RESEARCH ARTICLE

Validity and Necessity of Sub-classification of N3 in the 7th UICC TNM Stage of Gastric Cancer

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Abstract

<u>Background:</u> The 7th TNM staging is the first authoritative standard for evaluation of effectiveness of treatment of gastric cancer worldwide. However, revision of pN classification within TNM needs to be discussed. In particular, the N3 sub-stage is becoming more conspicuous. <u>Methods:</u> Clinical data of 302 pN3M0 stage gastric cancer patients who received radical gastrectomy in Tianjin Medical University Cancer Institute and Hospital from January 2001 to May 2006 were retrospectively analyzed. <u>Results:</u> Location of tumor, depth of invasion, extranodal metastasis, gastric resection, combined organs resection, lymph node metastasis, rate of lymph node metastasis, negative lymph nodes count were important prognostic factors of pN3M0 stage gastric cancers. TNM stage was also associated with prognosis. Patients at T2N3M0 stage had a better prognosis than other sub-classification. T3N3M0 and T4aN3aM0 patients had equal prognosis which followed the T2N3M0. T4aN3bM0 and T4bN3aM0 had lower survival rate than the formers. T4bN3bM0 had worst prognosis. In multivariate analysis, TNM stage group and rate of lymph node metastasis were independent prognostic factors. <u>Conclusions:</u> The sub-stage of N3 may be useful for more accurate prediction of prognosis; it should therefore be applied in the TNM stage system.

Keywords: Stomach cancer - UICC TNM - clinical stage - prognostic factors

Introduction

Although the 6th edition of the American Joint Committee on Cancer (AJCC) TNM classification is an excellent classification system and has been extensively used for gastric cancer staging worldwide (Greene, 2002), different lymph node staging systems between the Japanese Gastric Cancer Association (JGCA) classification and the AJCC classification had made it difficult to compare treatment outcomes in an international setting (Japanese, 1998; Ikeguchi et al., 2004; Aurello et al., 2007). In Aug, 19th, 2008, the member of AJCC, UICC and JGCA held the World Cancer Congress in Buffalo, New York, which aimed to revise and unify stage system of gastric cancer. In this conference, Japanese experts participated in revision of TNM stage for the first time. After then, in Japan, the 3th edition JGCA gastric cancer treatment guidelines were published at the beginning of 2010. The N stage of this guideline first coincided with the AJCC TNM stage. Since, the stage system of gastric cancer achieved unification among AJCC, UICC and JGCA in the world wide.

The 7th edition UICC TNM classification for gastric cancer has several changes from the previous edition. In particular, the classification of metastastic lymph nodes is recognized. According to this new edition TNM stage system, N stage was categorized to N0 (no regional lymph node metastasis), N1 (metastasis in 1-2 regional lymph nodes), N2 (metastasis in 3–6 regional lymph nodes), and N3 (metastasis in 7 or more regional lymph nodes). N3 stage included two sub-categorization N3a (7-15 regional lymph nodes metastasis) and N3b (>15 regional lymph nodes metastasis). However, in 7th edition UICC TNM stage, N3a and N3b had not applied in TNM stage group. T1N3M0 was classified in the new IIB category, T2N3M0 was classified in IIIA stage, T3N3M0 was classified in IIIB stage, and T4a-T4bN3M0 was classified in IIIC stage. The absence of N3a and N3b in these TNM stage group is tempting to wonder whether the sub-categorization of N3 is necessary. If it is necessary, we have to suspect if the new TNM stage can predict patients' prognosis accurately. The objective of the current study was to evaluate the necessity and clinical validity of the N3 sub-classification in the 7th TNM stage system based on cumulated single institution data from a China center.

Materials and Methods

Data collection

Eligibility criteria were: (1) Patients underwent curative resection for gastric cancer between January 2001 and May 2006 at the Tianjin Medical University Cancer Institute and Hospital. (2) Patients with gastric

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Table 1. Alteration of pN3M0 Gastric Cancer Staging in 7th TNM Staging Systems

The 6th TNM stage (N)			The 7th TNM stage (N)		
	N2	N3		N3a	N3b
T2	IIIA(28)	IV(6)	T2	IIIA(12)	IIIA(3)
T3	IIIB(97)	IV(62)	T3	IIIB(16)	IIIB(3)
T4	IV(55)	IV(54)	T4a	IIIC(97)	IIIC(62)
			T4b	IIIC(55)	IIIC(54)

adenocarcinoma identified with histopathologic examination, the postoperative pathological results demonstrated the margin was negative. (3) Patients without a history of prior malignancy, distant metastasis (such as liver, lung, brain, or bone-marrow metastasis), and peritoneal dissemination, (4) patients who underwent potentially curative gastrectomy plus lymphadenectomy (limited or extended), and (5) patients with no fewer than 15 dissected lymph nodes.

Follow-up plan: postoperative follow-up included clinical and laboratory examinations every 3 months for the first year, every 6 months for the second year, and annually thereafter at least until 5 years after operation or the date when the patient was dead.

Patients

Therefore, a total of 302 gastric cancer patients at pN3M0 enrolled in our study. The patients were composed of 203 males and 99 females, the radio of male to female was 2.05:1; Mean age was 59.6 years, the median age was 59.0 years. The most common site was the lower third of the stomach (127 Cases), followed by the middle third (78 cases),and 77 cases was upper third of gastric cancer and 20 cases diffused the whole stomach. Histologically, the undifferentiated type (230 cases) was more common than the differentiated type (72 cases). Concerning the depth of invasion, the number of cases with T2, T3, T4a and T4b stage was 15, 19, 159, and 108, respectively. 166 patients were at N3a stage, and 136 patients were at N3b stage.

Proximal, distal and total gastrectomy were performed in 51, 121 and 130 patient respectively. 227 Patients underwent D2 lymphadenectomy, 75 patients underwent D2+ and D3 lymphadenectomy. Of these patients, the mean and median rate of lymph node metastasis (Metastatic lymph nodes by H&E staining to the total number of dissected lymph nodes) were 66.0% and 66.6%, it ranged from 15.1%-100%. It was between 15.1% and 30% in 15 patients, between 30% and 60% in 101 patients, and 186 patients were ≥60%. The histological negative lymph node number ranged from 0 to 64. The mean and median negative lymph node number was 8.8 and 7.0. Negative lymph node number was ≤6 in 144 patients, between 7 and 15 in 104 patients, 54 patients had ≥16 negative lymph nodes. 70 patients had extranodal metastasis. 43 patients received combined devisceration. 176 patients received adjuvant chemotherapy postoperatively.

Methods

For statistical analysis, continuous variables are presented as mean (±standard deviation). Survival curves and univariate analysis were calculated according to the Kaplan-Meier method, the log-rank test was used to

Table 2. Univariate Analysis of Factors Affecting OS of pN3M0 Gastric Caner Patients

Factor	N	OS (months)	1-YSR	3-YSR	5-YSR	χ^2	P value
Age						0.172	0.268
<59	147	12	48.30%	12.6.%	4.20%		
≥59	155	15	58.10%	11.60%	3.90%		
Sex						0.158	0.691
Male	203	14	52.50%	11.5.%	4.00%		
Female	99	13	54.10%	13.3.%	4.10%		
Location of tumor						14.404	0.002
Upper one-third	77	14	58.40%	13.0.%	5.20%		
middle one-third	78	10	39.70%	6.40%	0.00%		
lower one-third	127	15	60.20%	15.00%	5.70%		
whole stomach	20	10	40.00%	15.00%	5.00%		
Histological type						0.204	0.651
undifferentiated	69	13	52.10%	12.70%	4.20%		
differentiated	223	13	52.60%	11.90%	4.00%		
Depth of invasion						17.507	0.001
T2	15	19	69.20%	23.10%	15.10%		
T3	19	15	57.90%	15.80%	5.30%		
T4a	159	13	60.10%	15.20%	3.80%		
T4b	109	10	41.10%	6.50%	2.80%		
Extranodal metastasis						3.707	0.054
No	224	14	55.00%	14.00%	4.80%		
Yes	68	12	46.40%	5.80%	1.40%		
Gastric resection						16.924	0
proximal gastrectomy	51	17	63.60%	15.90%	5.70%		
distal gastrectomy	121	15	64.20%	15.2.7%	6.80%		
total gastrectomy	130	10	38.00%	10.30%	0.80%		
Radical resection						0.029	0.865
D2	227	13	52.80%	11.10%	2.90%		
D2+ and D3	75	14	58.30%	15.10%	5.60%		
Combined organs resection						16.217	0
no	259	15	58.00%	12.90%	4.30%		
yes	43	7	28.30%	7.10%	2.40%		
Adjunct chemotherapy						2.544	0.111
No	126	11	45.50%	11.40%	3.30%		
Yes	176	14	59.00%	12.70%	4.50%		
Lymph node metastasis						12.073	0.001
N3a	169	15	62.20%	14.70%	6.10%		
N3b	133	11	42.20%	8.90%	1.50%		
Rate of metastatic lymph nodes						12.118	0.002
15.1%-30%	15	25	85.70%	30.50%	7.10%		
30%-60%	101	15	64.00%	16.00%	5.90%		
≥60%	186	11	45.10%	8.20%	2.70%		
Negative lymph node						19.89	0
0~6	144	11	44.40%	5.60%	0.00%		
7~15	104	14	56.70%	14.40%	7.70%		
≥15	54	18	71.20%	21.50%	7.70%		

evaluate statistically significant differences between two groups. Cox regression analysis was used in multivariate analysis of prognostic factors. A value of *P*<0.050 (two-sided) was regarded as statistically significant. All analyses were performed using SPSS version 17.0.

Results

Definition of the 7th TNM Classification

Table 1 showed the detailed classifications based on the 6th and 7th editions TNM stage system. The major revisions in the 7th edition TNM classification was that the definition of N3 and T4 was altered. Newly added IIIC stage was another change in 7th TNM stage.

Survival Analysis

The overall 1-, 3-, and 5-year survival rates (1, 3, 5-YSR) of the patients with pN3M0 stage gastric cancer were 53.4%, 12.1%, and 4.4% respectively. The overall median survival time (OS) was 14.0 months.

Univariate analysis of prognostic factors

With the univariate analysis, 7 factors were found

Table 3. TNM Stage Groups of pN3M0 Gastric Cancer

The TNM stage groups of pN3M0					Our suggested TNM stage groups of pN3M0				
TNM stage	n	OS (months)	χ^2	P value*	TNM stage	n	OS (months)	χ^2	P value*
T2N3M0	15	22			T2N3M0	15	22		
T3N3M0	19	15	0.803	0.37	T3N3M0+T4aN3aM0	116	15	1.573	0.21
T4aN3aM0	97	17	0.081	0.777	T4aN3bM0+T4bN3aM0	117	13	3.93	0.047
T4aN3bM0	62	12	2.74	0.098	T4bN3bM0	54	8	7.085	0
T4bN3aM0	55	13	0.094	0.76					
T4bN3bM0	54	8	3.951	0.047					

*Comparison of the OS with former TNM stage

Table 4. Multivariate Analysis of Factors Affecting OS of pN3M0 Gastric Caner Patients

Factors	P	HR	95.0% CI HR
Rate of metastatic lymph nodes	0.015	5.315	1.388~20.356
Our suggested TNM stage	0.008	1.119	1.030~1.217
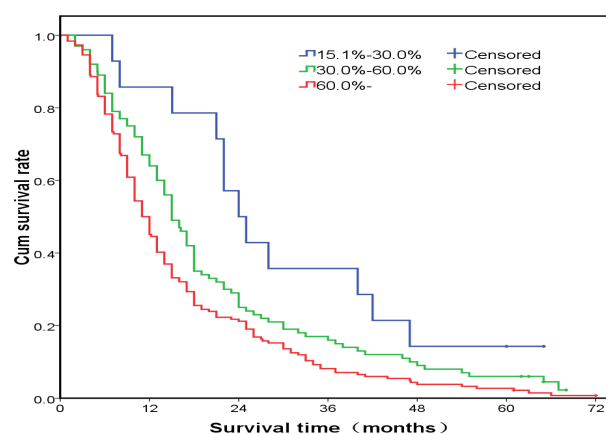
Figure 1. Survival Curves According to Rate of Metastatic Lymph Nodes

Figure 2. Survival Curves According to TNM Stage Group

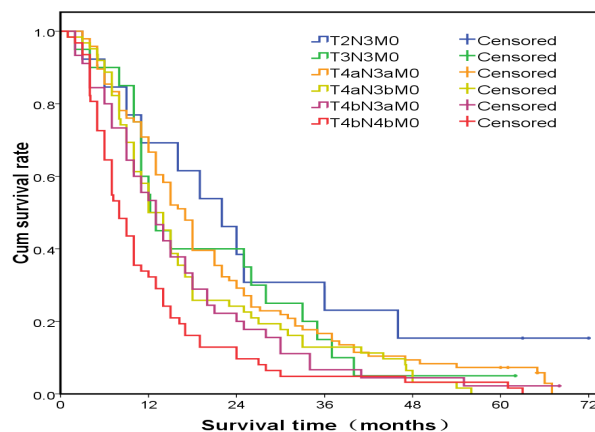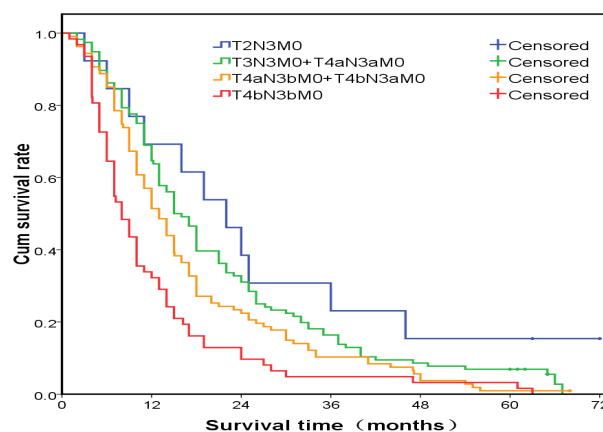**Figure 3. Survival Curves According to Our Suggested TNM Stage Group**

to have statistically significant associations with OS of gastric cancer patients after curative surgery (Table 2). They were: location of tumor, depth of invasion, gastric resection, combined organs resection, lymph node metastasis, rate of metastatic lymph nodes (Figure 1), negative lymph node.

Sub-classification of N3 stage

According to 7th TNM stage, the pN3M0 gastric patients could be staged to T2N3aM0, T2N3bM0, T3N3aM0, T3N3bM0, T4aN3aM0, T4aN3bM0, T4bN3aM0, and T4bN3bM0. Because of small sample of T2 and T3 gastric cancer, T2N3M0 and T3N3M0 can not divide significantly according to sub-stage of N3(Table 3). Patients at T2N3M0 stage had a better prognosis than other sub-classification. T3N3M0 and T4aN3aM0 patients had equal prognosis which followed the T2N3M0. T4aN3bM0 and T4bN3aM0 had lower survival rate than the formers. T4bN3bM0 had worst prognosis (Figure 2, 3).

Multivariate analysis of prognostic factors

All the aforementioned 8 variables (including our suggested Sub-classification of N3 stage) were included in a multivariate Cox proportional hazards model to adjust for the effects of covariates, (Table 4). Rate of metastatic lymph nodes and our suggested TNM stage were independent prognostic factors for pN3M0 gastric caners (Figure 1, Figure 3).

Discussion

The rational staging system plays a crucial role in diagnosis and management of gastric cancer. It can aid the clinician in the planning of treatment, give some indication of prognosis, assist in the evaluation of the results of treatment, and facilitate the exchange of information. The TNM system is accepted as a chief standard for the staging system of gastric cancer (Sobin, 2001). The revision of the 7th TNM stage bases on databases of different regions in the world, involving countries in Asian such as Korea and Japan. The 7th TNM stage is the first authoritative standard for evaluation the effectiveness of treatment of gastric cancer in the world wide. It can promote clinical research of gastric cancer all over the world.

The 7th edition UICC TNM classification for gastric cancer has several changes from the previous edition. The revision of the pN classification for the 7th TNM

classification will be more conspicuous and needs to be fully discussed (Deng et al., 2010; Chae et al., 2011; Jung et al., 2011). An ideal lymph node staging system for gastric cancer has been controversial and has changed whenever a revision in the TNM classification has been made (Klein et al., 2001; Yamashita et al., 2008; Jung et al., 2011). Furthermore, various factors such as different surgical techniques and pathological assessments have made standardized lymph node staging difficult. To overcome these problems, some investigators have proposed the metastatic lymph node rate (Katai et al., 2004; Marchet et al., 2007; Xu, 2010; Lemmens et al., 2011). In line with previous studies, it was showed that higher rate of lymph node metastasis was related to poor prognosis. The rate of lymph node metastasis has been identified as the most intensive indicator of gastric cancer after surgery, but it cannot avoid the bias of lymph node classification originating from the varied number of dissected lymph nodes.

Deng et al. (2010) suggested that prognostic prediction of metastastic lymph nodes rate could be improved by associating prognosis with negative lymph nodes. By increasing the negative lymph node counts, the chance of micrometastasis was remaining decrease (Kojima et al., 2008; Kim et al., 2009). It has been demonstrated that the micrometastasis were closely associated with recurrence and poor prognosis (Saito et al., 2007; Deng et al., 2010). In our studying, the less negative lymph node counts were also significant related with poor prognosis.

However, one of the drawbacks of both the N-rate and negative lymph nodes is that there are no standardized categories in literature. The role of staging according to N-rate and negative lymph nodes is therefore still not clear and should be further investigated.

Another concern for the 7th edition pN classification is the pN3 subgroup. Although the pN3 classification was comprised of pN3a and pN3b, both subgroups were not individual determinants of the final TNM stage. It seems that there should be a compensation for this problem. There was a significant difference in the 5-year survival rate between the 7th N3a and N3b (Ichikura et al., 1999; Saito et al., 2007; Chae et al., 2011). As several data indicated there was a significant difference in survivals between N2 and N3 in the 6th N classification (Ichikura et al., 1999; Kim et al., 2009). Therefore, it may be reasonable to subdivide gastric cancer TNM stage group according to the sub-stages of N3. We found that patients at T2N3M0 stage had a better prognosis than other sub-classification. T3N3M0 and T4aN3aM0 patients had equal prognosis which followed the T2N3M0. T4aN3bM0 and T4bN3aM0 had lower survival rate than the formers. T4bN3bM0 had worst prognosis. Usually, advanced gastric cancer is relatively more common in china. Only 1%-4% patients with T1 and T2 gastric cancer had >15 metastatic lymph nodes (Ahn et al., 2009; Jung et al., 2011). Therefore, T1-T2N3M0 gastric cancer has a lower incidence in China, as did our specimen. Because of the narrow definition, T3 gastric cancer also has a lower incidence (Chae et al., 2011; Qiu et al., 2011; Wang et al., 2011). So a multi-center observational study is necessary in exploration of N3 sub-stage in these patients. However,

in T4a and T4b gastric cancer, significant differences of prognosis can be seen between N3a and N3b sub-stage. Especially, patients at IIIC stage had significantly varied prognosis according to sub-classification of T4a, T4b and N3a, N3b. In particular, detailed staging of IIIC may be more demanded. In our opinion, the sub-stage of N3 may be useful for a more accurate prediction of patient survival and selection of therapeutic strategies. It should be applied in TNM stage group.

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