., Armonk, NY, USA).

Results

Threshold width and depth of invasion into the MP. The median width of invasion into the MP (WiMP) was 0.75 cm (range=0.02-9.85). Relapse-free survival rates were calculated for every 0.5-cm difference in the width of invasion to determine the appropriate threshold. The width of invasion associated with the largest hazard ratio (HR) as determined using the Cox proportional hazard regression model, was considered as the optimal cutoff point. The most significant difference in the survival rate was found at the threshold width of 1.5 cm (HR =3.552, p=0.002) (Table I).

The median depth of invasion into the MP was 1.4 mm (range=0.1-10.1). To determine the appropriate threshold, a similar analysis was performed for each 0.5-mm difference in the depth of invasion. The results revealed no significant prognostic impact at any depth of invasion. Accordingly, subsequent analyses were performed by dividing all of T2 gastric cancer patients by the WiMP.

Clinicopathologic characteristics according to the WiMP. Of the 113 patients with T2 gastric cancer, the WiMP was <1.5 cm in 85 patients (narrow WiMP group) and ≥1.5 cm in 28 patients (wide WiMP group). The clinicopathological factors were compared between these two groups (Table II). The wide WiMP group had a significantly larger tumor diameter (p=0.001) and significantly higher frequency of lymph node metastasis (p=0.014) than the narrow WiMP group.

Table I. *Hazard ratio (HR) according to width of invasion of the muscularis propria calculated by the Cox proportional hazards regression model using relapse-free survival.*

Threshold (cm)	HR	95% CI	p-Value
0.5	2.416	0.898-6.502	0.081
1.0	2.286	0.995-5.286	0.051
1.5	3.552	1.594-7.917	0.002
2.0	1.806	0.672-4.856	0.241
2.5	1.267	0.376-4.267	0.703

CI, Confidence interval.

Table II. Associations between clinicopathological parameters and width of invasion of the muscularis propria in all patients.

Variable	Narrow WiMP (n=85) n (%)	Wide WiMP (n=28) n (%)	p-Value
Age (years)			
<70	50 (58.8)	15 (53.6)	0.626
≥70	35 (41.2)	13 (46.4)	
Gender			
Male	59 (69.4)	20 (71.4)	0.840
Female	26 (30.6)	8 (28.6)	
Tumor size* (cm)	3.2 (0.6-11.5)	4.3 (2.5-12.2)	0.001
Gross type			
Circumscribed	66 (77.6)	19 (67.9)	0.298
Infiltrative	19 (22.4)	9 (32.1)	
Resection type			
Subtotal gastrectomy	73 (85.9)	21 (75.0)	0.182
Total gastrectomy	12 (14.1)	7 (25.0)	
Histologic type			
Differentiated	46 (54.1)	13 (46.4)	0.480
Undifferentiated	39 (45.9)	15 (53.6)	
Lymphatic invasion			
Negative	19 (22.4)	4 (14.3)	0.358
Positive	66 (77.6)	24 (85.7)	
Venous invasion			
Negative	31 (36.5)	10 (35.7)	0.942
Positive	54 (63.5)	18 (64.3)	
Lymph node metastasis			
Negative	53 (62.4)	10 (35.7)	0.014
Positive	32 (37.6)	18 (64.3)	
Adjuvant chemotherapy			
Negative	48 (56.5)	10 (35.7)	0.057
Positive	37 (43.5)	18 (64.3)	

WiMP, Width of invasion of the muscularis propria. *Data presented as median (range).

Correlation of the WiMP with the prognosis. The prognostic impact of the WiMP was evaluated by univariate and multivariate analyses (Table III). The 5-year relapse-free survival rate was 86.6% in the narrow WiMP group and 56.3% in the wide WiMP group (Figure 1), indicating a significantly

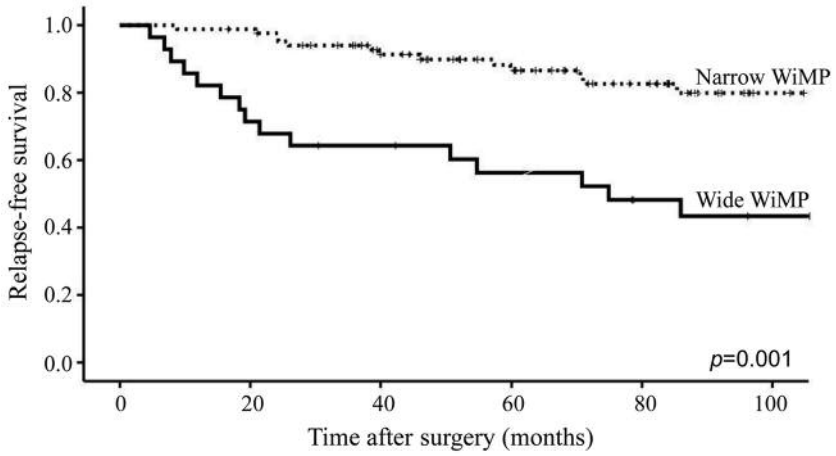

Figure 1. *Kaplan-Meier survival curves for relapse-free survival of all patients according to width of invasion of the muscularis propria (WiMP). The group with wide WiMP had a significantly poorer prognosis compared to the group with narrow WiMP. Narrow WiMP, Width of invasion of muscularis propria <1.5 cm; wide WiMP, width of invasion of muscularis propria ≥1.5 cm.*

poorer prognosis for the latter (p=0.001). Additionally to the WiMP, the other significant prognostic factors that were identified by the univariate analyses in the 113 patients were the age, tumor size, and lymph node metastasis. In multivariate analysis, age, lymph node metastasis, and WiMP were identified as independent prognostic factors.

Relationship between the WiMP and the prognosis according to the extent of lymph node metastasis. The influence of the WiMP on the prognosis was investigated according to the extent of lymph node metastasis. In the 63 AJCC N0 patients, the narrow (n=53) and wide (n=10) WiMP groups showed 5-year survival rates of 93.5% and 90.0%, respectively. In the 23 AJCC N1 patients, the narrow (n=17) and wide (n=6) WiMP groups showed 5-year survival rates of 71.1% and 66.7%, respectively. Thus, there was no significant difference in prognosis between the narrow and wide WiMP groups in both the N0 patients and N1 patients. The AJCC N2 and N3 patients were combined for the analysis, because there were only 16 N2 patients and 11 N3 patients. In the N2-N3 patients, the 5-year survival rates in the narrow (n=15) and wide (n=12) WiMP groups were 80.0% and 25.0%, respectively, with a significant difference between the two groups (p=0.015) (Figure 2). Besides the WiMP, univariate analysis identified that the adjuvant chemotherapy was a significant prognostic factor for the N2-N3 patients. These two parameters were also identified as independent prognostic factors in multivariate analysis (Table IV).

Relationship between the WiMP and the mode of recurrence. The recurrence rates in the narrow WiMP group was significantly lower than in the wide WiMP group [7.1% (6/85) and 28.6% (8/28), respectively; p=0.003]. A review of the mode of recurrence in the narrow WiMP group and wide WiMP group showed development of lymph node metastasis in 3.5% (3/85) and 14.3% (4/28) of the patients, respectively, hematogenous metastasis in 3.5% (3/85) and 10.7% (3/28) of the patients, respectively, and peritoneal metastasis 2.4% (2/85) and 3.6% (1/28) of the patients, respectively. The lymph node recurrence rate was significantly higher in the wide WiMP group (p=0.041).

Discussion

Studies on the clinical significance of the status of tumor invasion into the MP in patients with T2 gastric cancer have usually focused on the depth of tumor invasion into the MP (15-17). In these studies, the MP was divided for the invasion into a superficial layer composed of the inner circular muscle and a deep layer composed of the outer longitudinal muscle. Some studies have reported that gastric cancer patients showing invasion of the deep layer have a poorer prognosis than those with invasion of only the superficial layer (16, 17), whereas others have reported the absence of any significant difference in the prognosis between the two groups (15); thus, no consensus has been reached. Furthermore, few studies have investigated the horizontal width of tumor invasion into the MP in T2 gastric cancer patients (18). In the present study, we measured both the horizontal length and vertical length of tumor invasion into the MP to assess the clinicopathological significance of the status of tumor invasion into the MP.

Patients with wide WiMP had a significantly poorer prognosis than those with narrow WiMP. Multivariate analysis identified the WiMP as an independent prognostic factor. In the present study, we classified the MP into a superficial layer composed of the inner circular muscle and a deep layer

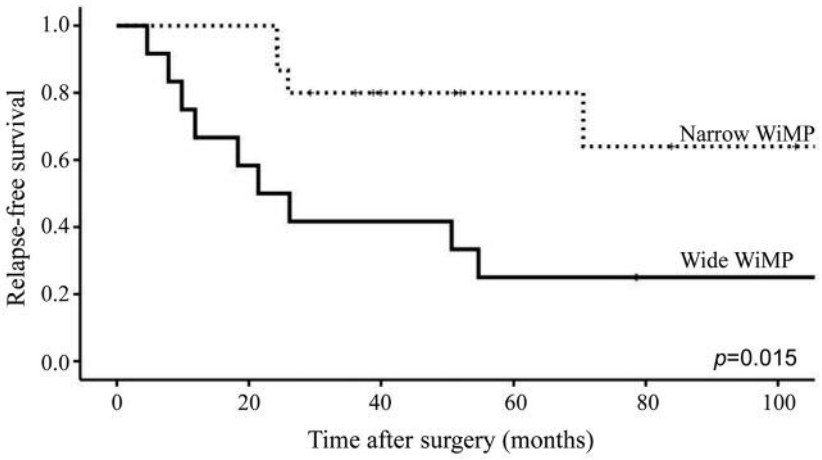

Figure 2. *Kaplan-Meier survival curves for relapse-free survival of AJCC N2-N3 patients according to width of invasion of the muscularis propria (WiMP). The group with wide WiMP had a significantly poorer prognosis compared to the group with narrow WiMP. AJCC, American Joint Committee on Cancer; narrow WiMP, width of invasion of muscularis propria <1.5 cm; wide WiMP, width of invasion of muscularis propria ≥1.5 cm.*

composed of the outer longitudinal muscle (data not shown). The proportion of patients with tumor invasion up to the deep layer was significantly higher in the wide WiMP group than in the narrow WiMP group (p=0.001). Therefore, the tumor burden in the MP was considered greater in the wide WiMP group than in the narrow WiMP group. Thus, the difference in prognosis between the two groups was considered to be caused by the difference in the tumor burden.

Moreover, in the present study, we measured the width and depth of tumor invasion into the MP, and identified only the width of invasion, and not the depth, as a significant prognostic factor. Several studies have simultaneously measured the width and depth of tumor invasion in submucosal gastric cancer and investigated which of the two is of greater clinicopathological significance (19-22). Sanomura *et al*. described that the horizontal width of invasion is a more useful predictor of lymph node metastasis than the depth of invasion (19), while similar results were also demonstrated by Fang *et al*. (21). Kim *et al*. reported that when the muscularis mucosa was thickened by tumor invasion, the vertical distance was not related to the extent of lymph node metastasis (20). In a study of advanced gastric cancer, Soga *et al*. measured the vertical distance in patients with tumor invasion of the subserosa and reported that the distance was not a prognostic factor (23). They discussed that the vertical distance is sometimes influenced by the tumor thickness due to interstitial fibrosis. Considering that the depth of tumor invasion was not associated with the prognosis in the present study, it was considered necessary to take into account secondary gastric wall thickening due to tumor penetration when measuring the depth of tumor invasion.

The analysis according to the AJCC N stage showed that there was no difference in the survival rate depending on the WiMP in N0 or N1 patients. On the other hand, multivariate analysis in the N2-N3 patients revealed that the WiMP was an independent prognostic factor. Liu *et al*. reported the prognosis according to the extent of lymph node metastasis in T2 gastric cancer patients without distant metastasis (24). They described 5-year survival in N2 and N3 patients of 42% and 35%, respectively, with a slight difference between the two groups. Sun *et al*. examined the 5-year survival of T2 gastric cancer patients according to the metastasis ratio and revealed that 5-year survival decreased with worsening of the metastasis ratio from 0 to 0.2, but remained constant at approximately 30% when the metastasis ratio became worse than 0.2 (16). In the present study also, examination of N2-N3 patients revealed no significant difference in the 5-year survival rate between N2 and N3 patients (p=0.632). The results suggested that the extent of lymph node metastasis may not be a prognostic factor in T2 gastric cancer patients with advanced lymph node metastasis. Based on the results of our study, we assume that classification according to the WiMP would be useful for patients with advanced lymph node metastasis. However, the number of patients in the present study was small, and further studies on a larger number of patients would be necessary to confirm the results.

In conclusion, the horizontal width of tumor invasion into the MP was found to be an independent prognostic factor in patients with T2 gastric cancer. Patients with wide width of tumor invasion had a significantly poorer prognosis than those with narrow width of tumor invasion. In patients with advanced lymph node metastasis, classification according to the width of invasion, and not classification according to the extent of lymph node metastasis, was correlated with the prognosis. Therefore, in the assessment of patients with T2 gastric cancer, it is important to classify the patients according

Table III. *Univariate and multivariate analyses of prognostic factors for relapse-free survival of all patients.*

Variables	Comparison	Relapse-free survival			
		Univariate analysis		Multivariate anaysis	
		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age (years)	<70 *vs.* ≥70	2.651 (1.233-5.703)	0.013	2.613 (1.203-5.676)	0.015
Gender	Male *vs.* female	0.801 (0.340-1.884)	0.611		
Tumor size (cm)	<6.0 *vs.* ≥6.0	2.649 (1.126-6.233)	0.026	2.035 (0.863-4.802)	0.105
Gross type	Circumscribed *vs.* infiltrative	1.207 (0.531-2.742)	0.653		
Resection type	SG *vs.* TG	1.397 (0.530-3.685)	0.499		
Histologic type	Differentiated *vs.* undifferentiated	0.526 (0.243-1.141)	0.104		
Lymphatic invasion	Negative *vs.* positive	4.116 (0.975-17.372)	0.054		
Venous invasion	Negative *vs.* positive	2.320 (0.941-5.725)	0.068		
Lymph node metastasis	Negative *vs.* positive	3.545 (1.599-7.861)	0.002	2.708 (1.217-6.030)	0.015
Adjuvant chemotherapy	Negative *vs.* positive	1.121 (0.533-2.361)	0.763		
WiMP (cm)	<1.5 *vs.* ≥1.5	4.165 (1.979-8.764)	0.001	3.614 (1.705-7.657)	0.001

CI, Confidence interval; HR, hazard ratio; SG, subtotal gastrectomy; TG, total gastrectomy; WiMP, width of invasion of the muscularis propria.

Table IV. *Univariate and multivariate analyses of prognostic factors for relapse-free survival of AJCC N2-N3 patients.*

Variables	Comparison	Relapse-free survival			
		Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age (years)	<70 *vs.* ≥70 years	1.176 (0.395-3.506)	0.771		
Gender	Male *vs.* female	1.050 (0.332-3.319)	0.934		
Tumor size (cm)	<6.0 *vs.* ≥6.0 cm	1.250 (0.382-4.088)	0.713		
Gross type	Circumscribed *vs.* infiltrative	2.050 (0.685-6.134)	0.199		
Resection type	SG *vs.* TG	0.932 (0.253-3.429)	0.916		
Histologic type	Differentiated *vs.* undifferentiated	1.032 (0.334-3.189)	0.956		
Lymphatic invasion	Ly1 *vs.* Ly2-Ly3	1.438 (0.468-4.419)	0.526		
Venous invasion	Negative *vs.* positive	2.629 (0.721-9.585)	0.143		
Lymph node metastasis	N2 *vs.* N3	1.032 (0.344-3.097)	0.955		
Adjuvant chemotherapy	Negative *vs.* positive	0.236 (0.068-0.820)	0.023	0.065 (0.011-0.383)	0.003
WiMP (cm)	<1.5 *vs.* ≥1.5	3.937 (1.204-12.867)	0.023	10.456 (2.008-54.437)	0.005

AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; SG, subtotal gastrectomy; TG, total gastrectomy; WiMP, width of invasion of the muscularis propria.

to the horizontal width of invasion of the MP invasion, into a narrow invasion group and wide invasion group.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in regard to this study.

Authors' Contributions

All Authors contributed to the design and implementation of the study, to the analysis of the results, and to the writing and final approval of the manuscript.

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