Tumor Index as a Combined Indicator of Tumor Depth and Size in Gastric Cancer

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Abstract. *Background: We investigated the utility of a novel combined indicator of both tumor depth and size in gastric cancer. Patients and Methods: A total of 938 patients with gastric cancer were analyzed. We tested tumor index (TI), calculated by T category × tumor size (mm) as a novel combined indicator of tumor depth and size. Results: Patients were classified into two groups using a cut-off value of 180 (p<0.0001) by the Kaplan–Meier method. TI was significantly positively correlated with older age, tumor located in the upper third of stomach, advanced type of macroscopic appearance, undifferentiated type, lymphatic invasion, venous invasion, lymph node metastasis, and recurrence. TI>180 only correlated with peritoneal recurrence (p=0.0394). A multivariate analysis identified TI>180 as an independent prognostic factor (hazard ratio=2.38, p=0.0004). Conclusion: TI may be a novel combined indicator of tumor status for predicting a poor prognosis and peritoneal recurrence in gastric cancer.*

Gastric cancer is one of the most common causes of death from cancer worldwide (1). Recent advances have been achieved in diagnostic techniques, less-invasive treatment techniques and perioperative management, and mortality and morbidity rates have been reduced by the earlier detection of gastric cancer (2). However, tumors with advanced-stage disease have a greater depth of invasion and still present a poor prognostic outcome. The tumor status is the strongest predictor of the prognosis of gastric cancer, and treatment strategy based on the tumor status is the most important clinical issue (3).

Tumor size as horizontal tumor invasion is utilized as an important staging factor in head and neck cancer, as well as in lung and breast cancer (4). Although tumor depth has been identified as a strong prognostic and staging factor in gastric cancer (5, 6), several recent studies suggested that tumor size as horizontal tumor invasion was a prognostic factor in gastric cancer (7-12). However, the combination of tumor depth and invasion as an indicator has not yet been examined. Therefore, we herein tested the combined indicator of tumor depth and size using the Tumor Index (TI), which was calculated by multiplying the numerical T category by the tumor size (in millimeters), and hypothesized that TI may be a prognostic factor with the ability to stratify the prognosis of each stage in gastric cancer. The results of our study suggest that TI represents a better system for tumor staging and may be an indicator for future treatment strategies in gastric cancer.

Patients and Methods

Patients and surgical procedures. We retrospectively analyzed 938 consecutive patients who underwent curative gastrectomy for gastric cancer at the Division of Digestive Surgery, Kyoto Prefectural University of Medicine, between 1997 and 2011. Curative gastrectomy with lymphadenectomy was performed mainly based on the Japanese gastric cancer treatment guidelines (13, 14). Resected specimens were examined by pathologists and evaluated based on the 14th Japanese Classification of Gastric Carcinoma (JCGC) (15) and the 7th Tumor-Node-Metastasis (TNM) classification (4). Written informed consent was obtained from each patient prior to treatment initiation. The clinicopathological findings of these patients were examined retrospectively from hospital records (Table I). Surgical procedures comprised of distal gastrectomy in 601 patients, total gastrectomy in 262 patients, and proximal gastrectomy in 75 patients according to the preoperative stage and tumor location. Japanese style D2 lymphadenectomy or more was performed in 507 patients and less than D2 lymphadenectomy was performed in 431 patients. As a result, disease in 575 patients was classified as pStage I, in 171 as pStage

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Key Words: Tumor size, tumor depth, prognosis, gastric cancer.

Table I. *Characteristics of 938 patients with gastric cancer.*

Variable		n=938	
Gender	Female	310	(33%)
	Male	628	(67%)
Age	≤65 Years	465	(50%)
	>65 Years	473	(50%)
Tumor site	Upper third	200	(21%)
	Middle third	431	(46%)
	Lower third	307	(33%)
Macroscopic appearance	0	577	(62%)
	1	30	(3%)
	2	104	(11%)
	3	172	(18%)
	4	55	(6%)
Histological type	Differentiated	467	(50%)
	Undifferentiated	471	(50%)
Lymphatic invasion	Negative	572	(61%)
	Positive	366	(39%)
Venous invasion	Negative	701	(75%)
	Positive	237	(25%)
pT Category	T1	525	(56%)
	T2	104	(11%)
	T3	148	(16%)
	T4	161	(17%)
pN Category	N0	641	(68%)
	N1	105	(11%)
	N2	93	(10%)
	N3	99	(11%)
pStage	I	575	(61%)
	II	171	(18%)
	III	192	(21%)
Recurrence	Absence	807	(86%)
	Presence	131	(14%)

II, and in 192 as pStage III. Patients with gastric cancer who underwent remnant gastrectomy and limited gastrectomy were excluded from this study.

Measurement of tumor diameter and calculation of TI. The resected stomach was opened, placed on a flat board with the mucosal side up, and fixed in 10% buffered formalin solution. After fixation, tumors in the resected stomach were sectioned on the maximum cross-sectional plane parallel to the lesser curvature line based on the general rules of the JCGC published by the Japanese Gastric Cancer Association (15). Tumors were generally sectioned in their entirety parallel to the reference line at 5-mm intervals. The resected specimens were embedded in paraffin and stained with hematoxylin and eosin. The longest tumor diameter was pathologically measured. TI was calculated by multiplication of the longest tumor size (mm) and pathological tumor (pT) stage (15); TI=pT category × tumor size (mm). Histological types were classified as differentiated (papillary adenocarcinoma or moderately or well-differentiated adenocarcinoma) or undifferentiated (poorly differentiated or undifferentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous adenocarcinoma) based on the 14th JCGC (15).

Statistical analysis. The χ^2 test and Fisher's exact probability test were performed for categorical variables, while the Student's *t*-test and Mann–Whitney *U*-test were performed for unpaired data of continuous variables to compare clinicopathological characteristics between the two groups. In order to analyze survival rates, survival curves were estimated using the Kaplan–Meier method and significant differences were examined using the log-rank test. Univariate and multivariate survival analyses were performed using the likelihood ratio test of the stratified Cox proportional hazards model. A *p*-value of less than 0.05 was considered significant. All statistical analyses were performed using the JMP 10.0 software program (Roppongi, Tokyo, Japan).

Results

Cut-off value of TI for stratifying prognosis. In order to properly classify the prognosis into four groups by TI, we performed detailed survival analyses using various cut-off interval values such as 10, 20, 30, 50, 70, and their multiples (Figure 1a-c). When increments of 30 or 90 were used as cut-off values, such as TI<90, 90≤TI<180, 180≤TI<270, and TI≥270, patients were more properly classified into four groups than when using other cut-off values ($p<0.0001$). The 5-year survival rates of patients with TI<90, 90≤TI<180, 180≤TI<270, and TI≥270 were 97.1%, 72.8%, 55.8% and 43.1%, respectively (Figure 1d). Furthermore, the cut-off value of 180 more significantly stratified the prognosis of gastric cancer patients into two groups ($p<0.0001$, 5-year survival rate; TI <180 *vs*. TI≥180: 92.7% *vs*. 48.5%) (Figure 2).

Comparison of clinicopathological factors between patients with TI<180 and TI≥180. We next compared clinicopathological factors between patients with TI<180 and TI≥180 (Table II). Older age ($p=0.0326$), tumor located in the upper third of stomach ($p=0.0066$), advanced type of macroscopic appearance ($p<0.0001$), undifferentiated type ($p<0.0001$), presence of lymphatic ($p<0.0001$) and venous invasion ($p<0.0001$), greater extent of lymph node metastasis ($p<0.0001$), and recurrence ($p<0.0001$) were significantly more frequent in patients with TI≥180 than in those with TI<180. A multivariate analysis using the Cox's proportional hazard model identified TI≥180 as an independent poor prognostic factor (hazard ratio=2.38, 95% confidence interval=1.47-3.92, $p=0.0004$) (Table III). We then compared the incidence of various recurrence patterns in 131 patients with recurrence according to TI. The incidence of peritoneal recurrence was significantly higher in patients with TI≥180 than in those with TI<180 ($p=0.0394$); no other relationship was observed between other types of recurrence and the incidence according to TI (Table IV).

Survival rates for different pathological tumor stages according to TI group. Table V shows the survival rates for each pT stage according to the TI cut-off value. TI had the ability to stratify the prognosis of patients with pT3 gastric cancer using all cut-off values ($p=0.0141$) and the cut-off

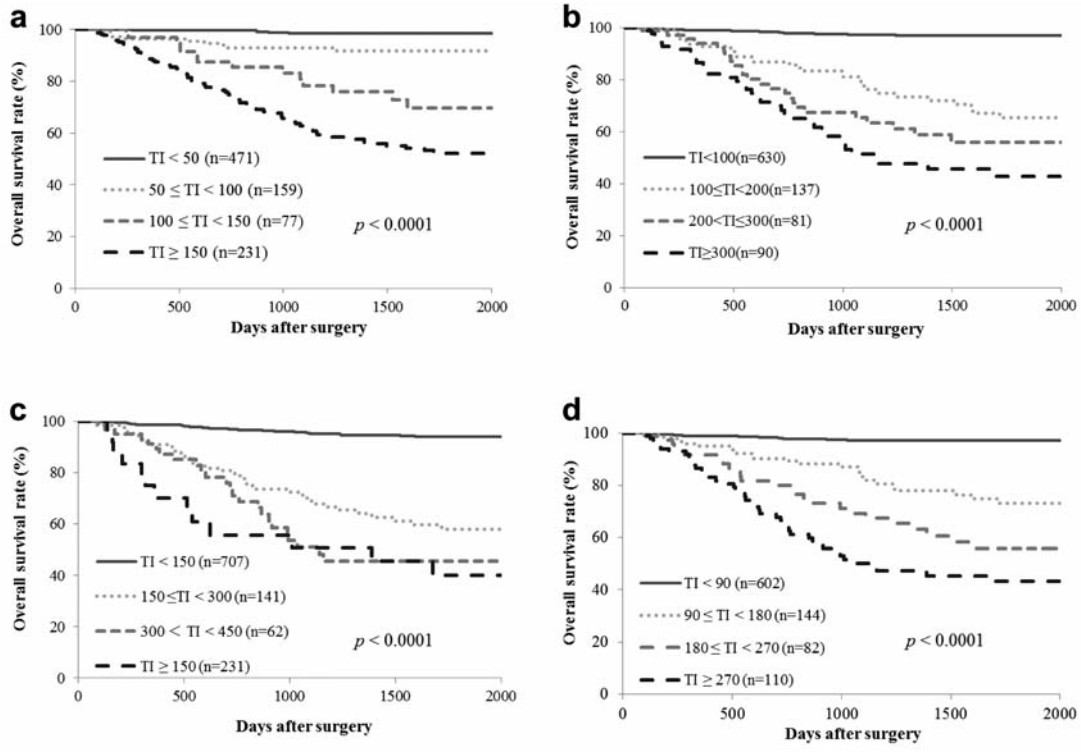

Figure 1. *Survival curves according to Tumor Index (TI) using cut-off values at 50 (a), 100 (b), and 150 (b) unit intervals. These cut-off values did not equally stratify the prognosis of patients with gastric cancer. d: Survival curves were equally subdivided by TI using 90-unit intervals as cut-off values. The 3-year survival rate was 97.1%, 83.0%, 67.3% and 50.1%, while the 5-year survival rate was 97.1%, 72.8%, 55.8% and 43.1%, respectively.*

value of 270 (p=0.0032). In pStage II gastric cancer, TI also had the ability to stratify the prognosis of patients using all cut-off values (p=0.0052) and the cut-off value of 270 (p=0.0011). About pStage III gastric cancer, prognosis of patients tend to be stratified using all cut-off value of 270 (p=0.1723) (Table VI). These results indicated that TI can contribute to decision-making on treatment strategies for patients with pT3 and pStage II-III gastric cancer by stratifying the prognosis of these patients.

Discussion

Although tumor depth has been identified as one of the most crucial factors for staging in gastric cancer (4, 15), tumor size as an indication of horizontal tumor invasion is also known to be an important prognostic factor in gastric cancer as with other solid cancers (5-12). The combined indicator of both tumor depth and size has not been examined before to our knowledge. Therefore, we herein developed a novel combined indicator, the TI. TI was associated with poor clinical outcomes and may be an independent poor prognostic factor. Furthermore, TI had the ability to stratify the prognosis of patients with pT3 and pStage II disease, and therefore may contribute to decision-making regarding treatment strategies for gastric cancer.

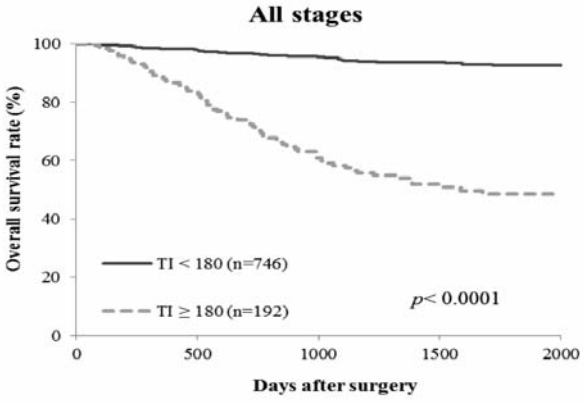

Figure 2. *The Tumor Index (TI) cut-off value of 180 correlated with prognosis (p<0.0001). The 5-year survival rates of patients with TI<180 and TI≥180 were 92.7% and 48.5%, respectively.*

Previous studies reported the significance of tumor size in predicting the prognosis of patients with gastric cancer. Kunisaki *et al*. examined 1,215 patients with gastric cancer

Table II. *Clinicopathological characteristics and Tumor Index in 938 patients with gastric cancer.*

Variable		N	Tumor Index				*p*-Value*
			<180	(%)	≥180	(%)	
Total		938	746		192		
Gender	Female	310	243	(32)	67	(35)	0.5432
	Male	628	503	(68)	125	(65)	
Age	≤65 Years	465	383	(51)	82	(43)	**0.0326**
	>65 Years	473	363	(49)	110	(57)	
Tumor site	Upper third	213	155	(21)	58	(30)	**0.0066**
	Middle/lower third	725	591	(79)	134	(70)	
Macroscopic appearance	0/1/2	709	653	(88)	56	(29)	**<0.0001**
	3/4	229	93	(12)	136	(71)	
Histological type	Differentiated	467	412	(55)	55	(29)	**<0.0001**
	Undifferentiated	471	334	(45)	137	(71)	
Lymphatic invasion	Negative	572	535	(72)	37	(19)	**<0.0001**
	Positive	366	211	(28)	155	(81)	
Venous invasion	Negative	701	612	(82)	89	(46)	**<0.0001**
	Positive	237	134	(18)	103	(53)	
pT-category	T1	525	525	(70)	0	(0)	**<0.0001**
	T2/T3/T4	413	221	(30)	192	(100)	
pN-category	N0	641	591	(79)	50	(26)	**<0.0001**
	N1/ N2/N3	297	155	(21)	142	(74)	
Recurrence	Absence	783	688	(92)	85	(49)	**<0.0001**
	Presence	155	58	(8)	97	(51)	

*χ^2 or Fisher's test, significant values are shown in bold.

Table III. *Results of a survival analysis with Cox's proportional hazard model.*

Factor		Univariate[a]		Multivariate[b]	
		p-Value*	HR	95% CI	*p*-Value*
Gender	Male *vs.* female	0.8490	1.199	0.786-1.799	0.3932
Age	>65 *vs.* ≤65 years	**0.0004**	1.630	1.103-2.432	**0.0141**
Tumor site	U *vs.* ML	**0.0057**	1.040	0.667-1.593	0.8586
Macroscopic appearance	Type 3, 4, 5 *vs.* type 0, 1, 2	**<0.0001**	1.814	1.154-2.896	**0.0095**
Histological type	Undiff. *vs.* Diff.	**0.0436**	1.100	0.723-1.658	0.6526
Lymphatic invasion	2/3 *vs.* 0/1	**<0.0001**	2.391	1.486-3.909	**0.0003**
Venous invasion	2/3 *vs.* 0/1	**<0.0001**	2.249	1.392-3.565	**0.0011**
pN- category	pN 2/3 *vs.* pN 0/1	**<0.0001**	3.081	1.844-5.243	**<0.0001**
Tumor Index	≥180 *vs.* <180	**<0.0001**	2.381	1.4698-3.924	**0.0004**

HR: Hazard ratio; CI: confidence interval; U: Upper third; ML: Middle/lower third; Undiff.: Undifferentiated; Diff.: Differentiated. [a]Kaplan–Meier method, significance was determined by the log-rank test. [b]Cox's proportional hazard model. *Significant values are shown in bold.

and classified them into two groups using a cut-off value of 100 mm as the maximal tumor diameter (9). This value may stratify the prognosis of stage II-III patients. Saito *et al.* also evaluated 1,473 patients with gastric cancer and divided them into two groups using a cut-off value of 80 mm for tumor size (8). Giuliani et al. categorized their patients with gastric cancer using a cut-off value of 25 or 50 mm (7). These findings suggested the clinical significance of various cut-off tumor sizes as an independent prognostic factor, but also showed that tumor size is not an alternative to the conventional factor of tumor depth because tumor depth has the ability to stratify the prognosis associated with larger or smaller tumors and is a prognostic factor itself independently of tumor size, as reported by Kunisaki *et al.* (9). This clinical issue prompted us to develop a combined indicator of tumor status, which included the benefits of both tumor depth and size.

Table IV. *Clinicopathological characteristics and Tumor Index in 131 patients with recurrence.*

Recurrence type		N	Tumor Index				*p*-Value*
			<180	(%)	≥180	(%)	
Total		131	49		82		
Peritoneal	Yes	66	19	(39)	47	(57)	**0.0394**
	No	65	30	(61)	35	(43)	
Hematogenous	Yes	27	13	(26)	14	(17)	0.2001
	No	104	36	(74)	68	(82)	
Lymph node	Yes	25	11	(22)	14	(17)	0.4521
	No	106	38	(78)	68	(82)	
Local	Yes	9	3	(6)	6	(7)	0.7922
	No	122	46	(94)	76	(93)	
Other	Yes	16	6	(12)	10	(12)	0.9933
	No	115	43	(88)	72	(88)	

*χ^2 or Fisher's test, significant values are shown in bold.

Table V. *Survival rates according to Tumor Index (TI) group in each pT Stage.*

TI		5-Year survival rate (%)			
		pT1 (n=525)	pT2 (n=104)	pT3 (n=148)	pT4 (n=161)
TI 1	TI <90	98.6	94.3	92.9	33.3
TI 2	90≤ TI <180	100.0	89.3	66.5	57.0
TI 3	180≤ TI ≤270	0	100.0	63.7	46.7
TI 4	TI ≥270	0	0	42.5	43.5
p-Value (all)*		0.7249	0.8264	**0.0141**	0.5672
p-Value (TI 1/2/3 *vs*. 4)*		N/A	N/A	**0.0032**	0.4918

N/A: Not applicable. *Log-rank test, significant values are shown in bold.

Table VI. *Survival rates according to Tumor Index (TI) group in each pStage.*

TI		5-Year survival rate (%)		
		pStage I (n=575)	pStage II (n=171)	pStage III (n=192)
TI 1	TI <90	99.3	90.2	55.5
TI 2	90≤ TI <180	100.0	75.9	51.2
TI 3	180≤ TI ≤270	100.0	93.8	41.0
TI 4	TI ≥270	0	60.6	36.9
p-Value (all)*		0.9112	0.0052	0.4983
p-Value (TI 1/2/3 *vs*. 4)*		N/A	**0.0011**	0.1723

N/A: Not applicable. *Log-rank test, significant values are shown in bold.

Table VII. *Peritoneal recurrence rates according to Tumor Index (TI) in each pStage.*

TI	Peritoneal recurrence rate (%)		
	pStage I (n=575)	pStage II (n=171)	pStage III (n=192)
<180	0.7 (4/573)	3.5 (4/115)	19.0 (11/58)
≥180	0.0 (0/2)	14.3 (8/56)	29.6 (40/134)
p-Value*	0.8672	**0.0125**	0.1091

*χ^2-squared test, significant values are shown in bold.

In our study, gastric cancer tumors with high TI presented aggressive malignant clinical behavior, such as a higher incidence of the advanced type of macroscopic appearance, undifferentiated type, lymphatic invasion, venous invasion, lymph node metastasis, and recurrence. A tumor size of 8 cm or greater has already been included in the criteria of a recent clinical trial on preoperative chemotherapy for clinically resectable type 4 or large type 3 tumors in JCOG0210 (16) and JCOG0501 trials (17). TI may be a more sensitive criterion for such trials because it includes the clinical feature of tumor depth in addition to tumor size. Concerning preoperative or postoperative adjuvant chemotherapy, patients with stage III

disease are considered to require further treatment strategies because the adjuvant chemotherapy trial of S-1 for gastric cancer trial did not demonstrate any survival benefit of postoperative adjuvant chemotherapy using the oral anticancer drug S-1 in these patients (18). Therefore, TI may also be a more useful indicator for selecting patients with stage III patients with poor outcomes in order to perform more intensive chemotherapy. Thus, TI may contribute to decision-making in future clinical trials.

Regarding recurrence, TI≥180 correlated with peritoneal recurrence (p=0.0394), among the various types of recurrence, in patients undergoing curative gastrectomy (Table IV). The rate of peritoneal recurrence in patients with 180< TI and TI <180 were 0% (0/2) and 0.7% (4/573) in pStage I, 14.3% (8/56) and 3.5% (4/115) in pStage II, and 29.6% (40/134) and 19.0% (11/58) in pStage IIII, respectively (Table VII). These results strongly suggested that a high TI may be a pivotal predictor of peritoneal recurrence; high TI may be an indicator in a meticulous follow-up for the early detection of peritoneal recurrence and for intensive adjuvant chemotherapy to prevent peritoneal recurrence.

Nevertheless, there are still limitations to this study. This was a retrospective single-center study. Furthermore, our identified TI cut-off value is still controversial. Preoperative TI, which was estimated by endoscopy or other modalities before surgery for the purpose of preoperative chemotherapy, may also need further investigation because preoperative tumor size may differ from pathological tumor size after gastrectomy. Therefore, a prospective observational study using several large cohorts may be needed to validate the significance of TI.

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