Primary Tumor Score Based on Tumor Depth and Length Predicts Prognosis in Esophageal Squamous Cell Carcinoma

TAKA AKI ARIGAMI¹, YASUTO UCHIKADO², ITARU OMOTO², KEN SASAKI²,
YOSHIAKI KITA², TETSUHIRO OWAKI³, SHIGEHIRO YANAGITA², SHINICHIRO MORI²,
HIROSHI KURAHARA², HIROSHI OKUMURA², KOSEI MAEMURA² and SHOJI NATSUGOE^{1,2}

¹Department of Onco-biological Surgery, Kagoshima University Graduate
School of Medical and Dental Sciences, Kagoshima, Japan;

²Department of Digestive Surgery, Breast and Thyroid Surgery,
and ³Education Center for Doctors in Remote Islands and Rural Areas,
Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

Abstract. Aim: To examine the depth of tumor invasion and tumor length and assess the clinical impact of the primary tumor score (PTS), based on a combination of tumor invasion and tumor length, in patients with esophageal squamous cell carcinoma (ESCC). Patients and Methods: A total of 237 patients with ESCC were classified into three PTS groups based on cut-off values for deeper tumor invasion (pT2-T4) and greater tumor length (≥ 44 mm). A PTS of 2 indicated the presence of both of these abnormalities, 1 indicated one of these abnormalities, and 0 indicated neither abnormality. Results: PTS was significantly positively correlated with depth of tumor invasion, lymph node metastasis, lymphovascular invasion, and stage (all $p < 0.001$). The prognosis differed significantly among the three groups based on PTS ($p < 0.0001$). Multivariate analysis demonstrated that PTS was an independent prognostic factor ($p = 0.0004$). Conclusion: PTS has a clinical utility as a prognostic predictor in patients with ESCC.

Esophageal squamous cell carcinoma (ESCC) is one of the most aggressive malignancies in patients with gastrointestinal cancer and is the seventh leading cause of cancer-specific death in Japan (1). The 5-year survival rates of patients with stage I, II, III, and IV ESCC are 90%, 45%, 20%, and 10%, respectively (2). Even patients with

submucosal invasion have a high potential for lymph node metastasis, and the metastatic rate of lymph nodes in these patients is reported to be 16-62% (3). The 5-year disease-specific survival rate of patients with deep submucosal invasion is 68.6-78.8% (3). These findings indicate that it is difficult to plan a therapeutic strategy in the clinical management of ESCC. Although induction of adjuvant chemotherapy to prevent disease recurrence after surgery is clinically recommended in patients with pathological stage II or III gastric cancer, the clinical impact of adjuvant chemotherapy in patients with ESCC remains unclear (4). Carcinoembryonic antigen (CEA), squamous cell carcinoma antigen (SCC), and p53 are used as representative blood markers for predicting disease recurrence in the postoperative management of ESCC. However, the sensitivity of these conventional serum markers for predicting disease recurrence in patients with ESCC is 25-40% (5). Promising predictors of tumor progression and prognosis are awaited in the clinical management of ESCC.

Currently, postoperative patients with ESCC are categorized and staged by pathological examinations based on the criteria of the tumor-node-metastasis (TNM) classification of esophageal carcinoma established by the Union for International Cancer Control (UICC) (6). The TNM classification is based on three clinicopathological factors: the depth of tumor invasion, and the presence of lymph node metastases, and distant metastases. It is impossible to determine TNM stage without information on these three factors. If a new pathological score determined by primary tumor information alone had the same clinical utility as TNM stage, it would be possible to predict disease recurrence and prognosis without requiring information about the presence or absence of lymph node and distant metastases.

In this study, we focused on tumor depth and length and defined a primary tumor score (PTS) based on these two

Correspondence to: Takaaki Arigami, MD, Ph.D., Department of Onco-biological Surgery, Kagoshima University Graduate School of Medical and Dental Sciences, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan. Tel: +81 992755361, Fax: +81 992657426, e-mail: arigami@m.kufm.kagoshima-u.ac.jp

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primary tumor factors. To date, the clinical significance of PTS determined by tumor depth and length has not been assessed in patients with ESCC.

The aim of the present study was to investigate tumor depth and length in patients with ESCC, and examine the relationship between PTS, clinicopathological factors and long-term outcomes for assessing its clinical utility as a prognostic combined marker.

Patients and Methods

Patients. Data were retrospectively reviewed from 237 patients (209 men and 28 women; age range=37-87 years; average=65.3 years) with ESCC who underwent esophagectomy with lymphadenectomy at the Kagoshima University Hospital (Kagoshima, Japan) between January 1998 and December 2012. Patients who had received endoscopic treatments, palliative resection, preoperative chemotherapy, or radiotherapy were excluded. None of the enrolled patients had synchronous or metachronous cancer in other organs. In the present study, patients were classified and staged based on the TNM classification of esophageal carcinoma established by the UICC (6). Table I shows the clinicopathological factors. All patients were followed-up every 3 to 6 months after surgery at the Kagoshima University Hospital with regular clinical diagnostic examinations, including tumor marker (CEA, SCC, and p53) studies, radiography, ultrasonography, and computed tomography. The median follow-up period was 26 months (range=1-182 months).

The Ethics Committee of the Kagoshima University approved this observational study (approval number 180058).

Pathological examination for tumor depth and length. The depth of tumor invasion was determined by the TNM classification of esophageal carcinoma. According to this classification, tumors are pathologically grouped into four divisions: pT1, pT2, pT3, and pT4. Tumor length was calculated based on the Japanese Classification of Esophageal Cancer (11th edition) (7). The resected esophagus was opened along the longitudinal line on the side opposite to the lesion. Tumor length was defined as the greatest longitudinal dimension.

The primary end-point was overall survival. Overall survival was defined as the period between surgery and death. All deaths, including those from other diseases, were considered to be events. Data for patients without an event were censored at the date of the final observation.

Statistical analysis. The chi-square test and Fisher's exact test were used to evaluate the relationships between tumor depth and categorical clinicopathological factors. Differences in the relationships between tumor length and clinicopathological features were assessed by the Wilcoxon rank sum test. Receiver operating characteristic (ROC) curves were constructed and the area under the curve (AUC) was calculated to estimate the predictive ability of tumor length for distinguishing patients with stage I from those with stage II or III cancer. The relationship between PTS and clinicopathological factors was evaluated by the chi-square test or Fisher's exact test. Survival curves were generated by the Kaplan-Meier method, and differences in survival were examined by the log-rank test. Prognostic factors were assessed by univariate and multivariate analyses (Cox proportional hazards regression model). All statistical calculations were performed with SAS statistical

Table I. Clinicopathological factors of 237 patients with esophageal squamous cell carcinoma.

Characteristic	Value
Gender, n (%)	
Male	209 (88.2%)
Female	28 (11.8%)
Mean age (range), years	65.3 (37-87)
Tumor location, n (%)	
Upper	42 (17.7%)
Middle	115 (48.5%)
Lower	80 (33.8%)
Mean tumor length(range), mm	48.4 (4-155)
Depth of tumor invasion, n (%)	
pT1	119 (50.2%)
pT2	25 (10.5%)
pT3	82 (34.6%)
pT4	11 (4.6%)
Lymph node metastasis, n (%)	
Negative	113 (47.7%)
Positive	124 (52.3%)
Stage, n (%)	
I	86 (36.3%)
II	69 (29.1%)
III	82 (34.6%)
Venous invasion, n (%)	
Negative	99 (41.8%)
Positive	138 (58.2%)
Lymphatic invasion, n (%)	
Negative	94 (39.7%)
Positive	143 (60.3%)

software (SAS Institute Inc., Cary, N.C., USA). A *p*-value of less than 0.05 was considered to represent a statistically significant difference.

Results

Correlation between clinicopathological factors and tumor depth or length. One hundred and nineteen, 25, 82, and 11 patients had pT1, pT2, pT3, and pT4 tumors, respectively. The relationships between tumor depth and clinicopathological factors are shown in Table II. Tumor depth was significantly positively correlated with lymph node metastasis, stage, venous invasion, and lymphatic invasion (all *p*<0.0001).

Tumor length ranged from 4 to 155 mm. The mean tumor length ($\pm$ SD) was 48.4 $\pm$ 25.5 mm. The tumor length was significantly correlated with the depth of tumor invasion (Figure 1A; *p*<0.0001). Tumor length was significantly greater in patients with lymph node metastases (n=124) than in those without (n=113) (Figure 1B; *p*=0.0066). Tumor length was significantly correlated with the presence venous invasion (Figure 1C; *p*=0.0025), but was not significantly correlated with lymphatic invasion (Figure 1D; *p*=0.0842).

Table II. Correlation between clinicopathological factors and tumor depth.

Factor	Depth of tumor invasion, n (%)				p-Value
	pT1 (n=119)	pT2 (n=25)	pT3 (n=82)	pT4 (n=11)	
Gender					
Male	103 (86.6)	23 (92.0)	74 (90.2)	9 (81.8)	0.7021
Female	16 (13.4)	2 (8.0)	8 (9.8)	2 (18.2)	
Age					
<70 Years	93 (78.2)	16 (64.0)	61 (74.4)	8 (72.7)	0.5134
≥70 Years	26 (21.8)	9 (36.0)	21 (25.6)	3 (27.3)	
Lymph node metastasis					
Negative	77 (64.7)	9 (36.0)	24 (29.3)	3 (27.3)	<0.0001
Positive	42 (35.3)	16 (64.0)	58 (70.7)	8 (72.7)	
Stage					
I	77 (64.7)	9 (36.0)	0 (0.0)	0 (0.0)	<0.0001
II	36 (30.3)	9 (36.0)	24 (29.3)	0 (0.0)	
III	6 (5.0)	7 (28.0)	58 (70.7)	11 (100.0)	
Venous invasion					
Negative	77 (64.7)	6 (24.0)	14 (17.1)	2 (18.2)	<0.0001
Positive	42 (35.3)	19 (76.0)	68 (82.9)	9 (81.8)	
Lymphatic invasion					
Negative	68 (57.1)	7 (28.0)	15 (18.3)	4 (36.4)	<0.0001
Positive	51 (42.9)	18 (72.0)	67 (81.7)	7 (63.6)	

There was a significant positive relationship between tumor length and stage (Figure 1E; $p<0.0001$).

ROC analysis was used to assess the predictive power of tumor length for discriminating patients with early cancer from those with advanced cancer. The cutoff value of tumor length was set at 44.0 mm by ROC analysis (Figure 1F). The AUC, sensitivity, and specificity were 0.679, 0.656, and 0.640, respectively. Based on the cutoff value of tumor length, patients were divided into two groups with tumor length of ≥ 44 mm ($n=130$) and <44 mm ($n=107$). This binary classification was used in subsequent analyses.

Definition of PTS. PTS was assigned based on tumor depth and length. PTS was defined as 2 for presence of both deeper tumor invasion (pT2-T4) and greater tumor length (≥ 44 mm); 1 when either deeper tumor invasion or greater tumor length were found; or 0 when neither deeper tumor invasion nor greater tumor length were found.

Seventy patients (29.5%) had a PTS of 0, 86 patients (36.3%) had a PTS of 1, and 81 patients (34.2%) had a PTS of 2.

Correlation between clinicopathological factors and PTS. PTS was significantly positively associated with depth of tumor invasion, lymph node metastasis, stage, venous invasion, and lymphatic invasion ($p<0.0001$, $p<0.0001$, $p<0.0001$, $p<0.0001$, and $p=0.0001$, respectively) (Table III).

Table III. Correlation between clinicopathological factors and primary tumor score (PTS).

Factor	PTS, n (%)			p-Value
	0 (n=70)	1 (n=86)	2 (n=81)	
Gender				
Male	59 (84.3)	78 (90.7)	72 (88.9)	0.4536
Female	11 (15.7)	8 (9.3)	9 (11.1)	
Age				
<70 Years	53 (75.7)	65 (75.6)	60 (74.1)	0.9654
≥70 Years	17 (24.3)	21 (24.4)	21 (25.9)	
Depth of tumor invasion				
pT1	70 (100.0)	49 (57.0)	0 (0.0)	<0.0001
pT2	0 (0.0)	14 (16.3)	11 (13.6)	
pT3	0 (0.0)	21 (24.4)	61 (75.3)	
pT4	0 (0.0)	2 (2.3)	9 (11.1)	
Lymph node metastasis				
Negative	49 (70.0)	41 (47.7)	23 (28.4)	<0.0001
Positive	21 (30.0)	45 (52.3)	58 (71.6)	
Stage				
I	49 (70.0)	34 (39.5)	3 (3.7)	<0.0001
II	18 (25.7)	30 (34.9)	21 (25.9)	
III	3 (4.3)	22 (25.6)	57 (70.4)	
Venous invasion				
Negative	43 (61.4)	44 (51.2)	12 (14.8)	<0.0001
Positive	27 (38.6)	42 (48.8)	69 (85.2)	
Lymphatic invasion				
Negative	39 (55.7)	37 (43.0)	18 (22.2)	0.0001
Positive	31 (44.3)	49 (57.0)	63 (77.8)

Figure 1. Correlation between tumor length and clinicopathological features in 237 patients with esophageal squamous cell carcinoma. Tumor length was significantly positively associated with depth of tumor invasion (A), lymph node metastasis (B), venous invasion (C), and stage (E), but not with lymphatic invasion (D). Horizontal bars indicate mean tumor length. F: The receiver operating characteristic curve for discriminating patients with early cancer from those with advanced cancer based on tumor length. The area under the curve (AUC) was 0.679.

Prognostic analyses based on PTS. The 5-year survival rate of patients with a PTS of 0, 1, and 2 was 74.1%, 65.7%, and 36.6%, respectively ($p < 0.0001$) (Figure 2).

Univariate analysis indicated that lymph node metastasis, venous invasion, lymphatic invasion, and PTS were

significantly inversely related to survival ($p < 0.0001$, $p = 0.0029$, $p < 0.0001$, and $p < 0.0001$, respectively) (Table IV). Multivariate analysis selected lymph node metastasis and PTS as being independent prognostic factors ($p = 0.0079$ and $p = 0.0004$, respectively) (Table IV).

Table IV. Univariate and multivariate analyses for survival.

Independent factor	Comparison	Univariate analysis			Multivariate analysis		
		Hazard ratio	95% CI	p-Value	Hazard ratio	95% CI	p-Value
Lymph node metastasis	Positive vs. negative	3.64	2.21-6.24	<0.0001	2.24	1.23-4.27	0.0079
Venous invasion	Positive vs. negative	2.05	1.27-3.42	0.0029	1.22	0.74-2.08	0.4478
Lymphatic invasion	Positive vs. negative	3.28	1.93-5.90	<0.0001	1.62	0.84-3.26	0.1523
Primary tumor score	1/2 vs. 0	3.25	2.06-5.18	<0.0001	2.37	1.47-3.87	0.0004

Discussion

In the present study, we propose PTS, determined from the combination of tumor depth and length, as a new prognostic scoring method. We assessed the clinical impact of PTS in 237 patients with ESCC who underwent esophagectomy with lymphadenectomy.

The depth of tumor invasion is well known as the T factor in TNM classification. In this study, patients with deeper invasion had tumors with increasing burden of lymph node metastasis or advanced stage. Moreover, the log-rank test showed a statistically significant difference in survival between patients with pT1 tumors and patients with pT2, pT3, or pT4 tumors ($p<0.0001$) (data not shown). These results indicate that the depth of tumor invasion is one of the most important prognostic factors among several kinds of information derived from primary tumor sites.

The clinical significance of tumor length remains unclear in patients with malignancies, including ESCC. Recently, several investigators have demonstrated a close relationship between tumor length and malignant behavior in patients with ESCC (8-12). Zhang *et al.*, in a study of 387 patients with ESCC after surgical resection, reported that tumor length was closely related to the pathological status of tumor depth, lymph node metastasis, and TNM stage ($p=0.003$, $p=0.024$, and $p=0.019$, respectively). Their study showed that patients with a tumor length >35 mm had more aggressive tumors, as indicated by tumor depth, lymph node metastasis, venous invasion, and stage, than those with a tumor length of 35 mm or less (12). Similarly, we showed in the present study that tumor length was significantly correlated with well-known prognostic factors such as depth of tumor invasion, presence of lymph node metastasis, and stage. Interestingly, ROC analysis demonstrated that tumor length might have clinical utility as a surrogate marker for stratifying patients into those with early and advanced stages of disease. These findings suggest that tumor length, as well as the depth of tumor invasion, are promising factors derived from primary tumor information for predicting tumor progression in patients with ESCC.

Figure 2. Kaplan–Meier survival curves for patients with esophageal squamous cell carcinoma based on primary tumor score (PTS). The 5-year survival rates were significantly poorer in patients with higher PTS ($p<0.0001$).

In a previous study, we reported the clinical significance of PTS calculated from tumor invasion and size in patients with gastric cancer. According to that study, patients with higher PTS were more likely to have lymph node metastasis and advanced-stage cancer than those with lower PTS ($p<0.0001$ for both comparisons) (13). Therefore, we examined the relationship between PTS and clinicopathological factors in patients with ESCC. In the present study, the incidence of lymph node metastasis in patients with a PTS of 2 was higher than that in patients with a PTS of 0 (71.6% vs. 30.0%, respectively). The incidence of stage III cancer in patients with a PTS of 2 and 0 was 70.4% and 4.3%, respectively. These results show that in patients with ESCC, PTS, based on primary tumor information alone, is a useful predictor of tumor progression, similarly to metastatic status of lymph nodes and stage.

Finally, we focused on the prognostic impact of the PTS group in this study. Patients with a higher PTS had a significantly poorer prognosis than those with a lower PTS.

In particular, the 5-year survival rate of patients with a PTS of 2 was 36.6%. Surprisingly, multivariate analysis demonstrated that PTS was one of the most important prognostic factors. Accordingly, the PTS may be a simple tool for predicting disease recurrence and long-term outcome in patients with ESCC. Our hypothesis suggests that PTS as well as conventional TNM stage may support the clinical selection of patients needing adjuvant chemotherapy in the postoperative management of ESCC.

The present study had several limitations. This preliminary study was a retrospective analysis with a small sample size conducted at a single institution. The median follow-up period was short (26 months). These limitations may have affected several results. Larger validation studies are needed to strengthen our results obtained in patients with ESCC.

In conclusion, we demonstrated that PTS, determined by tumor depth and length, had a clinical utility as a predictor of tumor progression and prognosis in patients with ESCC. The PTS system may be a useful tool for planning therapeutic strategies to prevent disease recurrence in postoperative patients with ESCC.

Conflicts of Interest

The Authors have no conflicts of interest or financial ties to disclose.

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