

Comparison of Prognostic Compatibility between Seventh AJCC/TNM of the Esophagus and 14th JCGC Staging Systems in Siewert Type II Adenocarcinoma

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Abstract. *Background and Aim:* The Seventh American Joint Committee on Cancer (AJCC)/TNM classification defined that the classification for adenocarcinoma of the esophagogastric junction (AEG) was included in the esophageal category. However, there still remain various classifications in AEG such as the Seventh AJCC/TNM of the esophagus and the 14th Japanese Classification of Gastric Cancer staging system (JCGC) in Japan. This study was designed to evaluate the compatibility of both the Seventh AJCC/TNM of the esophagus and the 14th JCGC staging systems in Siewert type II adenocarcinoma. *Patients and Methods:* Between 1999 and 2011, 47 consecutive patients with Siewert type II adenocarcinoma underwent curative surgery at our Institution. We reviewed their hospital records retrospectively. *Results:* Overall survival rates at 3 and 5 years were 44.3% and 33.4%, respectively. Multivariate analyses revealed that the extent of lymph node metastasis was the only independent prognostic factor ($p=0.0194$, $HR=12.927$). In the $\leq pN2$ group by 14th JCGC, deeper tumor depth was significantly correlated with poor prognosis, whereas in the $\geq pN3$ group, deeper tumor depth did not affect prognosis, suggesting a strong effect of nodal factor on prognosis and more similar prognostic stratification to the Seventh edition of the AJCC/TNM classification of the esophagus. *Conclusion:* Nodal involvement status might be a more important prognostic factor than tumor depth in patients with Siewert

type II adenocarcinoma. The Seventh classification of AJCC/TNM of the esophagus might be more compatible with Siewert type II adenocarcinoma.

Over the past few decades, adenocarcinoma of the esophagogastric junction (AEG), representing adenocarcinoma involving the anatomical border between the esophagus and the stomach, has markedly increased in Western and Eastern countries (1, 2). According to the definition of AEG proposed by Siewert and Stein (3), Kusano *et al.* reported that in Japanese, the proportion of Siewert type II and type III adenocarcinoma was 60% and 40%, respectively, and that of type I adenocarcinoma was approximately 1%. The number of Siewert type II adenocarcinomas is reported to have markedly increased by two-fold during the past decade (4). This implies that more cases with AEG, particularly Siewert type II adenocarcinoma, will be encountered in the future and several issues will need to be solved.

Currently, one possible problem is that there are still three different staging systems for AEG in Japan, the Seventh AJCC/TNM of the esophagus, the 14th Japanese Classification of the Gastric Cancer (JCGC) (which is same as the Seventh AJCC/TNM of the stomach), and the 10th Japanese Classification of Esophageal Cancer (JCEC) staging system, although the Seventh AJCC/TNM staging system of the esophagus (5) was defined as the only staging system for AEG in Western countries. AEG is known to show clinicopathological characteristics different from those of gastric adenocarcinoma and esophageal squamous cell carcinoma, and to have a poorer prognosis and higher incidence of lymph node and hematogenous metastasis (6, 7). However, the 14th JCGC staging system was established mainly based on adenocarcinoma of the middle or distal stomach, whereas the 10th JCEC was mainly based on squamous cell carcinoma of thoracic esophagus in Japan.

In this study, we evaluated the clinicopathological characteristics and prognostic outcomes in 47 consecutive

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Key Words: Esophagogastric junctional carcinoma, Siewert type II adenocarcinoma, AJCC, TNM, JCGC, staging system.

patients with Siewert type II adenocarcinoma because its clinical behavior might be the most typical among AEG subtypes of Siewert classification. Furthermore, we compared the compatibility of the Seventh AJCC/TNM of the esophagus and the 14th JCGC staging systems, in order to detect the most appropriate staging system for Siewert type II adenocarcinoma.

Patients and Methods

A total of 47 consecutive patients with Siewert type II adenocarcinoma(3), which underwent curative resection at the Kyoto Prefectural University of Medicine between 1999 and 2011, were enrolled in this study. We precisely defined Siewert type II adenocarcinoma based on pathological mapping and macroscopic measurement of the distance between the tumor epicenter and the esophagogastric junction (EGJ) in each case. We retrospectively analyzed clinicopathological features and prognostic outcomes, and evaluated the compatibility of the Seventh AJCC/TNM of the esophagus and the 14th JCGC staging systems. The follow-up program after surgery at our Institution comprises a regular physical examination and laboratory blood tests, chest X-rays at every three or six months, and yearly endoscopy and ultrasonography, or computer tomography for the first five years, if possible.

Statistical analysis. For the analysis of survival, Kaplan–Meier survival curves were constructed for groups based on univariate predictors and differences between groups were tested with the log-rank test. Univariate and multivariate survival analyses were performed using the likelihood ratio test of the stratified Cox proportional hazards model. Differences were assessed with a two-sided test and were considered significant at the $p < 0.05$ level.

Results

Clinicopathological features of 47 consecutive patients with Siewert Type II adenocarcinoma. Table I shows the clinicopathological features of the 47 consecutive patients with Siewert type II adenocarcinoma. All 47 patients underwent various kinds of surgery, with the majorly undergoing total gastrectomy or proximal gastrectomy with esophagectomy (57% and 36%, respectively). All patients underwent at least regional lymphadenectomy. Two surgical approaches, abdominal and thoracic approach, were employed in the cohort. The median follow-up period was 16 months. Recurrence occurred in 20 patients (42%). Overall survival rates at 3 and 5 years were 44.3% and 33.4%, respectively. These rates were compatible with those of previous reports (8, 9). As for the pathological staging, the tumor depth (T-stage) and the nodal stage (N-stage) of each case in the current study was based on the 14th JCGC staging system.

Evaluation of subgroup outcomes: overall survival after surgery according to pT1-3 vs. pT4 in the 47 consecutive patients with Siewert type II cancer. We performed subgroup

Table I. *Clinicopathological features of 47 consecutive patients with Siewert type II cancer.*

Variable	n	%
Gender		
Male	40	85%
Female	7	15%
Median age, years (range)	67 (28-82)	
Median follow-up periods, days (range)	578 (27-3113)	
Macroscopic type		
Type 0-2/type 3-5	23/24	49/51%
Histological type		
Differentiated	26	56%
Undifferentiated	19	40%
Other	2	4%
Tumor depth (histological)		
T1/T2/T3/T4	3/6/15/23	6/13/32/49%
Nodal stage (histological)		
0/1/2/3	13/4/12/18	28/8/26/38%
Peritoneal metastasis		
Yes	42	89%
No	5	11%
pStage (JCGC)		
I II III IV	6/10/20/11	13/21/43/23%
Approach		
Abdominal	24	51%
Thoracotomy	23	49%
Type of gastrectomy		
Total	27	57%
Total + lower esophagectomy	3	6%
Proximal + esophagectomy	17	36%
Splenectomy		
Yes/no	26/21	55/45%
Lymphatic invasion		
Yes/no	38/9	81/19%
Histological venous invasion		
Yes/no	28/19	60/40%
Lymph node count (mean)		
Metastatic	7	
Dissected	30	
Recurrence		
Yes/no	20/27	43/57%
Overall survival (%)		
5-Year	34.3	
3-Year	44.3	

analyses to evaluate the compatibility of the Seventh AJCC/TNM of the esophagus and the 14th JCGC staging systems. In the 14th JCGC staging system, patients with pathological N3 (pN3) disease were divided into several stages according to each pathological T (pT) stage such as pT2/pN3 in stage II, pT3/pN3 in stage IIIB and pT4a/pN3 in stage IIIC. On the other hand, in the Seventh AJCC/TNM staging system, all patients with pN3 disease were divided into stage IIIC regardless of the pT status (Table III) (5). In the current study, in order to evaluate overall survival rates after surgery, we stratified the clinical factor of tumor depth (pT1-3 vs. pT4) in

Table II. Cox proportional hazard regression analysis for overall survival in 47 consecutive patients with Siewert type II adenocarcinoma.

Variable	Univariate <i>p</i> -value ¹	Multivariate ²		
		HR	95% CI	<i>p</i> -value ³
Gender				
Male vs. female	0.0561	-	-	-
Age				
<67 vs. >68	0.3494	-	-	-
Approach				
Abdominal vs. thoracotomy	0.1276	-	-	-
Histological type				
Differentiated vs. undifferentiated and others	0.3904	-	-	-
Macroscopic type				
Type 0-2 vs. type 3-5	0.0018	-	-	-
Tumor depth				
pT1-2 vs. pT3-4	0.0513	-	-	-
pT1-3 vs. pT4	0.0049	-	-	-
Lymph node involvement				
Negative vs. positive	0.0001	12.9270	1.512-110.533	0.0194
Lymphatic invasion				
Negative vs. positive	0.0077	-	-	-
Histological venous invasion				
Negative vs. positive	0.7160	-	-	-

¹Univariate analysis using the log-rank test. ²Cox proportional hazard regression analysis for overall survival. Considered significant at 0.05. HR, Hazard ratio; CI, 95% confidence interval.

Siewert type II adenocarcinoma with a pN0-2 or pN3 status. After resection of Siewert type II adenocarcinoma (n=47), the 5-year overall survival rate was significantly better in the group of patients with tumor depth pT1-3 (n=24, 51%) than in the group of patients with tumor depth pT4 (n=23, 49%) ($p=0.0049$) (Figure 1). In combined analyses of patients with Siewert type II adenocarcinoma with a pN0-2 status (n=29), patients with pT1-3 had significantly better outcomes than those with pT4 ($p=0.007$), whereas for those with a pN3 status (n=18), patients with pT1-3 disease did not have significantly better outcomes than those with pT4 disease ($p=0.660$) (Figure 2). Namely, in the \leq pN2 cohort, deeper tumor depth was significantly correlated with poor outcome, whereas in the \geq pN3 cohort, deeper tumor depth did not have a significant correlation with poor outcome. As shown in the multivariate analysis (Table II), these results also demonstrated that nodal involvement status may be a more important factor than the tumor depth for prognosis for patients with in advanced stages of Siewert type II adenocarcinoma, suggesting a better compatibility with the Seventh AJCC/TNM staging system of esophageal cancer than the 14th JCGC staging system in Siewert type II adenocarcinoma.

Discussion

Long-term survival following curative surgery for adenocarcinoma of the distal esophagus and gastric cardia, so-called AEG, is only 20% (10, 11). It goes without saying

Table III. 14th Japanese Classification of Gastric Cancer and seventh American Joint Committee on Cancer (AJCC)/TNM classification in gastric category (A).

pT	pN				
	A	N0	N1	N2	N3
T1a, T1b	IA	IB	IIA	IIB	IIIC
T2	IIA	IIIB	IIIC	IIIA	IIIB
T3	IIIA	IIIB	IIIC	IIIA	IIIB
T4a	IIIA	IIIB	IIIC	IIIA	IIIB
T4b	IIIA	IIIB	IIIC	IIIA	IIIB

Table III. Seventh AJCC/TNM classification in the esophageal category (B).

pT	pN				
	B	N0	N1	N2	N3
T1a, T1b	IA	IB	IIA	IIIB	IIIC
T2	IIA	IIIB	IIIC	IIIA	IIIB
T3	IIIA	IIIB	IIIC	IIIA	IIIB
T4a	IIIA	IIIB	IIIC	IIIA	IIIB
T4b	IIIA	IIIB	IIIC	IIIA	IIIB

that the attitude of Japanese surgeons to curable AEG has been radical surgery because curative surgery has been considered to be the only chance of a cure. However, it is fact

that only a few patients with AEG have been encountered in Japan and other Eastern countries, and there is fewer available and convincing clinical data than for Western countries. Considering the recent marked increase of AEG in Japan (4) and other Eastern countries, it is time we realized that there are various problems to be discussed.

In this study, we firstly evaluated clinicopathological features of 47 consecutive patients with Siewert type II adenocarcinoma in order to understand the prognostic factors. As a result, the extent of lymph node metastasis was the only independent prognostic factor by Cox proportional hazard regression analysis for overall survival ($p=0.0194$, $HR=12.927$) (Table II). Unexpectedly, the status of tumor depth was not an independent prognostic factor despite the extent of lymph node metastasis and the status of tumor depth being known as independent prognostic factors in gastric adenocarcinoma. Therefore, we hypothesized that it might be unsuitable to use the 14th JCGC staging system for Siewert type II adenocarcinoma.

To verify this hypothesis, we evaluated the compatibility of the classification based on the Seventh AJCC/TNM of the esophagus and the 14th JCGC staging system. In the 14th JCGC staging system, pathological N3 (pN3) cancer are divided into several stages according to each pathological T (pT) stage. On the other hand, in the Seventh AJCC/TNM staging system for the esophagus, all pN3 patients were divided into stage IIIC regardless of the pT status (Table III) (5). In our study, for the patients with Siewert type II adenocarcinoma $\leq pN2$, deeper tumor depth was a significantly correlated with poor outcome. On the other hand, in the patients with $\geq pN3$ disease, deeper tumor depth did not have a significant correlation with poor outcome. These results indicate that nodal involvement status may be more important than the depth of tumor for prognosis in advanced stages of Siewert type II adenocarcinoma. Therefore, the Seventh AJCC/TNM staging system might be more suitable than the JCGC staging system.

Furthermore, we also demonstrated that the Seventh AJCC/TNM staging system for the esophagus may be a more suitable staging system than the 10th JCEC (12) (data not shown). Possible reasons for the superiority of the Seventh AJCC/TNM staging system are both 14th JCGC and 10th JCEC staging systems for Siewert type II adenocarcinoma might be the differences in the tumor location and the histological type. The Seventh AJCC/TNM staging system for the esophagus was established mainly based on adenocarcinoma of the esophagus in Western countries; in contrast, the 14th JCGC and 10th JCEC staging systems were established based on adenocarcinoma located at the middle or distal stomach and squamous cell carcinoma of the thoracic esophagus, respectively.

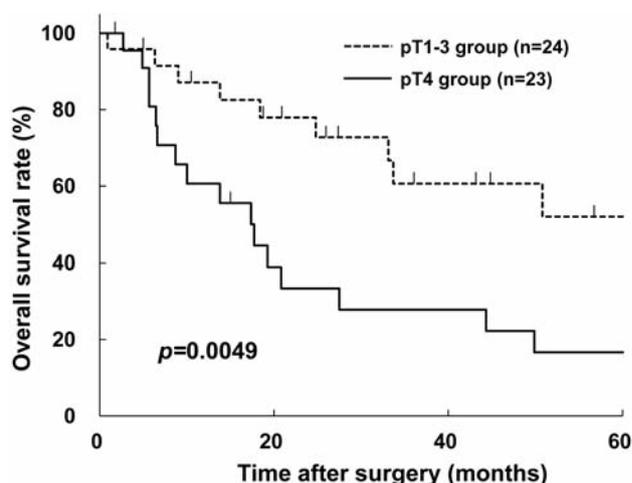


Figure 1. Overall survival rates after surgery of Siewert type II adenocarcinoma ($n=47$). The 5-year overall survival rate is significantly better in the group of patients with tumor depth pT4 ($n=23$, 49%) than in the group of patients with tumor depth pT1-3 ($n=24$, 51%) ($p=0.0049$).

Another recent report came to a different conclusion, that the Seventh AJCC/TNM staging system for the esophagus did not show sufficient compatibility and the Seventh AJCC/TNM staging system for gastric cancer, which is same as the 14th JCGC staging system, is more appropriate for early-stage I and II of Siewert type II and III adenocarcinoma (13). This finding might be affected by the influence of Siewert type III adenocarcinoma because the clinicopathological characteristics of patients with Siewert type III adenocarcinoma are similar to those of patients with adenocarcinoma of the gastric cardia (14). Therefore, to summarize: the Seventh AJCC/TNM staging system of the esophagus might be suitable for Siewert type I and II adenocarcinoma and the Seventh AJCC/TNM staging system of the stomach or the 14th JCGC staging system might be suitable for Siewert type III adenocarcinoma. However, further larger studies might be necessary to test this hypothesis and establish a more suitable staging system for AEG.

In conclusion, nodal involvement status might be a more important factor than tumor depth for prognosis of patients with Siewert type II adenocarcinoma. Currently, the Seventh AJCC/TNM staging system for the esophagus might be the most appropriate staging system for Siewert type II adenocarcinoma.

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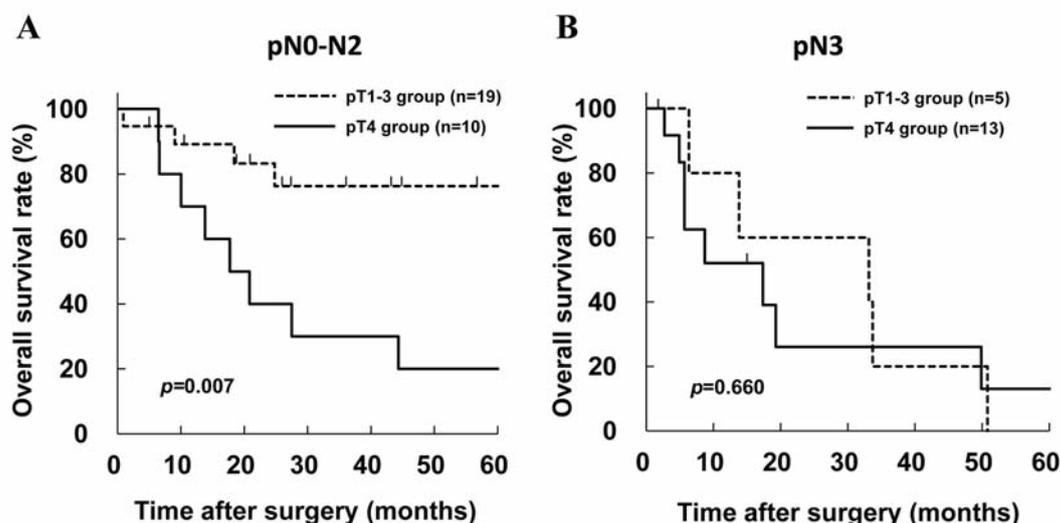


Figure 2. Overall survival rates after resection by stratification analysis of tumor depth (pT1-3 group vs. pT4 group) in Siewert type II adenocarcinoma with a pN0-2 status (n=29) or pN3 status (n=18). A: In Siewert type II adenocarcinoma pN0-2, the pT1-3 group had significantly better outcomes than the pT4 group of patients ($p=0.007$). B: In Siewert type II adenocarcinoma with pN3, the pT1-3 group of patients did not have significantly better outcomes than those of the pT4 group ($p=0.660$).

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Received April 29, 2013

Revised May 24, 2013

Accepted May 28, 2013