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N3 Subclassification Incorporated into the Final Pathologic Staging of Gastric Cancer

A Modified System Based on Current AJCC Staging

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Abstract: The seventh edition of the American Joint Committee on Cancer (AJCC) TNM classification system for gastric cancer (GC) was established in 2009. We assessed the unmet medical needs of patients with the N3 classification of the seventh TNM staging system by comparing survival according to the extent of nodal involvement, with a particular focus on the cutoff points for the number of involved nodes in the N3 classification.

We retrospectively reviewed 3178 patients with GC who were registered in the GC database of the Department of General Surgery at the Chang Gung Memorial Hospital between 1994 and 2010. Among them, 884 patients undergoing curative intent resection had N3 lymph node involvement. The clinicopathological features and surgical outcomes were compared among all patients with GC and between the N3a and N3b groups.

N3b might impose GC patients with poor clinical outcome. We proposed a modified staging system, based on AJCC seventh edition, accordingly. T1-3N3 might be not simply categorized into stage IIIA as seventh AJCC suggested. Taking N3a and N3b into consideration, T1-3N3 might be further categorized into stage IIIB and IIIC, respectively, as we proposed, based on survival analysis. In addition, T4bN3bM0 is as dismal as M1 disease. In our proposed staging system, good discriminations between different stages are still maintained.

The N3 category should be subclassified as N3a or N3b due to the survival differences. Furthermore, T1-3N3aM0 could be categorized as stage IIIB, T1-3N3bM0 could be categorized as stage IIIC, T4aN3bM0 could be categorized as stage IIID, and T4bN3bM0 might be regarded as stage IV as we proposed.

(*Medicine* 94(8):e575)

Abbreviations: AJCC = American Joint Committee on Cancer, CA = carbohydrate antigen, CEA = carcinoembryonic antigen, CGMH = Chang Gung Memorial Hospital, CT = computed tomography, GC = gastric cancer, LN = lymph node, US = ultrasonography.

Editor: Neil Merrett.
Received: November 21, 2014; revised: January 8, 2015; accepted: January 30, 2015.
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The authors have no conflicts of interest to disclose.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000000575

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer and the third most common cause of cancer death worldwide. In 2012, there were an estimated 952,600 new GC patients and 723,000 deaths worldwide (GLOBOCAN 2012, http://globocan.iarc.fr). In Taiwan, GC is the sixth leading cause of cancer-related mortality, causing approximately 2446 patient deaths in 2009.[1] Surgical resection is the only curative modality for GC. Among experienced surgeons worldwide, extended D2 lymph node (LN) dissection is considered the essential part of curative gastrectomy.[2–4] However, approximately 25% to 40% of patients inevitably experience tumor recurrence within 5 years after curative surgery.[2–4]

LN metastasis is the most important survival predictor for GC.[5,6] To date, 3 main classifications of LN metastasis have been applied to predict the prognosis of GC patients worldwide, including classifications based on the number and location of positive nodes and on the ratio between the metastatic and examined nodes.[5,7,8] The precise evaluation of LN metastasis is the most important guarantee of the accurate prediction of the prognosis of patients with GC.[9–11] The latest revision of the American Joint Committee on Cancer (AJCC) TNM staging system was presented in the seventh edition in 2009 (Supplementary Table 1, http://links.lww.com/MD/A213). The most significant change in N staging stated by the seventh edition of the TNM classification for GC is that the number of positive nodes is deliberately subdivided for all N substages.[7] Many previous studies have considered that N staging of the seventh AJCC system is a better classification for the prediction of patient prognosis compared with that described in the fifth/sixth editions.[9,12–14]. Although the N staging of the seventh edition of the TNM classification for GC may include some theoretical defects[15,16] that should be further validated in large-scale clinical investigations, this system nevertheless represents an improved method of classification for predicting the prognosis of GC currently, comparing with other systems.[9]

However, an unmet medical demand has been noted during our clinical practice and in some studies,[17] especially for patients with GC having the N3 status. Currently, the N3 subclassification (N3a and N3b) is not incorporated into the final staging stratification. In other words, N3a and N3b do not differ with regard to the final pathologic stage. In this study, we focused on N3 patients and compared the survival impacts caused by this nodal difference (N3a vs N3b). According to the results of the survival analysis, we proposed a modified

staging system based on the current AJCC system to help clinicians make better survival predictions for patients with GC.

MATERIALS AND METHODS

Between 1994 and 2010, 3178 consecutive patients with histologically verified GC underwent surgeries, including curative intent resection, palliative gastrectomy, bypass surgery, feeding jejunostomy, and surgical biopsy, at the Department of Surgery, Chang Gung Memorial Hospital (CGMH), Linkou, Taiwan. The Institutional Review Board of our hospital has approved the retrospective study. Gastrectomy with LN dissection number >15 is defined as curative intent. Meanwhile, curative resection is defined as not only curative intent surgery but also the presence of negative resection margins observed via pathological examination. We revised the pathologic stages of patients who were diagnosed with GC before the publication of seventh edition of the TNM system according to the latest edition of the system in order for further analysis.

Protocol-based preoperative evaluations, including serum carcinoembryonic antigen (CEA), upper gastrointestinal series, abdominal ultrasonography (US), computed tomography (CT), magnetic resonance imaging, and endoscopic US, were conducted based on the individual condition. Patients consuming aspirin, antiplatelet or anticoagulant agents were asked to stop the medications at least 5 days before the procedures. All patients received general supportive care after procedures, and intensive care unit admission was arranged according to the patients' surgical risks and other unexpected intraoperative conditions. When complication was suspected clinically or on the radiographic findings, further CT scans were conducted before any interventional procedure was performed. Surgical mortality was defined as death occurring within 1 month after surgery. Inhospital mortality was defined as death occurring after surgery without discharge. We excluded patients with either condition of surgical or inhospital mortality.

Disease stage was defined according to the seventh edition of the TNM classification proposed by the AJCC. The N3 category was subclassified into N3a and N3b. N3a was defined as 7–15 LNs; N3b was defined as >15 LNs. Adjuvant chemotherapy was systemically performed with a 5-fluorouracil-based regimen in the patients with positive LN metastasis, local recurrence, or systemic metastasis. Meanwhile, adjuvant radiotherapy was administered for selected patients after radiooncologist consultation and evaluation.

Follow-Up Study

The follow-up evaluation included clinical physical examinations and blood chemistry tests performed at each clinic visit. Additionally, serum CEA and carbohydrate antigen (CA) 19–9 levels were measured, and the liver was examined by abdominal US every 3 months. When abdominal US revealed a new lesion or when elevated CEA or CA 19–9 levels were noted, abdominal CT with contrast was performed. If any of the above examinations indicated possible recurrence, the patient was admitted for comprehensive assessments, including gastric endoscopy and whole-body CT. The methods for treating recurrence included palliative surgery, systemic chemotherapy, external-beam radiotherapy, endoscopic stenting, and conservative treatment, as appropriate. Before analysis, we confirmed the survival status of patients by both records of the last clinic visit and information from the governmental sector (Health Promotion Administration, Ministry of Health and Welfare, ROC).

Statistical Analysis

The overall survival rates were calculated by the method of Kaplan–Meier. The comparison of survival was done by log-rank test. Statistical procedures and figures were operated and produced by using the statistical software packages of rms and survival in Rstudio version 0.98.945 with R core version 3.0.2 (http://www.r-project.org/).

RESULTS

Clinicopathological Features

A total of 3178 patients with GC underwent surgery. Table 1 summarizes their demographic and clinicopathological features. There were 2014 men and 1164 women, with a median age of 65.3 years. The lower third of the stomach was the most common location of the GC, and subtotal gastrectomy was the most common procedure. The 1-month surgical mortality rate and inhospital mortality rate were 1.7% and 3.5%, respectively. Among the total population of patients, 884 (27.8%) who underwent curative intent surgeries had the N3 status (the GC-N3 group). Of the 884 patients, 128 had R1 resection (microscopic margin involvement). All patients with the N3 status were noted with adequate lymphadenectomy according to pathologic examination. They were further classified into N3a and N3b groups for analysis.

Survival Analysis of Patients With GC Who Underwent Radical Gastrectomy: Comparison of N3a and N3b Statuses

Table 2 summarizes the survival analysis of the patients with GC who underwent gastrectomy and provides a

TABLE 1. Demographic Data of the 3178 Taiwanese Patients With Gastric Cancer Who Underwent Gastrectomy

Age (median/range)(y)	65.3 (21–102)
Gender (Male: Female)	2014:1164
Location of gastric cancer	
Upper third	548 (17.2%)
Middle third	606 (19.1%)
Lower third	1885 (59.3%)
Diffuse	106 (3.3%)
Others	33 (1.0%)
Differentiation	
Well	372
Moderate	974
Poor	1056
Signet-ring	698
Mucinous	62
Undifferentiated	16
Surgical procedure	
Curative intent resection	2843 (89.5%)
Subtotal gastrectomy	1673
Total gastrectomy	368
Gastrectomy with other organs resection	802
Palliative procedure or surgical biopsy	335 (10.5%)
Positive *Helicobacter pylori* infection	658 (20.7%)
Positive vascular invasion	392
Positive lymphatic invasion	1556
Positive perineural invasion	1278
Inhospital mortality	110 (3.5%)
Surgical mortality	53 (1.7%)

TABLE 2. Survival Analysis of 884 Patients With Gastric Cancer Having N3 Stage Tumors

	Survival Time (mo)		Survival Rate (%)		
	Median Survival	**LCL/UCL (95%)**	**5-Year Survival**	**95% CI**	***P***
T1N3aM0 (n = 15)	52.0	14.1/NA	34.6	13.5–88.8	0.243
T1N3bM0 (n = 3)	11.1	10.8/NA	0.0	NA	
T2N3aM0 (n = 32)	63.0	52.8/NA	53.8	35.4–81.7	0.057
T2N3bM0 (n = 10)	14.2	12/NA	17.0	26.9–92.9	
T3N3aM0 (n = 34)	130.7	33.6/NA	61.8	14.0–39.7	0.102
T3N3bM0 (n = 19)	40.1	18.9/NA	0.0	NA	
T4aN3aM0 (n = 420)	26.4	22.2/29.0	23.3	19.3–28.0	<0.0001
T4aN3bM0 (n = 262)	14.8	13.2/17.8	14.0	10.2–19.3	
T4bN3aM0 (n = 60)	17.1	13.1/23.6	14.4	7.1–29.1	0.007
T4bN3bM0 (n = 30)	8.7	7.1/15.7	0.0	NA	

CI = confidence interval, LCL = lower confidence limit, NA = not available, UCL = upper confidence limit.

comparison of their N3a and N3b statuses. Generally, patients with GC in the N3 category might be subclassified into N3a and N3b due to the significantly different survival for T4a, and T4b stages with different N status and a trend of inferior survival for T1, T2, and T3 patients with N3b. ($P = 0.243$, 0.057, and 0.102, respectively; Table 2 and Figure 1).

Proposed Modified Seventh AJCC TNM Stage Classification for GC

Under the impression and the trend that N3b might impose GC patients with poor clinical outcome, we proposed a modified staging system, based on AJCC seventh edition (Table 3). Figure 2 reveals the comparison between our proposed modified system and the seventh edition of the AJCC system. We

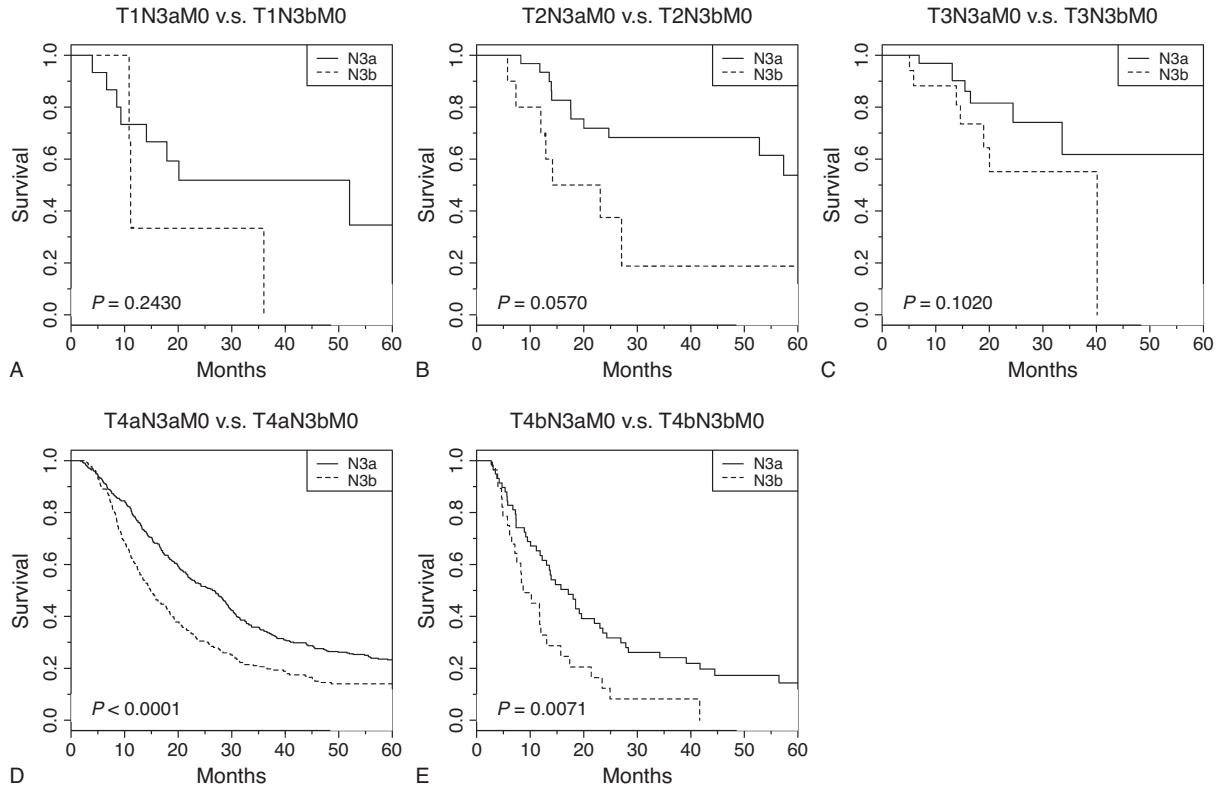

FIGURE 1. Survival analysis of patients with gastric cancer undergoing curative intent surgery, in which N3a and N3b statuses are compared in terms of different T stages. (A) T1N3a versus T1N3b, (B) T2N3a versus T2N3b, (C) T3N3a versus T3N3b, (D) T4aN3a versus T4aN3b, and (E) T4bN3a versus T4bN3b. The *P* values for the survival comparison were determined by the log-rank test.

TABLE 3. The Proposed Staging System Based on Seventh Edition American Joint Committee on Cancer TNM Staging Classification for Gastric Cancer

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
Stage IIIB	T4b	N0 or N1	M0
	T4a	N2	M0
	T1-3	**N3a**	**M0**
Stage IIIC	T4b	N2	M0
	T1-3	**N3b**	**M0**
	T4a or T4b	**N3a**	**M0**
Stage IIID	**T4a**	**N3b**	**M0**
Stage IV	**T4b**	**N3b**	**M0**
	Any T	Any N	M1

depicted the background dot-and-dash survival curves with survival condition of our GC cohort and then superimposed red lines on it, which represented different proposed stages. The overall survival of the patients with proposed IIIB is similar to that of the patients with AJCC stage IIIB while proposed stage IV, including T4bN3bM0, is similar with AJCC stage IV. According to our result, T1-3N3 might be not simply categorized into stage IIIA as seventh AJCC suggests. Taking N3a and N3b into consideration, T1-3N3 might be further categorized into stage IIIB and IIIC, respectively, as we proposed and significant difference is noted (Figure 2). In addition, T4bN3bM0 is as dismal as M1 disease (Figure 2). Based on our proposed staging system, good discriminations between different stages are still maintained (Figure 3).

DISCUSSION

A previous report has demonstrated that classification based on the number of positive nodes is able to better predict the prognosis of patients with GC compared with other classifications of LN metastasis, especially when the number of examined nodes is over 15.[18] The 5-year survival rate of GC markedly decreases as the number of positive nodes increasing. Over recent years, increasing numbers of surgeons at medical centers in Western countries, including the USA, have performed extended lymphadenectomy for GC with sufficiently

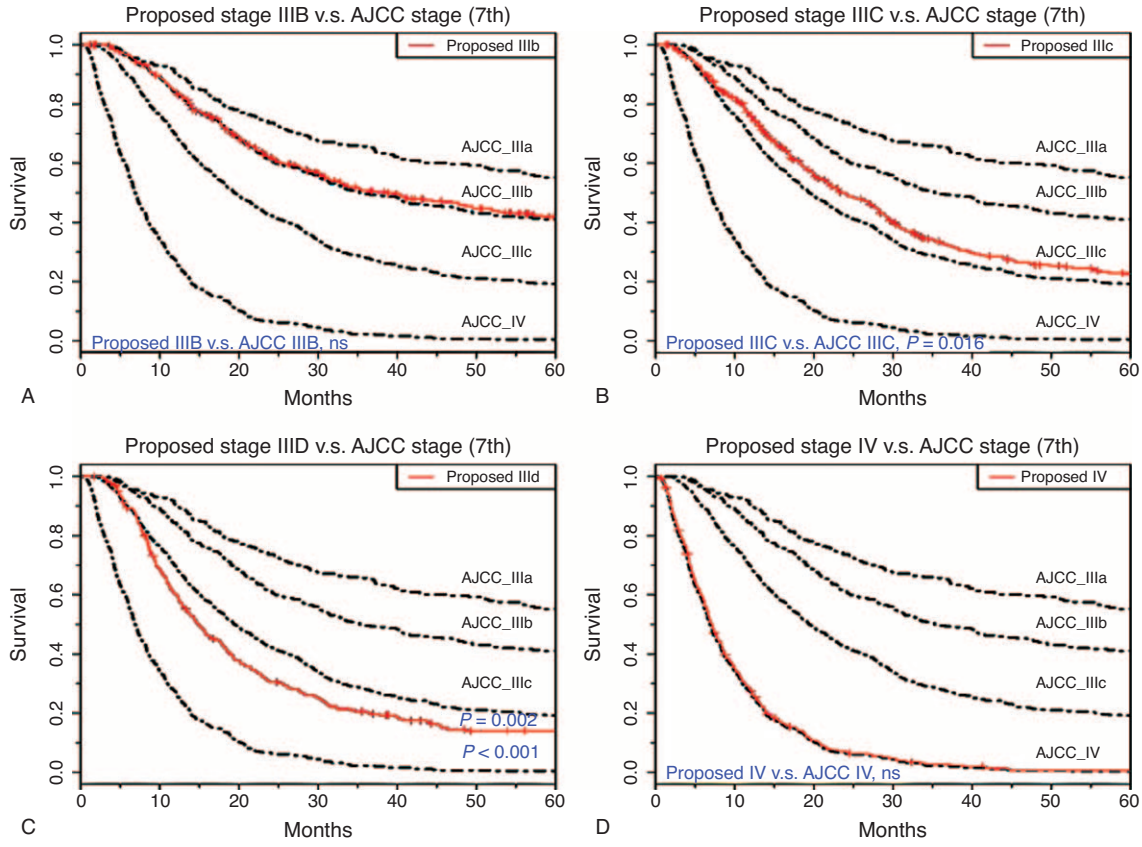

FIGURE 2. Comparison of survival curve between our proposed system (modified from the seventh AJCC system) versus the AJCC seventh edition staging system. (A) Proposed stage IIIB (T4bN0-1M0, T4aN2M0, and T1-3N3aM0) versus original stage IIIB. (B) Proposed stage IIIC (T4bN2M0, T1-3N3bM0, and T4a-4bN3aM0) versus original stage IIIC. (C) Proposed stage IIID (T4aN3bM0) versus original stage IIIC and stage IV. (D) Proposed stage IV (T4bN3bM0 and any M1 disease) versus original stage IV. The *P* values for survival comparison were determined by the log-rank test. AJCC= American Joint Committee on Cancer.

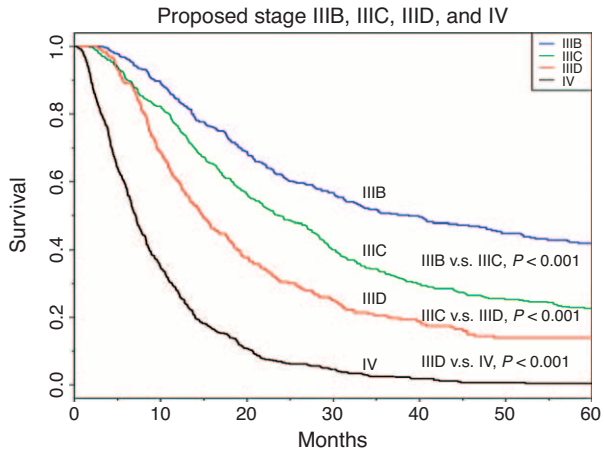

FIGURE 3. The survival analysis of gastric cohort from Chang Gung Memorial Hospital, based on proposed staging system.

low mortality after the completion of the training course.[9] Many investigators have considered that extensive lymphadenectomy is the premise of the accurate staging of LN metastasis and improve the prognosis of patients with GC.[11] However, an unmet medical demand has been noted during our clinical practice and in some studies,[17] especially for those patients with GC having the N3 status. Consequently, the N stage may require revision for further adaptation to allow for precise survival prediction and to determine its relevance to future treatment strategies. Our study implicated the unmet medical needs of patients due to the N3 classification of the seventh AJCC TNM staging classification system for GC. The subclassifications of N3a and N3b may significantly impact on survival according to our retrospective study. Further survival analysis should be performed involving the N3a and N3b subcategories rather than assessing them as a single category of N3 in order to confirm the survival impact caused by extensive lymphatic involvement, such as that observed with N3b. However, there is an aspect from our result, which could not be explained well. In our study, T3N3 patients seemed to have better survival than patients with T1-2N3 (Table 2), irrespective of N status. The small number of patients (T1/T2/T3, 18/43/53) might be the reason. Further study with large volume is necessary for validation.

Current TNM classification neglects N3a and N3b in determining the final pathologic stage, which may cause serious problems in underestimating the GC severity. We have illustrated the significant influence of N3b when we tested our proposed staging system in Figure 3. N3a and N3b might represent diseases with different severity. In our study, we demonstrated that survival of the patients with T1-3N3aM0 (proposed IIIB) was similar to that of the patients with stage IIIB while the survival of the patients with T1-3N3bM0 (proposed IIIC) was similar to that of the patients with AJCC stage IIIC tumors; survival of T4aN3bM0 (proposed IV) was inferior to that of the patients with AJCC stage IIIC tumors but superior to that of the patients with stage IV tumors; and The survival of the patients with T4bN3bM0 was as poor as that of the patients with stage IV tumors. All of these results implicated that difference between N3a and N3b matters in the aspect of disease severity. The accurate assessment of disease severity will aid in the further development of individualized adjuvant therapies for different stages to provide survival benefits. Therefore, revising the current AJCC staging system for GC by introducing more sophisticated N3 statuses may be reasonable. In addition, not only the provision of better survival prediction but also the better categorization of the different disease severities may be achieved by our modified staging system, as demonstrated in Figure 3. Studies of postoperative adjuvant therapies may take N3 status of each patient into consideration to evaluate the treatment effect rather than just stratifying patients based on AJCC staging system in future.

Although our results might support the proposed modified seventh AJCC TNM staging system for GC, there were several limitations inherent to this study. First, this study was retrospective, with clinical data from a time period spanning 15 years extracted from the database. Neither advances in surgical treatments nor improvements in medical oncology were taken into consideration in this study. Second, the precise evaluation of LN metastasis is the most important guarantee for the prediction of the prognosis of GC patients. However, many factors have potentially significant influences on the evaluation of LN metastasis in GC, including the surgery performed, pathological examination, immune condition, and anatomic variation. Third, our proposal was based on the analysis for the difference between N3a and N3b statuses, just as illustrated in Table 1. However, there was no significance when comparing in conditions of T1, T2, and T3 stages. The most obvious pitfall is that there were not enough patients in those subgroups. If we had more patients with T2 and T3 diseases, we would probably have a positive result rather than just a trend. However, it would be an odd combination of T1 and N3 clinically. For patients with T1N3 status, biological behavior of the tumors might be interesting, and detailed evaluation for the tumors might be indicated. In addition, further analysis should be considered to clarify stage IV of our proposed system. Due to the inclusion of only those patients who were initially admitted to the surgical ward in this study, future studies must include all stage IV patients to thoroughly assess our proposed staging system.

To overcome all of these limitations, our results should be confirmed by performing further prospective case-control studies or interinstitute validations.

In conclusion, the N3 category might be subclassified as N3a or N3b due to the differences in survival. We further propose that T1-3N3aM0 could be categorized as stage IIIB, T1-3N3bM0 as stage IIIC, and T4aN3bM0 as stage IIID. T4bN3bM0 might be regarded as stage IV.

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