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A better prognostic stratification for the 8th edition of the AJCC staging system of gastric cancer by incorporating pT4aN0M0 into stage IIIA

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ABSTRACT

Introduction: The aim of this study was to analyze the prognosis of gastric cancer patients categorized as pT4aN0M0, pT1N3aM0/pT2N2M0/pT3N1M0 of stage IIB and stage IIIA and to compare the optimistic prognostic stratification between the AJCC 8th edition staging system and the AJCC modified 8th (m8th) edition staging system by incorporating pT4aN0M0 into stage IIIA.

Material and methods: A total of 1770 patients who underwent gastrectomy were enrolled in this study. The homogeneity, the discriminatory ability, the monotonicity of the gradient assessments, and the discriminatory ability of the AJCC 8th and m8th edition staging systems were compared by using the likelihood ratio $\chi 2$ test, a linear trend $\chi 2$ test, the Akaike information criteria (AIC) and Bayesian information criterion (BIC) calculations, respectively.

Results: For patients staged IIB, the 5-year survival rate of the patients categorized as pT4aN0M0 were significantly worse than that of the patients categorized as pT1N3aM0/pT2N2M0/pT3N1M0 (59.9% vs. 72.4%, P = 0.036). By contrast, the prognoses of the patients between the pT4aN0M0 category and those staged IIIA were analogous (59.9% vs. 61.5%, P = 0.693). Compared with the 8th edition system, the modified 8th edition staging system had a better homogeneity (higher likelihood ratio χ [2] score, 441.17 vs. 436.24), discriminatory ability, monotonicity of gradients (higher linear trend $\chi 2$ score, 436.78 vs. 416.15) and smaller AIC (10364.98 vs. 10369.91) and BIC values (10447.13 vs. 10452.06).

Conclusions: The prognosis of pT4aN0M0 was poorer than those of pT1N3aM0, pT2N2M0, and pT3N1M0, which were staged IIB. There is a better prognostic stratification for the AJCC 8th edition staging system of gastric cancer by incorporating pT4aN0M0 into stage IIIA.

1. Introduction

Gastric cancer (GC) is one of the most important worldwide health problems. Especially in mainland China [1], GC remains the third most prevalent cancer and the third leading cause of cancer-related death. The incidence and mortality in China is much higher than that in any other country, with nearly one-half of the global incidence [1,2]. Recurrence or metastasis following radical surgery is a major problem, which is the ultimate cause of death. A number of studies suggest that peritoneal metastasis is the most common form of metastasis [3–7]. The depth of tumor invasion is one of the most important independent prognosis factors, which is demonstrated by several reports from Europe and the United States [8–10]. One study analyzed the patterns and timing of recurrence after curative resection for gastric cancer in China and found that T staging was the high risk factor for peritoneal metastasis rather than N staging [11]. Studies in Japan and Italy also found that the prognosis of gastric cancer patients with serosal invasion is very poor, with peritoneal dissemination as the most common type of recurrence [12–14].

Currently, the most commonly used staging system for gastric cancer is the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) system, which stages patients on the basis of the

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depth of the primary tumor invasion (T), the number of regional lymph nodes with metastases (N), and distant metastasis (M) [15]. The AJCC TNM staging system has undergone several editions in its half-century history. The 8th edition of the AJCC cancer staging manual is the most recently published edition [16,17]. The modifications of the 8th edition are mainly based on databases of the 25,411 patients from Japan, Korea, other Asian nations, and the West, with most cases collected from Japan and Korea (41.8% and 43.3%, respectively) and only 979 cases from China (3.9%) [18]. Furthermore, the databases of the 25,411 patients reflect some differences between different countries, such as the much higher proportion of pT1 (early gastric cancer) in Japan (58%) and Korea (48%) compared with western nations (28%). In China, the proportion of pT4 (serosal invasion) is 59.6%–66.3%, as reported by some centers [19,20]. By reason of the meager Chinese data contained in the databases of the 25,411 patients, it may cause limitations, thus leading to the impetus for our study. There are four categories staged IIB in the 8th edition of the AJCC staging system, including pT1N3aM0, pT2N2M0, pT3N1M0, and pT4aN0M0. The last category has serosal invasion only. Our research aimed to verify the hypothesis that the prognosis of pT4aN0M0 was poorer than others that were staged IIB, and it is more reasonable to incorporate pT4aN0M0 into stage IIIA for the AJCC 8th edition staging system.

2. Material and Methods

2.1. Patients

The eligibility criteria included (1) histologically confirmed gastric adenocarcinoma and R0 resection, which was defined as no macroscopic and microscopic residual tumor; (2) no other synchronous malignancy; (3) no preoperative chemotherapy or radiotherapy; (4) gastrectomy and lymphadenectomy based on the Japanese Gastric Cancer treatment guidelines [21]; (5) more than 14 retrieved lymph nodes; (6) a postoperative survival time of more than 1 month; and (7) distant metastases patients with pyloric obstruction, stomach bleeding or perforation who underwent surgery. Lastly, (8) patients with carcinoma of the gastric stump after gastric resection for benign disease were excluded from the study. Between January 2000 and December 2012, 1770 patients underwent surgery at the Department of Gastric & Pancreatic Surgery, Sun Yat-sen University Cancer Center were included in the current study. Fig. 1 shows the data extraction diagram for our study. The clinicopathological data collected from the database included gender, tumor size, histological grade, depth of invasion (pT), nodal status (pN), distant metastasis (pM), and the number of retrieved lymph nodes. Pathological staging was according to the 8th [16,17] edition of the AJCC cancer staging manual.

The study was approved by the Research Ethics Committee of Sun Yat-Sen University Cancer Center. Written informed consent was obtained from all individual participants included in the study.

2.2. Follow up and data

The follow-up was done by telephone, email or outpatient department visits. The last follow-up date was December 2017. The postoperative follow-up included clinical and laboratory examinations every 3 months for the first 2 years at our outpatient department, every 6 months from the third to the fifth years, and annually thereafter until at least 5 years after the operation or until the patient died. The overall patient survival was defined as the time from the operation to death or the last follow-up.

2.3. Statistical analysis

The survival time was calculated from the day of the surgery to the date of death or the last day of follow-up. The 5-year overall survival rate was estimated with the Kaplan-Meier method, and a univariate comparison between groups was performed using the log-rank test. In the multivariate analysis, the Cox's proportional hazards model was carried out to calculate the relative risks and to identify the significant prognostic factors. An evaluation of the homogeneity, distinctiveness, and monotonicity was conducted to assess and compare the prognostic ability of the AJCC 8th and m8th staging system. The likelihood ratio $\chi 2$ test, related to the Cox regression model, was used to measure homogeneity. The discriminatory ability and monotonicity of the gradient assessments were measured with the linear trend $\chi 2$ test. The Akaike information criteria (AIC) and Bayesian information criterion (BIC), within a Cox regression model, were also calculated for each system to demonstrate its discriminatory ability. A smaller AIC or BIC value indicated a better optimistic prognostic stratification. All the data analysis was performed by using STATA software (version 14.0, Stata Corporation, Texas, USA). A P value less than 0.05 (two-sided) was considered statistically significant.

3. Results

3.1. Clinic-pathological characteristics

Of the 1770 patients, 1177 (66.5%) were male, and the mean age was 56.0 ± 12.1 years old. The median number of lymph nodes retrieved was 26 (range 16–120). The median follow-up was 80 months (range 1–202 months). The overall 5-year survival rate for all the patients was 56.3%, and 1001 patients were alive when our follow-up completed.

Seven parameters were significantly associated with the overall survival using the univariate analysis, which were age, tumor size, histological grade, adjuvant chemotherapy status (no matter the drugs or circles), pT, pN and pM (Table 1). In the multivariate analysis, we demonstrated that age, tumor size, histological grade, adjuvant chemotherapy status, pT, pN, and pM stageremained independent prognostic factors (Table 1). The details of the population distribution of the AJCC 8th edition staging system is described in Table 2 (except the patients of staging IV, n = 1622).

3.2. AJCC stage groupings

The 5-year survival rates for all the stages, according to the AJCC 8th edition staging system, were as follows: IA: 95.5%; IB: 92.6%; IIA: 86.5%; IIB: 63.8%; IIIA: 61.5%; IIIB: 41.4%; IIIC: 18.3%; IV: 16.6% (Fig. 2). Statistically significant differences in survival were found between all the TNM stage groupings, with the exception of stages IIB and IIIA (P = 0.516). Thus, the prognoses among the distinct subsets of patients within the two stages mentioned above were investigated (Fig. 3). For patients staged IIB, the 5-year survival rate of the patients categorized as pT4aN0M0 were significantly worse than that of the patients categorized as pT1N3aM0/pT2N2M0/pT3N1M0 (59.9% vs. 72.4%, P = 0.036). The patients staged IIIA were also significantly worse than that of categorized as pT1N3aM0/pT2N2M0/pT3N1M0 (61.5% vs. 72.4%, P = 0.041). By contrast, the prognoses of the patients between the pT4aN0M0 category and those staged IIIA were analogous (59.9% vs. 61.5%, P = 0.693), with the Clinic-pathological characteristics showed in Table 3.

3.3. Modified prognostic groupings

Based on the aforementioned findings, an optimized staging system was constructed. Herein, the pT4aN0M0 category was incorporated into the modified stage IIIA from stage IIB, because its survival data matched with stage IIIA. As obvious from the Kaplan-Meier plot, there were no overlapping survival curves among all the eight stage groups in the AJCC modified 8th edition (m8th edition) staging system (Fig. 4). Significant differences in the 5-year survival rate were observed between the modified stage IIB and IIIA (72.4% vs. 61.0%, P = 0.031).

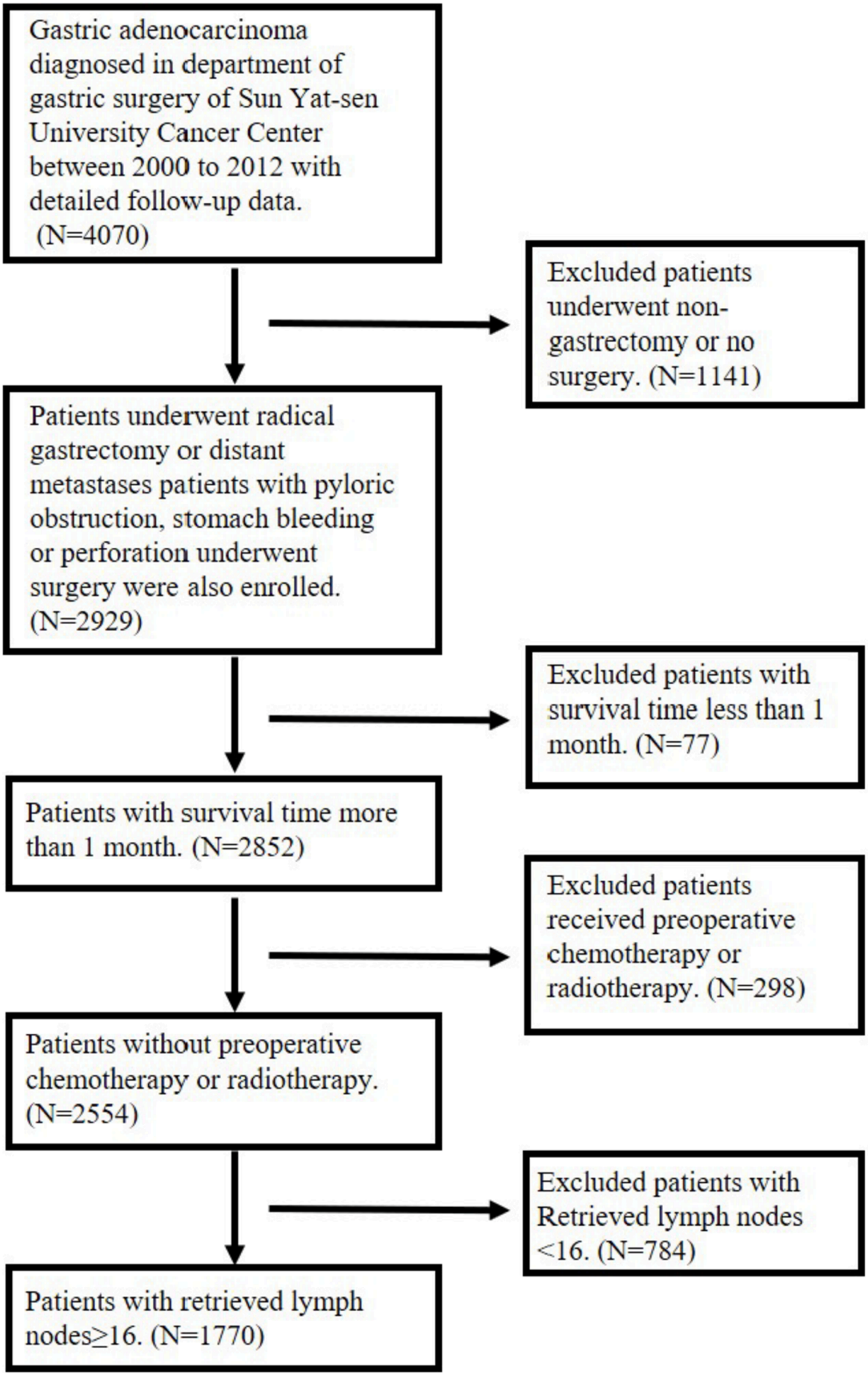

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Fig. 1. The data extraction diagram.

Table 1
Clinic-pathological characteristics and the univariate and multivariate survival analysis in gastric cancer patients.

Variables	n (%)	5-year survival rate (%)	p	HR (95% CI)	p	adjusted HR (95% CI)	p
Gender			0.809				
Female	593 (33.5)	56.7		ref.		ref.	
Male	1177 (66.5)	56.1		1.02 (0.88–1.18)	0.810	1.00 (0.85–1.16)	0.953
Age (y)			0.004				
< 40	181 (10.2)	61.4		ref.		ref.	
40～	860 (48.6)	58.4		1.12 (0.87–1.45)	0.377	1.11 (0.86–1.44)	0.430
60～	729 (41.2)	52.5		1.40 (1.08–1.79)	0.012	1.51 (1.16–1.97)	0.002
Tumor size (cm)			< 0.001				
≤5.0	1148 (64.9)	63.8		ref.		ref.	
> 5.0	622 (35.1)	42.2		1.86 (1.61–2.15)	< 0.001	1.20 (1.03–1.39)	0.019
Histological grade			0.001				
Well/moderately differentiated	252 (14.2)	68.0		ref.		ref.	
Poorly differentiated	1135 (64.1)	54.7		1.56 (1.24–1.97)	< 0.001	1.25 (0.98–1.58)	0.069
Undifferentiated/signet ring cell carcinoma	383 (21.6)	53.3		1.63 (1.25–2.11)	< 0.001	1.31 (1.00–1.71)	0.054
Adjuvant chemotherapy status			0.015				
No	812 (45.9)	51.9		ref.		ref.	
Yes	958 (54.1)	60.6		0.82 (0.70–0.96)	0.013	0.86 (0.74–0.99)	0.043
Depth of invasion			< 0.001				
T1	198 (11.2)	94.9		ref.		ref.	
T2	211 (11.9)	82.3		3.49 (1.84–6.65)	< 0.001	2.82 (1.48–5.39)	0.002
T3	341 (19.3)	60.0		8.28 (4.59–14.95)	< 0.001	4.86 (2.66–8.89)	< 0.001
T4a	951 (53.7)	42.7		14.05 (7.93–24.90)	< 0.001	7.82 (4.35–14.03)	< 0.001
T4b	69 (3.9)	30.1		18.76 (9.92–35.48)	< 0.001	10.06 (5.22–19.39)	< 0.001
Nodal status			< 0.001				
N0	526 (29.7)	78.5		ref.		ref.	
N1	259 (14.6)	70.0		1.43 (1.08–1.90)	0.012	1.05 (0.79–1.39)	0.748
N2	301 (17.0)	60.1		2.05 (1.59–2.64)	< 0.001	1.28 (0.99–1.66)	0.057
N3a	401 (22.7)	40.2		3.55 (2.85–4.43)	< 0.001	2.05 (1.63–2.59)	< 0.001
N3b	283 (16.0)	17.4		6.89 (5.51–8.63)	< 0.001	3.35 (2.60–4.32)	< 0.001
Distant metastasis			< 0.001				
M0	1622 (91.6)	59.6		ref.		ref.	
M1	148 (8.4)	16.6		3.87 (3.15–4.75)	< 0.001	2.25 (1.81–2.79)	< 0.001
Retrieved lymph nodes	26 (20–33)	–	0.428				
≤25	852 (48.1)	57.8		ref.		ref.	
> 25	918 (51.9)	54.8		1.06 (0.92–1.22)	0.431	0.88 (0.76–1.02)	0.098

Table 2
The details of population distribution of the AJCC 8th edition staging system (except the patients of staging IV, n = 1622).

The AJCC 8th edition staging system	N0	N1	N2	N3a	N3b
T1	IA (n = 147)	IB (n = 31)	IIA (n = 13)	IIB (n = 4)	IIIB (n = 1)
T2	IB (n = 100)	IIA (n = 42)	IIB (n = 31)	IIIA (n = 28)	IIIB (n = 5)
T3	IIA (n = 76)	IIB (n = 54)	IIIA (n = 72)	IIIB (n = 78)	IIIC (n = 40)
T4a	IIB (n = 187)	IIIA (n = 107)	IIIA (n = 159)	IIIB (n = 235)	IIIC (n = 151)
T4b	IIIA (n = 6)	IIIB (n = 14)	IIIB (n = 8)	IIIC (n = 14)	IIIC (n = 19)

Table 4 showed the prognostic impacts of the TNM system on survival in the multivariate Cox proportional hazards models by adjusting for the effects of the covariates. Compared with stage IA, the hazard ratio (HR) of the 8th edition stage IIB did not significantly differ from that of stage IIIA (8.07 vs. 8.27, P = 0.844). With respect to the modified staging system, the HR of the patients in stage IIB was lower than that of the patients in stage IIIA in comparison with stage IA (5.55 vs. 8.65, P = 0.036).

3.4. Prognostic ability of the staging system

The performance of the 8th edition and the m8th edition staging system was assessed by the linear trend χ [2], the likelihood ratio χ [2], and the AIC and BIC tests (Table 5). Compared with the 8th edition system, the m8th edition staging system had a better homogeneity (higher likelihood ratio χ [2] score), discriminatory ability, and monotonicity of the gradients (higher linear trend χ2 score). Moreover, the m8th edition staging system had smaller AIC and BIC values, suggesting the optimum prognostic stratification.

4. Discussion

According to the AJCC 8th edition staging system, there were four categories staged IIB including pT1N3aM0, pT2N2M0, pT3N1M0, and pT4aN0M0. The last category had serosal invasion only. In our study, we found that there were similar survival curves between stages IIB and IIIA (P = 0.516), while the Kaplan-Meier plot showed no overlapping survival curves among the other stages. Upon further analysis, the distance between the curves of pT4aN0M0 and IIIA became narrower in the OS Kaplan–Meier curves (Fig. 2), reflecting similar mortality risks for the patients categorized as pT4aN0M0 and staged IIIA. Significant differences in the 5-year survival rate were observed between the categories of pT1N3aM0/pT2N2M0/pT3N1M0 versus pT4aN0M0 (P = 0.036) and the categories of pT1N3M0/pT2N2M0/pT3N1M0

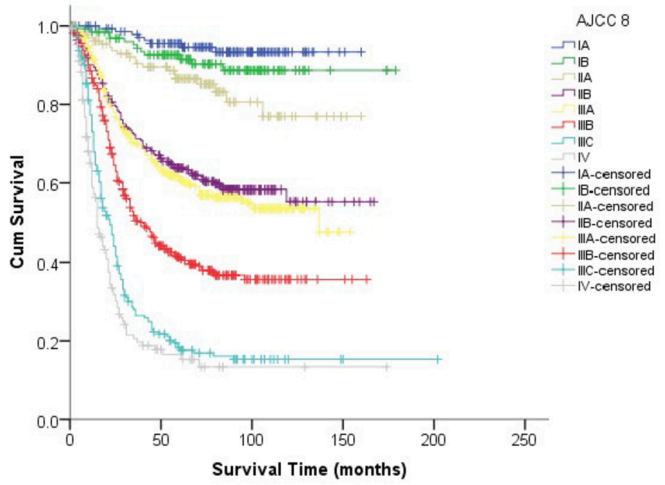

Fig. 2. The 5-year survival analysis for all the stages according to the AJCC 8th edition staging system.

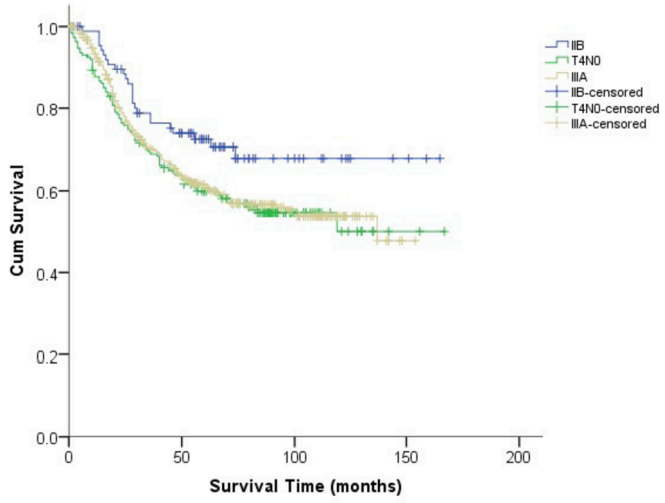

Fig. 3. The 5-year survival analysis for pT4aN0M0, pT1N3aM0/pT2N2M0/pT3N1M0 and IIIA.

versus stage of IIIA (P = 0.041), with the exception of the category of pT4aN0M0 versus stage of IIIA (P = 0.693). These finding revealed that the prognosis of the patients categorized pT4aN0M0 was similar to IIIA, but not pT1N3M0/pT2N2M0/pT3N1M0.

The prognosis of the patients categorized pT4aN0M0 was worse than those categorized as pT1N3aM0/pT2N2M0/pT3N1M0, due to its

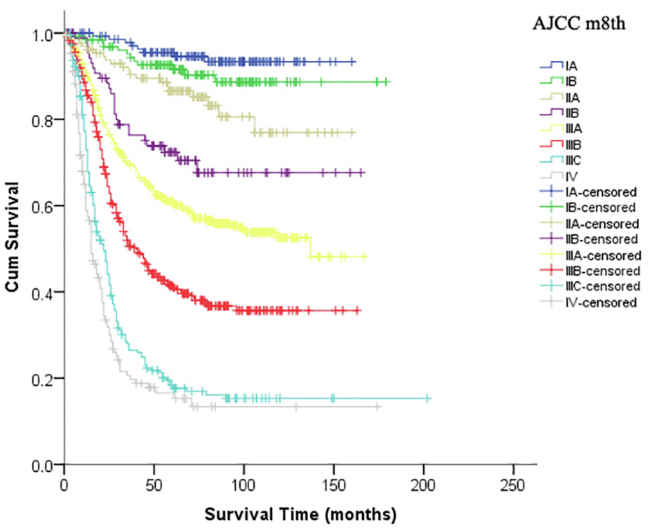

Fig. 4. The 5-year survival analysis for all the stages according to the AJCC m8th edition staging system.

Table 4
Multivariate survival analysis of the TNM staging system.

	AJCC 8th edition		AJCC m8th edition	
	HR	p	HR	p
IA	ref.		ref.	
IB	1.66 (0.68–4.07)	0.265	1.67 (0.68–4.07)	0.264
IIA	2.72 (1.20–6.18)	0.017	2.72 (1.20–6.18)	0.017
IIB	8.07 (3.93–16.57)	< 0.001	5.55 (2.50–12.32)	< 0.001
IIIA	8.27 (4.05–16.90)	< 0.001	8.65 (4.26–17.55)	< 0.001
IIIB	14.07 (6.90–28.68)	< 0.001	14.08 (6.91–28.70)	< 0.001
IIIC	26.64 (13.02–54.51)	< 0.001	26.62 (13.01–54.47)	< 0.001
IV	34.96 (16.94–72.15)	< 0.001	35.03 (16.97–72.28)	< 0.001

Table 5
Comparison of the performance of the two TNM staging systems.

Staging	Linear trend χ [2]	Likelihood ratio χ [2]	AIC	BIC
AJCC 8th edition	416.15	436.24	10369.91	10452.06
AJCC m8th edition	436.78	441.17	10364.98	10447.13

serosa invasion, which causes peritoneal metastasis. As described before, peritoneal metastasis is the most common form of metastasis of gastric cancer [3–7]. It is clear that one of the most important

Table 3
Clinic-pathological characteristics in gastric cancer patients categorized as pT4aN0M0, pT1N3aM0/pT2N2M0/pT3N1M0 and stage IIIA.

Variables		pT1N3aM0/pT2N2M0/pT3N1M0 (n = 89)	pT4aN0M0 (n = 187)	IIIA (n = 372)	P
Gender	Male	59 (66.3)	116 (62.0)	248 (66.7)	0.542
	Female	30 (33.7)	71 (38.0)	124 (33.3)	
Age (y)	< 40	10 (11.2)	17 (9.1)	24 (6.5)	0.082
	40～	38 (42.7)	104 (55.6)	179 (48.1)	
	60～	41 (46.1)	66 (35.3)	169 (45.4)	
Tumor size (cm)	≤5.0	66 (74.2)	127 (67.9)	237 (63.7)	0.150
	> 5.0	23 (25.8)	60 (32.1)	135 (36.3)	
Histological grade	Well/moderately differentiated	17 (19.1)	43 (23.0)	57 (15.3)	0.155
	Pooly differentiated	53 (59.6)	116 (62.0)	252 (67.7)	
	Undifferentiated/signet ring cell carcinoma	19 (21.3)	28 (15.0)	63 (16.9)	
Adjuvant chemotherapy status	Yes No	52 (58.4) 37 (41.6)	114 (61.0) 73 (39.0)	234 (62.9)138 (37.1)	0.714
Retrieved lymph nodes		27 (21–34)	24 (20–30)	24 (19–32)	0.169

prognostic indicators in gastric cancer is the depth of the wall invasion. For gastric cancer patients with serosa invasion, peritoneal recurrence is common after curative resection because the free intraperitoneal cancer cells are exfoliated from the serosal surface [5]. There were many studies indicating that in patients with serosa invasion who received curative gastrectomy, as high as 50% of the patients died from peritoneal recurrence within 2 years [5,22,23]. A previous study verified that serosa invasion is the high-risk factor for peritoneal recurrence after curative surgery for gastric cancer by serosal stamp cytology plus RT-PCR [24]. In their study, a total of 70 patients who underwent gastrectomy were enrolled. Since 21 of the 70 patients were either stamp cytology-positive or RT-PCR analysis-positive, these 21 patients were considered to be positive for cancer cells exposed to the serosa of the primary gastric tumor. The 3-year recurrence-free survival rate of the patients considered to be positive for cancer cells exposed to the serosa of the primary gastric tumor by their method (41.7%) was significantly (log rank P = 0.0002) worse than that of the patients with negative results (81.0%).

Several investigators reported that a conventional pN0 diagnosis after radical surgery for gastric cancer was not a guarantee against recurrence because of lymph node micrometastasis [25–27]. A study from Korea indicated that lymph node micrometastasis is clinically significant as a risk factor for recurrent gastric cancer, where 62.2% of the cases had lymph node micrometastasis in 164 cases diagnosed with pT4aN0M0 by immunohistochemical staining with an anti-cytokeratin antibody. In our study, we found that there were no significant differences between pN0 and pN1 by a multivariate survival analysis (adjusted HR = 1.08, P = 0.559) [28]. Therefore, we inferred that lymph node micrometastasis might be one of the explanations why the prognosis of the patients categorized pT4aN0M0 was similar to IIIA.

We modified the AJCC 8th edition staging system by incorporating pT4aN0M0 into IIIA. Our m8th edition staging system reveals a clear advantage over the 8th edition for the following reasons: (i) in the univariate analysis, the log-rank $\chi 2$ associated with the m8th edition staging system ($\chi 2 = 535.35$) was larger than that of the 8th edition ($\chi 2 = 530.67$), indicating a higher statistical significance; (ii) in the multivariate analysis, the HR of the patients staged IIIA was larger than that of the patients staged IIB (8.65 vs. 5.55) in the m8th edition staging system, whereas the HR of the 8th edition staged IIIA did not significantly differ from that of those staged IIB, and thus, the classification using the m8th edition staging system provided a better discrimination of the patients' prognostic risk profile; and (iii) the m8th edition staging system had a better homogeneity (higher likelihood ratio $\chi 2$ score, 441.17 vs. 436.24), discriminatory ability, monotonicity of the gradients (higher linear trend $\chi 2$ score, 436.78 vs. 416.15), and smaller AIC (10364.98 vs. 10369.91) and BIC values (10447.13 vs. 10452.06) (Table 5). These results demonstrated better prognostic stratifications of the AJCC m8th staging system than those of the 8th edition.

The team of Ueno evaluated a new western prognostic system (CLIP score) for hepatocellular carcinoma in 2001 [29]. They insisted the performance of the staging system could be evaluated as the homogeneity within the subgroups, the discriminatory ability between the different groups, and monotonicity of the gradients, as shown in the correlation between the stages and survival rates. In this study, the m8th staging system had a better homogeneity (higher likelihood ratio χ [2] score), discriminatory ability, and monotonicity of the gradients (higher linear trend χ [2] score).

We acknowledge several limitations in our study. Our sample population was from a single institution, and it was based on a retrospective data where the sample capacity of stage IIB was 275. Despite these limitations, we revealed a positive conclusion. Nevertheless, future studies should focus on a multi-center prospective study.

5. Conclusions

The prognosis of pT4aN0M0 was poorer than that of pT1N3aM0, pT2N2M0, and pT3N1M0, which were staged IIB. There is a better prognostic stratification for the AJCC 8th edition staging system of gastric cancer by incorporating pT4aN0M0 into stage IIIA.

Acknowledgements

The authors declare no conflicts of interest.

Abbreviations

GC	Gastric cancer
AJCC	American Joint Committee on Cancer
TNM	tumor-node-metastasis
AIC	Akaike information criteria
BIC	Bayesian information criterion
m8th edition	modified 8th edition

Author contributions

All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

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