Comparison the sixth and seventh editions of the AJCC staging system for T1 gastric cancer: a long-term follow-up study of 2124 patients

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Abstract

Background/Aim The aim of this study was to establish an appropriate TNM staging system for early gastric cancer.

Methodology We evaluated 2124 patients who had undergone gastrectomy for early gastric cancer between 1989 and 2001.

Results Using the seventh edition of the American Joint Committee on Cancer (AJCC) staging system, we found no significant differences in tumor recurrence and survival between N1 and N2 cancers or between N3a and N3b cancers, whereas the survival curves for N2 and N3 cancers were quite different. Similarly, using the classification in the sixth edition of the AJCC staging system, we found no significant difference in survival between the N2 and N3 cancer groups, whereas the survival curves for N1 versus N2 or N3 cancers were quite different.

Conclusions The classifications in the sixth and seventh editions of the AJCC staging system have a limitation for T1 gastric cancer (early gastric cancer).

Introduction

Early gastric cancers (EGCs; T1 cancer) make up more than 50 % of all gastric cancers [1, 2]. The survival rate of patients with EGC exceeds 90 % in Japan [3, 4] and in Western countries [5]. Variable rates of recurrence of EGC have been reported in these countries, ranging from 2.1 to 12.4 % [6–8]. The seventh edition of the American Joint Committee on Cancer (AJCC) staging system was published in 2010. However, this new AJCC TNM staging system is inadequate for EGC but is appropriate for advanced gastric cancer [9]. In patients with EGC, survival is affected by the presence of invaded lymph nodes not by the depth of penetration of the lesion or its size [10]. Therefore, the aims of this study were to evaluate tumor recurrence and long-term survival of patients with EGC in relation to the AJCC TNM staging system on the basis of the results of a large-scale study with long-term follow-up and to recommend a new TNM staging system.

Keywords Early gastric cancer · Nodal stage · TNM

Methods

We collected data on 8685 patients who had undergone surgery for gastric cancer from the databases and electronic medical records at Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea, between 1989 and December 2001. Of those patients, we retrospectively evaluated 2124 patients who had undergone curative gastrectomy for EGC (mucosal or submucosal). Figure 1 shows the data analysis flow diagram for this study. Clinicopathological characteristics and macroscopic findings were analyzed in accordance with the Japanese Classification of Gastric Cancer [11].

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Fig. 1 Data analysis flow diagram for this study. GC gastric cancer

We reviewed tumor recurrence patterns and prognosis of the patients undergoing gastrectomy for EGC, and related the results to the sixth and seventh editions of the AJCC staging system. We reclassified nodal stages to achieve appropriate staging for T1 gastric cancer: N1 as one to five lymph node metastases, N2 as six to ten lymph node metastases, and N3 as more than ten lymph node metastases.

We evaluated the categorical variables using the chi-square test and continuous variables using the Student *t* test. We evaluated the univariate risk factors for tumor recurrence using log-rank tests and evaluated multivariate risk factors using a Cox regression model, the hazard ratios, and the 95 % confidence intervals. The *C* index was evaluated to determine whether the most recent AJCC TNM staging system is suitable or not suitable for discrimination. The 95 % confidence intervals for the *C* index were obtained through the percentile bootstrap method (1000 replicates) [12]. Survival curves after tumor recurrence and recurrence probability curves after surgery were evaluated by the Kaplan–Meier method. All statistical analyses were performed with Statistical Package for the Social Sciences Windows version 19.0 (SPSS, Chicago, IL, USA). Significance was set at $p < 0.05$.

This study received institutional review board approval (protocol number 2012-0032).

Results

The general clinicopathological characteristics of the study cohort are summarized in Table 1. There were 1399 male patients (65.9 %) and 725 female patients (34.1 %). The mean follow-up period was 152.1 ± 52.6 months. Two hundred fifty-six patients (12.1 %) had lymph node

metastases. Ninety-seven patients (4.6 %) experienced tumor recurrence during the follow-up period: there was hematogenous recurrence in 41 patients, lymphatic recurrence in 11 patients, locoregional recurrence in 12 patients, peritoneal recurrence in 13 patients, and remnant stomach recurrence in 20 patients. Multiple synchronous EGC lesions were detected in 76 patients (3.6 %) at the time of surgery. Patients with recurrence had deeper invasion, more frequent excavated gross findings, more lymph node involvement, and more lymphovascular invasion than patients without recurrence.

Risk factors for tumor recurrence and prognostic factors

Depth of invasion, macroscopic findings, and microscopic lymphovascular invasion were risk factors in univariate analysis, and depth of invasion and lymph node metastasis were independent risk factors for tumor recurrence in the multivariate analysis ($p < 0.05$). In addition, lymph node metastasis has a larger hazard ratio than the depth of invasion. The results of univariate and multivariate analyses of prognostic factors for disease-related death are summarized in Table 2. Lymph node metastasis is the only independent prognostic factor in the Cox regression model.

Correlation with the seventh edition of the AJCC staging system

Table 3 shows tumor recurrence and survival according to the seventh edition of the AJCC cancer staging system. There were no significant differences in tumor recurrence and survival between the N1 (one or two nodes involved) and N2 (three to six nodes involved), N3a (7 to 15 nodes involved), or N3b (more than 15 nodes involved) cancer groups or between the *N1 (only one node involved) and N2 cancer groups ($p > 0.05$). Figure 2 shows the disease-related survival curve of patients according to the seventh edition of the AJCC staging system. There was no significant difference between N1 (stage IB) and N2 (stage IIA) cancer groups, but there was a marked difference in survival between N2 and N3 (stage IIB) cancer groups.

Correlation with the sixth edition of the AJCC staging system

The results of analyses of tumor recurrence and survival according to the sixth edition of the AJCC staging system are summarized in Table 3. There were significant differences in tumor recurrence between nodal stages ($p < 0.05$). However, there was no significant difference in survival between the N2 and N3 cancer groups ($p > 0.05$). Figure 2b presents the disease-related survival curves of the

Table 1 Clinicopathological characteristics for nonrecurrence and recurrence

Characteristic	All patients	Nonrecurrence (<i>n</i> = 2027)	Recurrence (<i>n</i> = 97)	<i>p</i>
Sex				NS
Male	1399 (65.9 %)	1367 (66.0 %)	62 (63.9 %)	
Female	725 (34.1 %)	690 (34.0 %)	32 (36.1 %)	
Age (years)	54.8 ± 11.5	54.7 ± 11.5	56.4 ± 11.8	NS
Follow-up (months)	151.8 ± 52.7	155.4 ± 49.6	79.0 ± 59.0	<0.001
Location of tumor				NS
Lower third	1298 (61.1 %)	1242 (61.3 %)	56 (57.7 %)	
Middle third	640 (30.1 %)	607 (29.9 %)	33 (34.0 %)	
Upper third	188 (8.8 %)	178 (8.8 %)	6 (8.2 %)	
Tumor size (mm)	30.5 ± 19.1	30.4 ± 19.1	32.7 ± 17.1	NS
Gastrectomy				NS
Subtotal	1886 (88.8 %)	1801 (88.9)	85 (87.6 %)	
Total	238 (11.2 %)	226 (11.1)	12 (12.4 %)	
Depth of invasion				< 0.001
Mucosa	1054 (49.6 %)	1029 (50.8 %)	25 (25.8 %)	
Submucosa	1070 (50.4 %)	998 (49.2 %)	72 (74.2 %)	
Macroscopic finding				0.025
Superficial	1783 (83.9 %)	1711 (84.4 %)	72 (74.2 %)	
Protruded	122 (5.7 %)	114 (5.6 %)	8 (8.2 %)	
Excavated	219 (10.3 %)	202 (10.0 %)	17 (17.5 %)	
Histological type				NS
Differentiated	1090 (51.3 %)	1043 (51.5 %)	47 (48.5 %)	
Undifferentiated	1034 (48.7 %)	984 (48.5 %)	50 (51.5 %)	
Lymph node metastasis				<0.001
No	1868 (87.9 %)	1816 (89.6 %)	52 (53.6 %)	
Yes	256 (12.1 %)	211 (10.4 %)	45 (46.4 %)	
Lymphatic/venous invasion				<0.001
No	1925 (90.6 %)	1852 (91.4 %)	73 (75.3 %)	
Yes	199 (9.4 %)	175 (8.6 %)	24 (24.7 %)	
Retrieved lymph nodes	24.7 ± 12.7	24.8 ± 12.7	24.3 ± 12.9	NS
Multiple cancers				NS
No	2048 (96.4 %)	1954 (96.4 %)	94 (96.9 %)	
Yes	76 (3.6 %)	73 (8.6 %)	4 (3.1 %)	

NS nonspecific

patients according to the classification in the sixth edition of the AJCC staging system. The survival curves for N1 cancer patients versus N2 or N3 cancer patients were quite different.

Correlation with the new recommended TNM staging system

Table 4 shows tumor recurrences and survival rates according to our recommended TNM staging system. There are significant differences in tumor recurrence

between N0 and N1 cancers, N1 and N2 cancers, and N2 and N3 cancers ($p < 0.05$). Figure 2c shows the survival curves of the patients according to our nodal stages. There are significant differences in survival between N0 and N1 cancers, N1 and N2 cancers, and N2 and N3 cancers ($p < 0.05$). Furthermore, the differences between the survival curves are evenly distributed.

Table 5 shows the calculated *C* index for each individual staging system. There is no significant difference in the *C* index

Table 2 Prognostic factors based on log-rank tests and a Cox regression model

Characteristic	Number	Univariate analysis		Multivariate analysis	
		Number	<i>p</i>	Hazard ratio ^a	<i>p</i>
Age (years)			0.046		
≤55	1042	36 (3.5 %)			
>55	1088	53 (4.9 %)		1.54 (0.98–2.32)	NS
Depth of invasion			<0.001		
Mucosa	1054	22 (2.1 %)			
Submucosa	1070	66 (6.1 %)		1.35 (0.79–2.30)	NS
Macroscopic findings			0.013		
Superficial	1783	65 (3.6 %)			
Protruded	122	8 (6.5 %)		1.14 (0.54–2.41)	NS
Excavated	219	16 (7.3 %)		1.42 (0.82–2.48)	NS
Lymph node metastasis			<0.001		
No	1868	41 (4.7 %)			
Yes	256	48 (18.7 %)		7.41 (4.63–11.86)	<0.001
Lymphatic/venous invasion			<0.001		
No	1925	64 (3.3 %)			
Yes	199	25 (12.6 %)		1.65 (0.97–2.74)	NS

NS nonspecific

^a The 95 % confidence interval is given in parentheses**Table 3** Recurrence and survival based on the Kaplan–Meier method using the log-rank test, according to the sixth and seventh editions of the American Joint Committee on Cancer (AJCC) staging system

Characteristics	Number (<i>n</i> = 2124)	Tumor recurrence		Disease-related death	
		Number	<i>p</i>	Survival rate (%)	<i>p</i>
AJCC staging system, 7th edition					
N0 vs N1	1868 vs 156	52 (2.8 %) vs 18 (11.5 %)	<0.001	97.8 vs 85.9	<0.001
N1 vs N2	156 vs 75	18 (11.5 %) vs 8 (10.7 %)	NS	85.9 vs 90.7	NS
N1 vs N3	156 vs 25	18 (11.5 %) vs 19 (76.0 %)	<0.001	85.9 vs 24.0	<0.001
N2 vs N3	75 vs 25	8 (10.7 %) vs 19 (76.0 %)	<0.001	90.7 vs 24.0	<0.001
N3a vs N3b	20 vs 5	14 (70.0 %) vs 5 (100.0 %)	NS	30.0 vs 0.0	NS
AJCC staging system, 6th edition					
N0 vs N1	1868 vs 231	52 (2.8 %) vs 26 (25.9 %)	<0.001	97.8 vs 87.4	<0.001
N1 vs N2	231 vs 20	26 (25.9 %) vs 14 (70.0 %)	<0.001	87.4 vs 30.0	<0.001
N1 vs N3	1868 vs 5	52 (2.8 %) vs 14 (70.0 %)	<0.001	87.4 vs 0.00	<0.001
N2 vs N3	20 vs 5	14 (70.0 %) vs 5 (100.0 %)	NS	30.0 vs 0.00	NS

NS nonspecific

Discussion

Lymph node metastasis is a significant risk factor for EGC recurrence and the most valuable prognostic factor for EGC [13–15]. Early tumor recurrence has been associated with lymph node metastasis and a poor prognosis [7, 16, 17]. In our study we observed that tumor recurrence and prognosis of T1a (tumor invades mucosa) cancer were similar to those for T1b (tumor invades submucosa) cancer ($p > 0.05$), and we identified lymph node metastasis as an independent risk factor for tumor recurrence, as well as an

independent prognostic factor. This result shows that T1 cancer (EGC) stages mostly depend on nodal status.

More than 50 % of all gastric cancers are diagnosed as T1 (invading the mucosa or submucosa) cancers, and early detection of gastric cancer is increasing steadily. However, the classification in the seventh edition of the AJCC staging system is based on advanced gastric cancer [9], and treatment modalities and survival predictions have followed the AJCC TNM staging system. So far, there has been no report focusing on a TNM staging system for T1 cancer. Therefore, we investigated tumor recurrence and survival

Fig. 2 Survival by nodal stage. **a** There was no significant difference between N1 and N2 cancers in the seventh edition of the American Joint Committee on Cancer staging system. **b** There was no significant difference between N2 and N3 cancers in the sixth edition of the American Joint Committee on Cancer staging system. **c** Survival as defined by the proposed new nodal staging system.

There were significant differences between N0 and N1 cancers, N1 and N2 cancers, and N2 and N3 cancers ($p < 0.05$); N1 corresponds to one to five lymph node metastases, N2 corresponds to six to ten lymph node metastases, and N3 corresponds to more than ten lymph node metastases

Table 4 Recurrence and survival based on the Kaplan–Meier method using the log-rank test, according to the recommended nodal stages

Characteristic	Number ($n = 2124$)	Tumor recurrence		Disease related death	
		Number	p	Survival rate (%)	p
N0 vs N1	1868 vs 222	52 (2.8 %) vs 26 (11.7 %)	<0.001	97.8 vs 86.9	<0.001
N1 vs N2	222 vs 24	26 (11.7 %) vs 10 (41.6 %)	<0.001	86.8 vs 58.3	<0.001
N1 vs N3	222 vs 10	26 (11.7 %) vs 9 (90.0 %)	<0.001	86.9 vs 10.0	<0.001
N2 vs N3	24 vs 10	10 (41.6 %) vs 9 (90.0 %)	0.012	58.3 vs 10.0	0.014

Table 5 C index determined through the percentile bootstrap method (1000 replicates)

C index	Recurrence	Death	Related death
AJCC staging system, 6th edition	0.6992 (0.6475–0.7510)	0.5611 (0.5415–0.5807)	0.7310 (0.6774–0.7846)
AJCC staging system, 7th edition	0.6994 (0.6475–0.7512)	0.5613 (0.5416–0.5810)	0.7318 (0.6780–0.7856)
New nodal staging system	0.6993 (0.6475–0.7510)	0.5611 (0.5415–0.5807)	0.7310 (0.6774–0.7846)

The 95 % confidence interval is given in parentheses

AJCC American Joint Committee on Cancer

of patients with T1 cancer on the basis of a large sample and long-term results, and we examined these results in relation to the classifications in the sixth and seventh editions of the AJCC staging system. We found that these classifications were not well distributed in the survival curve. Hence, we developed a new classification—N1, one to five lymph node metastases; N2, six to ten lymph node metastases; and N3, more than ten lymph node metastases—and found that this classification gave satisfactory survival curves. However, we could not prove that the most recent TNM classification is not appropriate in regard to survival prediction using the C index.

Our study had some limitations of note. This is a retrospective study. Lymph node metastasis is rare in EGC (12.1 % in our study). Furthermore, N2 or N3 cancers were very rare. Although we evaluated 2024 patients with EGC, 256 patients are really involved in the nodal group. So, the statistical power of our analysis was limited by the relatively small number of each TNM stage. Finally, our cutoff value of lymph node metastasis could not be high because lymph node metastasis was rare in EGC and the statistical power was not high. Therefore, the accuracy of this article still needs to be discussed.

In conclusion, the classifications in the sixth and seventh editions of the AJCC staging system have a limitation for disease-related death from T1 gastric cancer (EGC). However, we could not prove that the most recent TNM classification (seventh edition of the AJCC staging system) is appropriate in regard to survival prediction.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for their being included in the study.

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