



Tumor Volume Index as a Prognostic Factor in Patients after Curative Esophageal Cancer Resection

Hiroshi Miyamoto, MD, PhD¹, Chikara Kunisaki, MD, PhD¹, Sho Sato, MD, PhD¹, Yusaku Tanaka, MD¹, Kei Sato, MD¹, Takashi Kosaka, MD², Norio Yukawa, MD, PhD¹, Hirotoshi Akiyama, MD, PhD², Yusuke Saigusa, PhD³, and Itaru Endo, MD²

¹Department of Surgery, Gastroenterological Center, Yokohama City University, Yokohama, Japan; ²Department of Gastroenterological Surgery, Graduate School of Medicine, Yokohama City University, Yokohama, Japan; ³Department of Biostatistics, Graduate School of Medicine, Yokohama City University, Yokohama, Japan

ABSTRACT

Background. The tumor, node, metastasis classification system for staging esophageal cancer does not include tumor volume although it may be an important prognostic factor. We evaluated the prognostic value of tumor volume in esophageal cancer.

Methods. We performed a retrospective study in patients with histologically confirmed primary esophageal cancer who underwent curative esophagectomy at our facility between April 1992 and December 2013. The Tumor Depth Parameter (TDP) was defined as mucosa = 1, sub-mucosa = 2, muscularis propria = 3, adventitia = 4, and invasion into adjacent organs = 5. The pathological Tumor Volume Index (TVI) was defined as the major axis × the minor axis × TDP. The appropriate tumor diameter and TVI cutoff values were determined by the Youden index obtained from the receiver operating characteristic curve. Prognostic factors for overall survival were evaluated by univariate analysis and Cox proportional hazards regression models.

Results. We enrolled 302 patients. In the univariate analysis, patient age and sex, thoracoscopic surgery, tumor depth of invasion and diameter, lymph node metastasis, and the TVI were significantly associated with overall

survival. In our multivariate analysis, patient age and sex, thoracoscopic surgery, lymph node metastasis, and the TVI were independently associated with overall survival.

Conclusions. The pathological TVI was an independent prognostic factor in patients with esophageal carcinoma and could be included in the staging system of esophageal cancer.

The prognosis of esophageal carcinoma remains poor, as most patients have advanced disease at the time of diagnosis.¹ Prognostic factors play an essential role in predicting survival and determining optimal therapeutic strategies in patients with esophageal cancer. Thus, identification of new, uncomplicated, and readily available prognostic factors could facilitate the application of risk-adapted treatment strategies in this population.

The International Union Against Cancer (UICC) TNM Classification of Malignant Tumours is a widely used prognostic system for staging esophageal cancer and includes information about primary tumor invasion, nodal metastasis, and distant metastasis (TNM).² According to the UICC TNM classification, tumor diameter is included in the staging systems for lung, breast, and many other cancers, because tumor diameter has prognostic value in these diseases. However, this is not the case for the esophageal or gastric cancer staging systems, although some studies have suggested that tumor diameter may have prognostic value in these malignancies.^{3–7}

Tumor volume may be correlated with overall survival in laryngeal, lung, renal, and prostate cancers according to some reports.^{8–11} Other studies reported that tumor volume measured by imaging tools, such as positron emission tomography (PET)-computed tomography (CT), also is a

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C. Kunisaki, MD, PhD

e-mail: s0714@med.yokohama-cu.ac.jp

prognostic factor in esophageal cancer.^{12–15} Our clinical experience led us to hypothesize that the diameter and volume of malignant esophageal tumors may affect patient outcomes regardless of the TNM stage. Therefore, we evaluated surgically resected malignant esophageal lesions to identify the impact of tumor volume on esophageal cancer prognosis.

MATERIALS AND METHODS

Patients

We performed a retrospective study in patients with histologically confirmed primary esophageal cancer who underwent curative esophagectomy at the Department of Surgery, Gastroenterological Center, Yokohama City University between November 1992 and December 2013. A total of 302 patients were included in this study. Patients who received neoadjuvant chemotherapy or chemoradiotherapy were excluded from this study. For each patient, data were retrieved from operative and pathological reports, and follow-up data were obtained from the outpatient clinical database. The facility's institutional review board approved the study.

Perioperative Examination

Preoperative imaging studies were routinely performed using an upper gastrointestinal barium meal, endoscopic examination, and CT scan, fluorine-18 fluorodeoxyglucose (FDG)-PET scan, or both to determine the tumor location, macroscopic appearance, diameter, and depth of invasion, and identify lymph node and distant metastases. However, EUS was not performed routinely, because the resectability of the tumor could be estimated by the other imaging modalities.

Experienced pathologists at each institution determined each tumor's histological diagnosis and TNM stage according to the UICC TNM Classification of Malignant Tumours, 7th edition ensuring favorable control of pathological diagnostic quality.²

Surgery

An open or thoracoscopic transthoracic esophagectomy was performed in all patients. Lymph node dissections were performed according to the tumor location.

Postoperative Follow-up

A follow-up was performed every 8–12 weeks for the initial 2 years and every 12–24 weeks for the next 3 years

according to our standard protocol. Surveillance included tumor-marker studies, endoscopic examinations, a CT scan, and chest radiography. If recurrence was suspected, additional FDG-PET evaluations were performed.

Adjuvant Chemotherapy

Adjuvant 5-fluorouracil and cisplatin (FP) combination chemotherapy (5-fluorouracil 800 mg/m² on days 1–5 and cisplatin 80 mg/m² on day 1) was administered to pStage II and III esophageal cancer patients with good performance status (PS 0–2) who gave informed consent. Finally, a total of 89 patients received adjuvant chemotherapy. Two courses of chemotherapy were administered, and treatment started within 12 weeks after surgery.

Tumor Volume Assessment

All specimens were fixed and processed using the whole mount technique with 3- to 5-mm transverse sections. Tumor volume was measured as part of the routine pathological assessment by visual estimation. The area of the tumor was outlined and measured in the x - and y -axes, where x was the diameter of the major axis and y was the diameter of the minor axis of the largest area. The Tumor Depth Parameter (TDP) was defined as mucosa = 1, submucosa = 2, muscularis propria = 3, adventitia = 4, and invasion into adjacent organs = 5. The Tumor Volume Index (TVI) was defined as $x \times y \times \text{TDP}$.

Statistical Analysis

Data were analyzed using SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY). We used the χ^2 test to compare the difference in proportions and Student's t test to evaluate continuous variables. Overall survival was calculated using the Kaplan–Meier estimation and examined by the log-rank test. Variables that were significant in univariate analysis were entered into multivariate analysis. Multivariate analysis was performed using the Cox proportional hazards regression model. Probability (P) values were considered statistically significant at the 0.05 level.

Correlation between two quantitative variables was done by using Pearson's correlation coefficient. Correlation coefficient ranges from 0 to 1—weak ($r = 0–0.24$), fair ($r = 0.25–0.49$), moderate ($r = 0.5–0.74$), strong ($r = 0.75–1$).

RESULTS

Patients

Open transthoracic esophagectomy and thoracoscopic esophagectomy were performed in 171 and 131 patients, respectively. Three-field lymph node dissection was performed in 47 cases of cervical or upper thoracic esophageal carcinoma, and two-field lymph node dissection was performed in 255 cases of middle or lower thoracic esophageal cancer. Eighty-nine patients with advanced esophageal cancer (pathological TNM stage II or III) were treated with postoperative chemotherapy. The median follow-up time was 46.1 months (range 1–239).

Stratification of Tumor Diameter and Volume

The median diameter of the major axis (x) and the minor axis of the largest area (y) were 45 mm (range 10–150) and 30 mm (range 5–90), respectively. The median TDP and TVI were 3 (range 1–5) and 4388 (range 119–34,440), respectively. To confirm the tumor diameter cutoff value, we used the receiver operating characteristic (ROC) curve (Fig. 1). The cutoff value determined by the Youden index was 58.0, and c-index was 0.572 in this analysis. Thus, we defined the tumor diameter cutoff value as 58 mm. Large tumors were, therefore, defined as those measuring ≥ 58 mm in diameter. A large tumor was present in 77 patients (25.5%).

In the same way, we used the ROC curve to confirm the TVI cutoff value (Fig. 2). The cutoff value determined by the Youden index was 5970, and c-index was 0.629 in this analysis. Thus, we defined the TVI cutoff value as 5970.

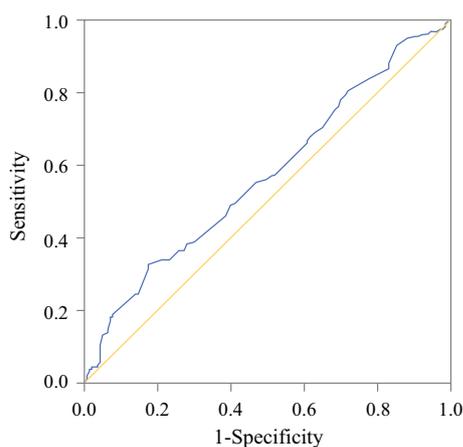


FIG. 1 Receiver operating characteristic (ROC) curve of the tumor diameter. ROC curve analysis for prognostic factor in patients with esophageal carcinoma determined that the cutoff value determined by the Youden index was 58.0. As a result, the prognostic tumor diameter cutoff value was set at 58 mm

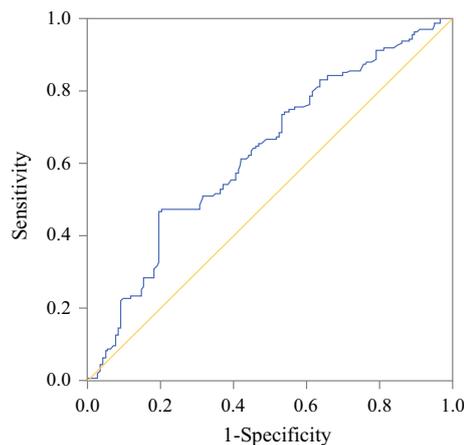


FIG. 2 Receiver operating characteristic (ROC) curve of the Tumor Volume Index (TVI). ROC curve analysis for prognostic factor in patients with esophageal carcinoma determined that the cutoff value determined by the Youden index was 5970. As a result, the prognostic TVI cutoff value was set at 5970

High-volume tumors, therefore, were defined as those with a TVI ≥ 5970 . A total of 102 patients (33.8%) had high-volume tumors.

Comparison of Clinicopathological Factors between the Low TVI Group and the High TVI Group

There were significant differences in depth of invasion, lymph node metastasis, and tumor diameter. High-volume tumors were significantly deeper and larger, and involved extended lymph node metastasis (Supplementary Table 1).

Relationship between the Clinical TVI and the Pathological TVI

The clinical TVI was assessed by the imaging modalities. The scatterplot suggested a definite relationship between the clinical TVI and the pathological TVI. There was a significant positive correlation between the two variables ($r = 0.665$, $P < 0.001$; Supplementary Fig. 1).

Prognostic Factors for Overall Survival

Univariate analysis showed that patient age and sex, thoracoscopic surgery, tumor depth of invasion and diameter, lymph node metastasis, and the TVI had a significant adverse effect on overall survival. Poor outcomes were associated with increased age, male sex, deep tumors, thoracoscopic surgery, extensive lymph node metastasis, large tumors, and high-volume tumors. The Cox proportional hazards regression model revealed that patient age and sex, thoracoscopic surgery, lymph node metastasis, and the TVI independently predicted a poor prognosis, whereas

TABLE 1 Cox proportional hazard regression model in all registered patients

Variable	<i>n</i>	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	<i>P</i> value	Hazard ratio (95% CI)	<i>P</i> value
Age, year			0.005		0.026
< 70	226	1		1	
≥ 70	76	1.626 (1.157–2.286)		1.491 (1.050–2.117)	
Sex			0.017		0.003
Female	54	1		1	
Male	248	1.753 (1.106–2.777)		2.009 (1.260–3.202)	
Location			0.566		
Ae	19	1			
Lt	120	1.316 (0.630–2.748)			
Mt	135	1.200 (0.577–2.496)			
Ut	21	1.658 (686–4.004)			
Ce	7	2.210 (0.693–6.483)			
Thoracoscopic surgery			0.008		0.006
No	171	1		1	
Yes	131	0.640 (0.461–0.888)		0.616 (0.436–0.871)	
Lymphnode dissection			0.660		
2-field	255	1			
3-field	47	1.096 (0.728–1.650)			
Adjuvant chemotherapy			0.395		
No	213	1			
Yes	89	1.152 (0.831–1.596)			
Histological type			0.575		
Well differentiated squamous cell carcinoma	83	1			
Moderately differentiated squamous cell carcinoma	137	1.089 (0.739–1.604)			
Poorly differentiated squamous cell carcinoma	54	1.380 (0.866–2.199)			
Other	28	1.173 (0.647–2.124)			
Depth of invasion			< 0.001		0.056
T1	98	1		1	
T2	69	2.564 (1.604–4.099)		1.815 (1.094–3.011)	0.021
T3	125	3.232 (2.119–4.930)		1.961 (1.189–3.233)	0.008
T4	10	2.875 (1.195–6.916)		1.631 (0.633–4.208)	0.311
Lymph node metastasis			< 0.001		0.012
N0	126	1		1	
N1	97	1.790 (1.214–2.638)		1.197 (0.793–1.806)	0.391
N2	55	3.523 (2.304–5.385)		2.090 (1.319–3.314)	0.002
N3	24	2.433 (1.358–4.360)		1.444 (0.763–2.732)	0.259
Tumor diameter (mm)			0.001		0.795
< 58	226	1		1	
≥ 58	77	1.859 (1.332–2.595)		1.060 (0.681–1.650)	
TVI			< 0.001		0.001
< 5970	200	1		1	
≥ 5970	102	2.497 (1.823–3.421)		1.936 (1.329–2.821)	

CI confidence interval, TVI Tumor Volume Index

adjuvant chemotherapy was not associated with prognosis (Table 1).

Overall Survival and Recurrence

The 5-year overall survival was 51.3% and median survival time was 62.0 months in all registered patients. Figure 3 shows overall survival in groups based on the TVI. Low- and high-volume tumors were associated with 5-year overall survival of 63.5% and 27.9%, respectively. In groups stratified by N stage, the TVI was an independent prognostic factor in patients with pN0/N1 tumors but not in those with pN2/N3 lesions (Table 2).

DISCUSSION

Our evaluation of surgically resected malignant esophageal lesions showed that patient age, sex and thoracoscopic surgery, lymph node metastasis, and tumor volume are independent prognostic factors in patients with esophageal cancer. However, tumor volume had no impact on prognosis in patients with advanced lymph node metastasis (pN2/N3).

Some studies reported that the number of metastatic lymph nodes and primary tumor diameter were independent prognostic factors in esophageal cancer.^{4,16–20} However, tumor diameter did not independently predict survival in our multivariate analysis. This result indicates that tumor volume has a significant impact on prognosis, whereas tumor diameter simply reflects longitudinal extension in patients with esophageal cancer. We can hypothesize that high-volume tumors would have an increased likelihood of nodal spread and systemic metastases in the deeper layer.²¹ Thus, effective treatments for patients with a high TVI could improve survival time.

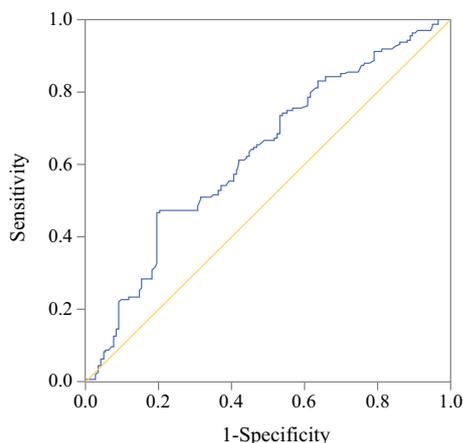


FIG. 3 Disease-specific survival curves in groups based on the tumor volume index reveal a significant difference in survival between patients with low- and high-volume tumors ($P < 0.0001$)

TABLE 2 Cox proportional regression hazard model according to lymph node metastasis

	χ^2	Hazard ratio (95% CI)	<i>P</i> value
pN0			
TVI			
≥ 5970/< 5970	18.834	3.627 (2.027–6.489)	< 0.001
pN1			
TVI			
≥ 5970/< 5970	7.040	2.072 (1.210–3.549)	0.008
pN2			
TVI			
≥ 5970/< 5970	1.300	1.453 (0.771–2.672)	0.254
pN3			
TVI			
≥ 5970/< 5970	0.001	1.020 (0.346–3.006)	0.972

CI confidence interval, TVI Tumor Volume Index

Recently, a study focusing on pathological tumor volume demonstrated the significant prognostic role of this factor in patients with esophageal carcinoma in a Western country.²² This previous study differs from ours, because the majority of tumors (79%) were adenocarcinomas. The incidence of esophageal adenocarcinoma is low in East Asian countries, including Japan. Therefore, our study is the first to report the significance of pathological tumor volume as a prognostic factor in squamous cell esophageal cancer.

The prognostic value of imaging-assessed tumor volume was evaluated in previous studies.^{12–15} These investigations concluded that tumor volume, predominantly assessed by PET/CT, was a significant survival indicator. In this study, imaging-assessed tumor volume also was correlated with pathological tumor volume but not strongly. It is unclear whether imaging-assessed tumor volume accurately reflects pathological tumor volume.^{14,23} PET/CT-assessed tumor volume does not represent real tumor volume, because malignant lesions do not always have a uniform shape and could contain necrotic areas. Moreover, it is not always possible to distinguish adjacent small lymph nodes from the primary tumor using PET/CT. Pathological tumor volume may be highly associated with prognosis in patients with esophageal cancer. Tumor diameter, easily calculated, also may provide useful information with clinical applications. Advancements in imaging technology may allow the accurate assessment of the TVI in the near future. As a result, this parameter, calculated preoperatively, could be included in the esophageal cancer staging system.

We evaluated the cutoff value obtained by the Youden index from ROC curve and analyzed prognostic factor using categorical classification of tumor diameter and volume. However, converting continuous predictor into categorical predictor sometimes reduces the prediction power. Therefore, we evaluated the impact of maximum tumor diameter and volume as prognostic factor by simultaneously inserting these variables in the fashion of continuous variables and the categorical variables into the Cox regression hazard model. In this additional analysis, categorical classification had stronger impact for prognostic factor (data not shown). Moreover, it is clinically available to use categorical classification, because we can conduct a therapeutic strategy by using the cutoff value. Therefore, we recommend categorical classification.

Patient age, sex, and thoracoscopic surgery also were selected as independent prognostic factors for OS in patients with esophageal cancer. Previously, a study reported that women, who underwent esophagectomy for esophageal squamous cell carcinoma, had better prognosis than men, and thoracoscopic esophagectomy can contribute to prolonged survival after surgery in patients with esophageal cancer by enabling precise thoracic lymph node dissection based on a close view and magnified surgical field.^{24,25} However, no report showed that elderly patients who underwent esophagectomy seemed to have poor prognosis. In this study, OS was analyzed, and so the high frequency of death due to other diseases in elderly patients caused the outcomes obtained.

In this study, HR of N2 in the multivariate analysis of prognostic factors for OS was higher than that of N3, although there was no significant difference in N3 ($P = 0.259$). The small number of patients in the N3 group and chemotherapeutic status after recurrence may affect this result. Relapse-free survival should be analyzed to clarify this issue.

The limitations of this study are its retrospective nature and limited number of patients. Therefore, our results should be confirmed in future prospective studies with larger patient cohorts. Second, the correlation between the TVI and actual tumor volume is unclear, because it is very difficult to measure actual tumor volume.

In conclusion, the present study suggests that the pathological TVI is an important independent prognostic factor in patients with esophageal carcinoma and could be included in the staging system of esophageal cancer.

DISCLOSURE Hiroshi Miyamoto has no disclosures to declare.

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