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Original research

The rationality of N3 classification in the 7th edition of the International Union Against Cancer TNM staging system for gastric adenocarcinomas: A case-control study

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HIGHLIGHTS

- We examine clinicopathologic characteristics and survival rate in N3 gastric cancer patients.
- Overall survival rates of N3a gastric cancer was higher than that of N3b gastric cancer.
- Survival rates differed significantly between patients with T3N3a and T3N3b sub-stages.
- Survival rates differed significantly between patients with T4aN3a and T4aN3b sub-stages.

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ABSTRACT

Background: The 7th edition of the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) tumor-node-metastasis (TNM) classification system for gastric cancer is more detailed than the 6th edition with respect to tumor depth and lymph node metastasis. The purpose of this study was to evaluate the rationality of the 7th UICC/AJCC TNM classification system, focusing on N3 gastric cancers.

Methods: A total of 338 patients with N3 gastric cancer who underwent curative resection with ≥16 retrieved lymph nodes at two institutions between January 1997 and December 2007 were included in this study. Patients were divided into the N3a ($n = 210$) and N3b ($n = 128$) groups. Clinicopathologic characteristics and survival rates were compared between groups.

Results: No difference in clinicopathologic characteristics, including age ($p = 0.989$), sex ($p = 0.382$), tumor location ($p = 0.124$), surgery type ($p = 0.909$), depth of invasion ($p = 0.313$), histologic type ($p = 0.111$), and Lauren classification ($p = 0.491$), was observed between patients with N3a and N3b gastric cancer. However, overall survival (OS) rates of patients with N3a gastric cancer were greater than that of patients with N3b gastric cancer (5-year OS, 46% vs. 28%; 10-year OS, 33% vs. 19%; both $p < 0.001$). Five-year survival rates differed significantly between patients with T3N3a and T3N3b ($p = 0.006$) sub-stages and between those with T4aN3a and T4aN3b ($p = 0.004$) sub-stages.

Conclusions: The results of this study support N3 sub-classification for gastric cancers, which warrant differential consideration according to TNM stage.

1. Background

Gastric cancer (GC) remains the fourth most common cancer worldwide and the second leading cause of cancer-related deaths [1]. The tumor-node-metastasis (TNM) staging system provides a standard used to classify the anatomic extent of disease, predict prognosis, determine a treatment plan, and facilitate the exchange of information [2]. The staging system is revised periodically, and

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the 7th edition of the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) TNM classification system for GC was published in 2010. Although this staging system continues to use N classifications based on the absolute number of regional lymph node metastases, the revisions incorporated in the 7th edition permit more detailed staging in terms of depth of invasion (T), regional lymph node metastasis (N), and distant metastasis (M) compared with the 6th edition. The 7th edition of the TNM staging system redefines N stages: patients with 1–6 regional lymph node metastases are divided into stages N1 and N2 (corresponding to the N1 stage of the 6th edition), those with 7–15 such metastases are classified as stage N3a (N2 in the 6th edition), and patients with >15 regional lymph node metastases are classified as stage N3b. The 7th edition of UICC TNM stage does subclassify the N3 classification into N3a and N3b but this does not influence the final stage of the disease. Several investigators have proposed that the 7th-edition N3 classification be sub-classified as N3a and N3b to permit more accurate prediction of cancer prognosis [3,4]. However, the evidence supporting the necessity and rationality for N3 sub-classification is insubstantial. The purpose of this study was to evaluate the effectiveness of the 7th edition of the TNM staging system focusing on N3 GCs.

2. Methods

2.1. Patients

Between January 1997 and December 2007, 382 patients with N3 gastric adenocarcinoma underwent gastrectomy at two institutions. Data from these patients were entered into a prospectively maintained database. The Institutional Review Boards approved the study protocol (no. OC12RISE0127) (no. VC13RIMI0122). All the enrolled patients had the following curative aim for their operative procedures: 1) total or subtotal gastrectomy depending on the location and 2) D2 or higher lymphadenectomy. Exclusion criteria for this study were (1) non-curative resection, (2) multiple primary malignancies, (3) remnant GC, (4) ≤15 retrieved lymph nodes, and (5) mortality within 30 days after surgery. After the application of these criteria, 338 patients were included in the current study. Data from these patients were re-evaluated using the 7th edition of the UICC/AJCC TNM classification system.

The patients comprised 237 males and 101 females with a mean age of 59.7 (range, 29–89) years. Tumors were located in the upper third of the stomach in 42 (12.4%) patients, the middle third in 80 (23.7%) patients, the lower third in 208 (61.5%) patients, and the entire stomach in 8 (2.4%) patients. Two hundred and four (60.4%) and 134 (39.6%) patients underwent subtotal and total gastrectomies, respectively. Histologically, undifferentiated cancers ($n = 201$) were more common than differentiated types ($n = 115$). According to the depth of invasion, the numbers of patients with stages T1b, T2, T3, T4a, and T4b were 10, 26, 84, 200, and 18, respectively. Two hundred and ten patients had stage N3a and 128 patients had stage N3b GC. Clinical and pathologic characteristics and survival rates were compared among patients with groups N3a and N3b GC. The patients were followed for a median of 45 (range, 1.4–187.1) months. Patient information was obtained from our database and that of the Korea Central Cancer Registry.

2.2. Statistical analysis

The study endpoint was overall survival defined as the time from the date of surgery to the date of death or last follow-up evaluation. Overall survival rates were compared between the N3a and N3b groups. We used the chi-squared or Fisher's exact test for all analyses except the comparison of age, which was performed using the Mann–Whitney *U*-test. Overall survival rates were calculated using the Kaplan–Meier method, and the log-rank test was employed to determine the significance of differences ($p < 0.05$).

Table 1
Patient characteristics.

Characteristics	N3a ($n = 210$)	N3b ($n = 128$)	*P* value
Age (year)			
Mean ± SD[a]	59.9 ± 12.13	59.6 ± 11.36	$P = 0.989$
Gender			
Male:Female (ratio)	152:58 (2.6:1)	85:43 (2.0:1)	$P = 0.382$
Location			
Upper	27	15	$P = 0.124$
Middle	43	37	
Lower	137	71	
Whole	3	5	
Type of surgery			
Distal gastrectomy	126	78	$P = 0.909$
Total gastrectomy	84	50	
Depth of invasion			
T1	8	2	$P = 0.313$
T2	19	7	
T3	48	36	
T4a	126	74	
T4b	9	9	
Differentiation			
Differentiated[b]	80	35	$P = 0.111$
Undifferentiated[c]	116	85	
Unknown	14	8	
Lauren classification			
Intestinal	85	56	$P = 0.491$
Diffuse	62	29	
Mixed	45	28	
Unknown	18	15	

[a] SD: standard deviation.
[b] Differentiated: papillary, well, and moderately differentiated.
[c] Undifferentiated: poorly differentiated, mucinous, and signet ring cell carcinoma.

3. Results

The clinicopathologic characteristics of the 338 patients with N3 GC are summarized in Table 1. No difference in these characteristics, including age ($p = 0.989$), sex ($p = 0.382$), tumor location ($p = 0.124$), surgery type ($p = 0.909$), depth of invasion ($p = 0.313$), histologic type ($p = 0.111$), and Lauren classification ($p = 0.491$), was observed between patients with N3a and N3b GC.

Differences in staging according to the 6th and 7th editions of the TNM system are shown in Table 2. Among patients with N3a GC, those classified as stage IIIA ($n = 67$) according to the 6th edition were re-classified as stages IIIA ($n = 19$) and IIB ($n = 48$) according to the 7th edition. Patients classified as stages IIIB ($n = 126$) and IV ($n = 9$) according to the 6th edition were re-classified as the new unified stage IIIC ($n = 135$) according to the 7th edition. Patients classified as stage IV ($n = 128$) according to the 6th edition were re-

Table 2
Stage migration.

Tumor depth	Involved node			
	N3a (7–15)		N3b (≥16)	
	6th Stage	7th Stage	6th Stage	7th Stage
T1 (a/b)	II (8)	IIB (8)	IV (128)	IIB (2)
T2	IIIA (67)	IIIA (19)		IIIA (7)
T3		IIIB (48)		IIIB (36)
T4a	IIIB (126)	IIIC (135)		IIIC (83)
T4b	IV (9)			

classified as stages IIB ($n = 2$), IIIA ($n = 7$), IIIB ($n = 36$) and IIIC ($n = 83$) according to the more detailed system of the 7th edition. Little difference in survival rates among the stages of each system were observed, presumably due to the small number of patients assigned to each stage (data not shown).

The 5-year and 10-year overall survival rates of patients with N3 GC were 39% and 28%, respectively. These rates were higher in the N3a group than in the N3b group (5-year survival, 46% vs. 28%; 10-year survival, 33% vs. 19%; both $p < 0.001$; Fig. 1).

We re-classified stage T3N3 (IIIB) as T3N3a and T3N3b and stage T4aN3 (IIIC) as T4aN3a and T4aN3b (Table 3). Five-year survival rates for these proposed staging groups differed significantly between T3N3a and T3N3b (45% vs. 24.7%; $p = 0.006$; Fig. 2A) and between T4aN3a and T4aN3b (43.5% vs. 22.9%; $p = 0.004$; Fig. 2B).

4. Discussion

Despite its declining global incidence, GC remains one of the most common malignancies in the world [1]. Half of all cases worldwide occur in East Asia [5]. In South Korea, GC is now the most prevalent malignant neoplasm, affecting >25,000 patients annually. It is also the second leading cause of cancer deaths after lung cancer and is responsible for >10,000 deaths per year [6]. Approximately 15,000 patients with GC undergo gastrectomy every year, excluding endoscopic resection, bypass surgery, and exploratory surgery. R0 curative resection was achieved in 92.4% of cases, with a mean of 38 retrieved lymph nodes [7].

The TNM classification is used worldwide for GC staging in clinical practice and research. Accurate staging is critical for predicting disease recurrence and survival, determining adjuvant treatment strategies, and comparing oncologic outcomes across institutions. Since the publication of the first edition in the 1960s, the UICC/AJCC TNM staging system has been revised several times [8–10]. In the 5th edition, nodal staging was based on the number of metastatic lymph nodes [9]. The 6th edition was published in 2009, and revisions incorporated in the 7th edition, published in 2010, enable even more detailed staging. The development of an appropriate lymph node staging system for GC has been controversial, involving frequent changes with proposed amendments to the TNM classification system [11–13]. In particular, the N classification used in the 7th edition requires careful consideration and discussion. In this edition, N classification has been redefined based on the absolute number of regional lymph node metastases, and pathologic assessment of ≥16 regional lymph nodes is recommended. The extent of lymph node dissection can influence nodal staging by affecting the number of lymph nodes examined pathologically, potentially leading to the stage reassignment of patients [14,15]. We enrolled in this study only patients who underwent

Table 3
The proposal TNM stage groups of pN3 gastric cancer.

7th Stage		Proposal TNM stage		
	N3 (a/b)		N3a	N3b
T3	IIIB	T3	T3N3a	T3N3b
T4a	IIIC	T4a	T4aN3a	T4aN3b

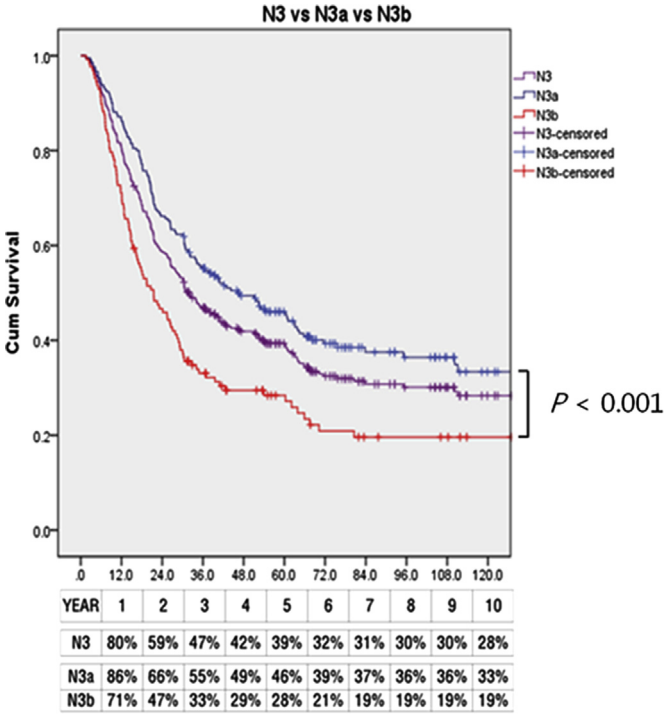

Fig. 1. Overall survival rates of patients with N3 gastric cancer.

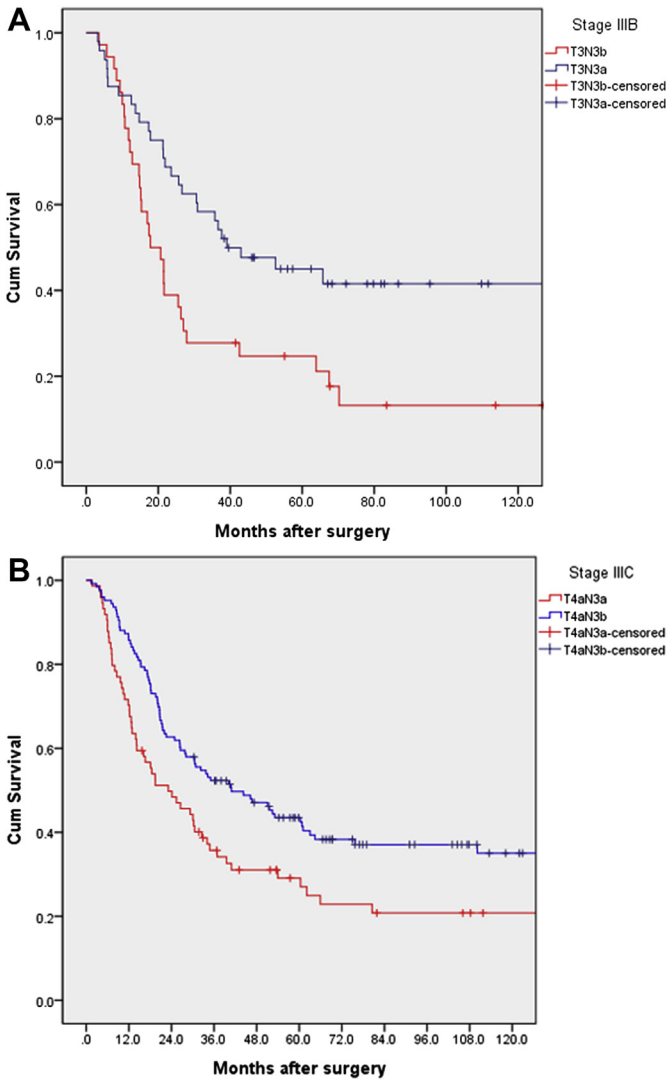

Fig. 2. Five-year survival rates according to proposed TNM staging for patients with (A) T3N3a versus T3N3b and (B) T4aN3a versus T4aN3b gastric cancer.

curative resection with dissection of ≥15 lymph nodes. This patient population was useful for the comparisons of staging according to different classification systems and evaluation of the prognostic impact of lymph node dissection according to nodal staging.

In the 7th edition of the TNM classification system, stage N3 is sub-categorized as N3a and N3b, but this sub-classification is not used for final staging. Stage N3b (IV in 6th edition) appears to be an important prognostic determinant that we propose should be regarded as a highly advanced stage. To enable such consideration, we sub-classified stage T3N3 into T3N3a and T3N3b and stage T4aN3 into T4aN3a and T4aN3b. Using this proposed TNM system, we found that 5-year survival rates differed significantly between patients with stage T3N3a and T3N3b and those with stage T4aN3a and T4aN3b GC. The results of this study support those of a previous study, which reported a significant difference in survival rate between patients with stages N2 and N3 (6th edition) GC [16,17]. Li et al. [4] also emphasized the illogicality of the 7th edition N3 classification system and the need to define N3 sub-stages (N3a and N3b). Dikken et al. [18] reported that overall stage-specific predictive accuracy was not improved in the 7th edition, and recommended an amended staging system with enhanced prognostic accuracy. Jung et al. [19] indicated that the low discriminative power of the N1 and N2 classifications may result in unnecessary stage reassignment, and that the N3 classification, which does not distinguish between N3a and N3b, certainly lowers the predicted relative risk in advanced N stage disease. Kim et al. [3] reported that the survival rate of patients with stage IIIC GC and >29 metastatic lymph nodes did not differ from that of patients with stage IV GC, and proposed this number of metastatic lymph nodes as a cutoff value for N classification.

This study has several limitations. First, the number of subjects was insufficient for detailed staging validation. Although most staging groups were represented by >15 patients, the stage IIB group comprised only 10 patients. Second, as this study population was representative of patients from only two Korean institutions, multinational validation of the proposed TNM staging system is needed. Despite these limitations, this study has considerable clinical significance, as the surgical procedures, pathologic examinations, and follow-up protocol were consistent throughout the study period.

5. Conclusions

In conclusion, the nodal sub-classification into N3a and N3b is present but does not translate into a change in final TNM stage. The proposed sub-classification of N3a and N3b GCs permits differential consideration of patients with these sub-stage assignments. Because of the limitations of retrospective analyses and patient selection bias, a multinational validation study is needed to reach definitive conclusions.

Ethical approval

The Institutional Review Boards of Incheon St. Mary's Hospital (no. OC12RISE0127) and St. Vincent's Hospital (no. VC13RIMI0122) approved the study protocol.

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No.

Author contribution

KH Jun, JH Park, and HM Chin designed the research; JH Kim, JJ Kim, and HM Chin performed the research; KH Jun and SM Park analyzed the data; KH Jun and SM Park wrote the paper.

Conflicts of interest

The authors declare no conflict of interest.

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