

Evaluation of the 7th AJCC TNM Staging System in Point of Lymph Node Classification

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Purpose: The 7th AJCC tumor node metastasis (TNM) staging system modified the classification of the lymph node metastasis widely compared to the 6th edition. To evaluate the prognostic predictability of the new TNM staging system, we analyzed the survival rate of the gastric cancer patients assessed by the 7th staging system.

Materials and Methods: Among 2,083 patients who underwent resection for gastric cancer at the department of surgery, Hanyang Medical Center from July 1992 to December 2009, This study retrospectively reviewed 5-year survival rate (5YSR) of 624 patients (TanyN3M0: 464 patients, TanyNanyM1: 160 patients) focusing on the number of metastatic lymph node and distant metastasis. We evaluated the applicability of the new staging system.

Results: There were no significant differences in 5YSR between stage IIIC with more than 29 metastatic lymph nodes and stage IV ($P=0.053$). No significant differences were observed between stage IIIB with more than 28 metastatic lymph nodes and stage IV ($P=0.093$). Distinct survival differences were present between patients who were categorized as TanyN3M0 with 7 to 32 metastatic lymph nodes and stage IV. But patients with more than 33 metastatic lymph nodes did not show any significant differences compared to stage IV ($P=0.055$). Among patients with TanyN3M0, statistical significances were seen between patients with 7 to 30 metastatic lymph nodes and those with more than 31 metastatic lymph nodes.

Conclusions: In the new staging system, modifications of N classification is mandatory to improve prognostic prediction. Further study involving a greater number of cases is required to demonstrate the most appropriate cutoffs for N classification.

Key Words: Stomach neoplasms, Neoplasm staging, Lymph nodes

Introduction

According to the 6th edition of AJCC tumor node metastasis (TNM) staging system, cases in which the number of metastatic lymph node are 1~6, 7~15 and greater than 16 are determined to be N1, N2 and N3, respectively. Of these, TanyN3M0 is determined to be stage IV.(1) According to the 7th edition of AJCC TNM staging system, which was newly revised, cases in which the number of

metastatic lymph node are 1~2, 3~6 and greater than 7 are determined to be N1, N2 and N3, respectively. Of these, the N3 group was sub-classified; cases in which the number of metastatic lymph node are 7~15 and greater than 16 are determined to be N3a and N3b, respectively. But TanyN3aM0 and TanyN3bM0 are classified as the same stage.(2) There are characteristics that the number of metastatic lymph node, based on which the N group is divided into N1 and N2, has a very narrow range but that, based on which it is classified into N3, has a very wide one. Besides, the N3 group is classified into stage IIb, IIIa, IIIb and IIIc although the number of metastatic lymph node is as the greatest can be. In various types of patients who were classified as the same stage, the difference in the survival rate should not reach a statistical significance ($P > 0.05$). In addition, if there should be a statistical significance in the differ-

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ence in the survival rate between the patients who were classified as the different stage ($P < 0.05$), the corresponding TNM staging system would be evaluated as appropriate. On the 6th edition, considering this, if the number of metastatic lymph node is greater than 16 (N3 based on the 6th edition of classification system), all the corresponding cases are classified as same stage. But there are problems that there was a significant difference in the survival rate between the group without a distant metastasis (TanyN3M0) which was classified as the stage IV and that (TanyNanyM1) which was classified as the same stage. On the 7th edition, a very simple classification system is applied based on the number of metastatic lymph node. It is necessary, however, to make a differentiation of and then to examine a prognosis of patients whose number of metastatic lymph node is very great of the groups whose number of metastatic lymph node is greater than 17. Besides, it would also be important to examine whether the new classification system might appropriately reflect a prognosis of the patients with gastric cancer based on the results of the above analysis.

Materials and Methods

Of 2,083 patients with gastric cancer who underwent gastrectomy at department of surgery at Hanyang University Medical Center during a period ranging from July of 1992 to December of 2009, in 464 patients without a distant metastasis with no respect to the degree of invasion to the gastric wall whose number of metastatic lymph node was greater than 7 (TanyN3M0) and 160 patients (stage IV) who had a distant metastasis with no respect to the degree of invasion to the gastric wall and the degree of lymph node metastasis based on the degree of lymph node metastasis and the presence of distant metastasis, the survival rate was examined and the validity of TNM staging system was analyzed. Of Stage IV patients, there were 53 cases of sub-total gastrectomy, 51 cases of total gastrectomy, 27 cases of bypass surgery and 29 cases of simple laparotomy. In regard to the sites of distant metastasis, there were 116 cases of peritoneal dissemination, 30 cases of hepatic metastasis, six cases in which there was a concurrent presence of peritoneal dissemination and hepatic metastasis, two cases of Virchow's lymph node metastasis, three cases of abdominal para-aortic lymph node metastasis and three cases in which there was a concurrent presence of Virchow's lymph node metastasis and abdominal para-aortic lymph node metastasis. Because there were cases in which there was a concurrent presence of the peritoneal dissemination, indications of the gastrectomy include cases in which the peritoneal

dissemination was restricted to the proximal peritoneum around the stomach and those in which it was present very restrictively to the peritoneum below the transverse colon. In regard to cases of hepatic metastasis, excluding cases in which there were a very great number of metastatic lesions on the bilateral lobules, the systemic anti-cancer chemotherapy following the gastrectomy with no concomitant use of hepatectomy was a standard treatment regimen. In regard to the scope of lymph node dissection, the extensive lymph node dissection (D2 or higher) was performed in most of the patients (93 cases). In 11 patients whose scope of metastatic lesions was relatively more severe, the local lymph node dissection (D1) was performed. In 56 patients, the lymph node dissection was not performed. In our clinical series of patients, the median value of follow-up period was 20.5 months (the time point of final follow-up: June 30, 2010) and the rate of follow-up was 96.6% (603/624). Statistical analysis was performed using SPSS ver. 13.0 (SPSS Inc., Chicago, IL, USA). Survival rate was calculated using a Kaplan-Meier analysis. The difference in the survival rate was analyzed using a log-rank test in order to demonstrate a statistical significance. In regard to the statistical significance, a P-value of < 0.05 was considered statistically significant.

Results

1. The distribution of the TNM stages in subject patients

In 464 TanyN3M0 patients who had no distant metastasis and whose number of metastatic lymph node was greater than 7, based on the distribution of the TNM stages, there were 15 cases of stage IIb, 26 cases of stage IIIa, 66 cases of stage IIIb and 357 cases of stage IIIc (Table 1). Besides, there were 160 cases of stage IV in which there was a distant metastasis (M1).

Table 1. Stage distribution of TanyN3M0 gastric cancer patients

	No.	No. of metastatic LN (7~30)	No. of metastatic LN (≥ 31)	Stage
T1b	15	14	1	IIb
T2	26	24	2	IIIa
T3	66	58	8	IIIb
T4a	307	256	51	IIIc
T4b	50	39	11	IIIc
Total	464	391	73	

LN = lymph node.

2. The distribution of the survival rate depending on the TNM stage

In a total of 624 subject patients, there was a significant difference in the survival rate depending on the TNM stage (Table 2).

3. A comparison of the survival rate depending on the number of metastatic lymph node between the stage III and IV

Following an analysis of the difference in the survival rate depending on the number of metastatic lymph node in Stage IIIc patients as compared with stage IV ones, there was no significant difference in the survival rate between stage IIIc (the number of metastatic lymph node >29) and stage IV (Table 3).

Table 2. Survival rate according to the stage

Stage	No.	5 YSR (%)	Mean±SD (month)	P-value
IIb	15	79.4	144.2±18.0	<0.0001
IIIa	26	66.9	107.9±12.5	
IIIb	66	59.0	74.2±7.0	
IIIc	357	30.8	65.8±4.6	
IV	160	11.2	22.7±2.9	

YSR = year survival rate; SD = standard deviation.

Table 3. Comparison of the survival rate between stage IIIc and stage IV according to the number of metastatic lymph nodes

Stage	No.	5 YSR (%)	Mean±SD (month)	P-value
Stage IIIc (mLN*≥27)	79	17.1	36.5±5.8	0.017
Stage IV	160	11.2	22.7±2.9	
Stage IIIc (mLN≥28)	75	16.6	36.1±5.8	0.018
Stage IV	160	11.2	22.7±2.9	
Stage IIIc (mLN≥29)	71	12.8	32.7±5.7	0.053
Stage IV	160	11.2	22.7±2.9	
Stage IIIc (mLN≥30)	67	13.0	33.1±5.8	0.051
Stage IV	160	11.2	22.7±2.9	
Stage IIIc (mLN≥31)	62	11.3	30.2±5.6	0.126
Stage IV	160	11.2	22.7±2.9	

YSR = year survival rate; SD = standard deviation. *Number of metastatic lymph nodes.

There was no significant difference in the survival rate between Stage IIIb (the number of metastatic lymph node >28) and stage IV (Table 4).

Because there were only two Stage IIIa cases in which the number of metastatic lymph node was greater than 26, a statistical analysis could not be performed.

4. A comparison of the survival rate depending on the number of metastatic lymph node between the TanyN3M0 group and the stage IV (TanyNanyM1) group

Of patients with TanyN3M0, in cases in which the number of metastatic lymph node was 7~32, the survival rate was significantly higher as compared with patients with stage IV. In patients whose number of metastatic lymph node was greater than 33, the difference in the survival rate reached no statistical significance as compared with stage IV patients (Table 5).

5. A comparison of the survival rate depending on the number of metastatic lymph node in the Tany N3M0 patient group

Of patients with TanyN3M0, there was a significant difference in the survival rate between the group where the number of metastatic lymph node was 7~30 and that where it was greater than 31 (Table 6).

Table 4. Comparison of the survival rate between stage IIIb and stage IV according to the number of metastatic lymph nodes

Stage	No.	5 YSR (%)	Mean±SD (month)	P-value
Stage IIIb (mLN*≥27)	10	30.2	45.1±13.0	0.034
Stage IV	160	11.2	22.7±2.9	
Stage IIIb (mLN≥28)	9	22.2	38.2±12.4	0.093
Stage IV	160	11.2	22.7±2.9	
Stage IIIb (mLN≥32)	8	25.0	41.3±13.6	0.075
Stage IV	160	11.2	22.7±2.9	
Stage IIIb (mLN≥33)	7	28.6	44.0±15.3	0.076
Stage IV	160	11.2	22.7±2.9	

YSR = year survival rate; SD = standard deviation. *Number of metastatic lymph nodes.

Table 5. Comparison of the survival rate between TanyN3M0 and TanyNanyM1 according to the number of metastatic lymph nodes

	No.	5YSR (%)	Mean±SD (month)	P-value
TanyN3M0 (mLN*≥26)	99	18.7	39.5±5.5	0.002
TanyNanyM1	160	11.2	22.7±2.9	
TanyN3M0 (mLN≥27)	93	19.7	40.5±5.8	0.002
TanyNanyM1	160	11.2	22.7±2.9	
TanyN3M0 (mLN≥28)	87	17.6	38.2±5.7	0.004
TanyNanyM1	160	11.2	22.7±2.9	
TanyN3M0 (mLN≥29)	82	14.5	35.5±5.7	0.012
TanyNanyM1	160	11.2	22.7±2.9	
TanyN3M0 (mLN≥30)	78	14.8	36.0±5.8	0.011
TanyNanyM1	160	11.2	22.7±2.9	
TanyN3M0 (mLN≥31)	73	21.7	33.6±5.9	0.029
TanyNanyM1	160	11.2	22.7±2.9	
TanyN3M0 (mLN≥32)	68	14.6	35.0±6.2	0.026
TanyNanyM1	160	11.2	22.7±2.9	
TanyN3M0 (mLN≥33)	65	13.7	33.3±6.1	0.055
TanyNanyM1	160	11.2	22.7±2.9	
TanyN3M0 (mLN≥34)	59	11.1	29.3±5.8	0.200
TanyNanyM1	160	11.2	22.7±2.9	

YSR = year survival rate; SD = standard deviation. *Number of metastatic lymph nodes.

6. A comparison of the survival rate depending on the number of metastatic lymph node between Stage IIIb, IIIc and stage IV

Following an analysis of the survival rate depending on the number of metastatic lymph node in patients who were classified as the same TNM stage, in patients with stage IIIb or stage IIIc, there was a significant difference in the survival rate between cases in which the number of metastatic lymph node was 7~30 and those in which it was greater than 31 (P=0.037, P<0.0001). Of patients with stage IIIb and IIIc, in cases in which the number of metastatic lymph node was greater than 31, there was no significant difference in the survival rate as compared with patients with stage IV (Table 7).

Table 6. Comparison of the survival rate in TanyN3M0 according to the number of metastatic lymph nodes

No. of mLN*	No.	5 YSR (%)	Mean±SD (month)	P-value
7~30	391	42.4	85.0±5.1	<0.0001
≥31	73	13.4	33.6±5.7	

YSR = year survival rate; SD= standard deviation. *Number of metastatic lymph nodes.

Table 7. Comparison of the survival rate according to the number of metastatic lymph nodes

Stage	No.	5 YSR (%)	Mean±SD (month)	P-value
Stage IIIb (mLN*: 7~30)	58	64.9	77.6±7.4	0.037 } <0.0001
Stage IIIb (mLN: ≥31)	8	25.0	41.3±13.6	
Stage IV	160	11.2	22.7±2.9	
Stage IIIc (mLN: 7~30)	295	34.8	72.0±5.3	<0.0001 } <0.0001
Stage IIIc (mLN: ≥31)	62	11.3	30.2±5.6	
Stage IV	160	11.2	22.7±2.9	

YSR = year survival rate; SD= standard deviation. *Number of metastatic lymph nodes.

Discussion

The TNM describes the anatomical scope of tumor. As shown in “Dukes(3) classification system” proposed for colorectal cancer in 1932, it was proposed based on the anatomical location of primary cancer. Thereafter, a French surgeon, Denoix(4) applied the TNM staging to cancers occurring in all the sites during a period ranging from 1943 to 1952. The stomach cancer was first included in the TNM staging in 1966.(5) In 1970, 1978 and 1987, the 2nd, the 3rd and the 4th edition were published, respectively. In 1997, on the 5th edition, great changes were made in the classification system. That is, the previous classification system for the N group was based on the anatomical location of lymph nodes.(6) The assessment of the stage of lymph nodes based on the anatomical location might be devoid of the accuracy. This might also lead to the decreased reproducibility of the assessment. This remains problematic when the TNM staging based on the anatomical location would be used as a universal method of the assessment from a worldwide

perspective.(7) According to the revised definition, on condition that a minimal number of the lymph nodes of 15 should be dissected, based on the number of metastatic lymph nodes, classifications were revised to N1 (the number of metastatic lymph nodes: 1~6), N2 (the number of metastatic lymph nodes: 7~15) and N3 (the number of metastatic lymph nodes: ≥ 16).^(5,8,9) Following a comparison between the 4th edition published in 1987 and the 5th edition published in 1997, Katai et al.,⁽¹⁰⁾ Karpeh et al.⁽¹¹⁾ and Klein Kranenbarg et al.⁽¹²⁾ reported that new classification system had a higher degree of applicability and predictability of the prognosis as compared with previous editions of the classification system. Mendes de Almeida et al.,⁽¹³⁾ however, there was no significant difference in the predictability of the prognosis between the two classification systems. Besides, da Manzoni et al.⁽¹⁴⁾ reported that the number of metastatic lymph node and the anatomical location are both independent prognostic factors. Lee et al.⁽¹⁵⁾ also reported that there was no significant difference in the predictability of the prognosis between the two classification systems. These authors were skeptical about the clarity of a cut-off point, which is currently used for the N classification. As described here, once the TNM staging system was revised, there was a variability of the assessment of its usefulness depending on the authors.⁽¹⁶⁻²²⁾ Thereafter, in 2002, with no changes made in the criteria for determining the N classification, the 6th edition of UICC/AJCC TNM classification was reported. In 2009, the 7th edition of TNM staging system was reported. Since January of 2010, it has been used for patients who were diagnosed with cancer.⁽²³⁾ Also at our medical institution, we reported that the 7th edition was more complicated than the 6th edition and there was an insufficient amount of the differentiation in the survival rate between the different TNM stages.⁽²⁴⁾ In association with the AJCC TNM staging, controversial opinions have long existed regarding the N classification. On the 6th edition of AJCC TNM staging system, cases in which the number of metastatic lymph nodes were 1~6, 7~15 and ≥ 16 were classified as N1, N2 and N3, respectively. Of these, the N3 was classified as stage IV. According to the 7th edition of AJCC TNM staging system which was newly revised, cases in which the number of metastatic lymph node are 1~2, 3~6 and greater than 7 are determined to be N1, N2 and N3, respectively. Of these, the N3 group was sub-classified: cases in which the number of metastatic lymph node are 7~15 and greater than 16 are determined to be N3a and N3b, respectively. Because N3a and N3b classified as the same TNM stage, however, the new classification system is of no significance. Moreover, cases corresponding to N1 and N2, there is

a narrow range of the number of metastatic lymph node (mean \pm standard deviation and median value of the number of metastatic lymph node: N1=1.40 \pm 0.49 and 1 and N2=4.30 \pm 1.10 and 4). In the N3 group, however, a wider range of the number of metastatic lymph node was defined as compared with the 6th edition (mean \pm standard deviation and median value of the number of metastatic lymph node=19.14 \pm 13.77, median value=15 and range=15~115). As described here, some cases were defined as the same TNM stage, although the range of the number of lymph node was too wide. Despite the same TNM stage, the difference in the survival rate based on a specific cut-off point might reach a statistical significance. The current study was therefore conducted. Of 2,083 patients with gastric cancer who underwent gastrectomy at department of surgery at Hanyang University Medical Center during a period ranging from July of 1992 to December of 2009, in 464 patients without a distant metastasis with no respect to the degree of invasion to the gastric wall whose number of metastatic lymph node was greater than 7 (TanyN3M0) and 160 patients (stage IV) who had a distant metastasis with no respect to the degree of invasion to the gastric wall and the degree of lymph node metastasis based on the degree of lymph node metastasis and the presence of distant metastasis, the survival rate was examined and the validity of TNM staging system was analyzed. Following an analysis of the difference in the survival rate depending on the number of metastatic lymph node in Stage IIIc patients as compared with stage IV ones, there was no significant difference in the survival rate between stage IIIc (the number of metastatic lymph node > 29) and stage IV (P=0.053). There was no significant difference in the survival rate between Stage IIIb (the number of metastatic lymph node > 28) and stage IV (P=0.093). As described here, as the number of metastatic lymph nodes was increased between the different TNM stages, the difference in the survival rate between the two groups gradually reached no statistical significance. Because there were only two Stage IIIa cases in which the number of metastatic lymph node was greater than 26, a statistical analysis could not be performed. If an analysis of the survival rate should be performed for a greater number of cases, however, there would be a cut-off value for the number of metastatic lymph nodes at which the difference in the survival rate reached no statistical significance even stage IIIa patients as compared with stage IV patients. Of patients with TanyN3M0 who had no distant metastasis and whose number of metastatic lymph nodes was greater than 7 with no respect to the degree of invasion to the gastric wall, following a comparison of the survival rate depending on the distribution of the number of meta-

static lymph nodes, in cases in which the number of metastatic lymph node was 7~32, the survival rate was significantly higher as compared with patients with stage IV. In patients whose number of metastatic lymph node was greater than 33, the difference in the survival rate reached no statistical significance as compared with stage IV patients. As described here, as the number of metastatic lymph nodes was increased, the degree of the differentiation in a prognosis depending on the TNM stages became obscure. In cases which were classified as the same TNM stage, a prognosis should have a consistency. In cases which were classified as the different TNM stage, there should be a notable difference in a prognosis. That is, so long as there should be similar cases from the perspectives of the prognosis and treatment effect, the corresponding classification system would be evaluated as appropriate. As described here, if the number of metastatic lymph nodes is greater than the specific value despite the same stage, there would be no significant difference in the survival rate from the higher stage. This suggests that the TNM staging system could not appropriately reflect a prognosis of cases in which the number of metastatic lymph nodes was too great. Based on the results of an analysis of the N3 cases in the current study, following an analysis of the survival rate depending on the number of metastatic lymph node in patients who were classified as the same stage, in patients with stage IIIb or stage IIIc, there was a significant difference in the survival rate between cases in which the number of metastatic lymph node was 7~30 and those in which it was greater than 31 ($P=0.037$ and $P<0.0001$, respectively). Of patients with stage IIIb and IIIc, in cases in which the number of metastatic lymph node was greater than 30, there was no significant difference in the survival rate as compared with patients with stage IV. According to the 7th edition of AJCC staging system, as compared with the 6th edition, cases in which the number of metastatic lymph nodes was greater than 7 were all classified as N3. There are also characteristics that no further higher TNM stages could be determined in cases in which the number of metastatic lymph nodes was as the greatest as can be. Based on the results of an analysis in the current study, however, as the number of metastatic lymph nodes was increased even within the same TNM stages, there was no significant difference in the survival rate as compared with the higher TNM stages. Besides, there was a significant difference in the survival rate despite the same TNM stages. As described here, the 7th edition of AJCC staging system is characterized by an insufficient differentiation in the survival rate as the number of metastatic lymph nodes became greater than a specific cut-off point. It can therefore be inferred that further revi-

sions are needed for the classification of lymph nodes. According to the 6th edition of AJCC TNM staging system, cases in which the number of metastatic lymph node are 1~6, 7~15 and greater than 16 are determined to be N1, N2 and N3, respectively. According to the 7th edition, however, cases in which the number of metastatic lymph nodes was greater than 7 were classified as the N3 group. In addition, following a comparison of the survival rate in a stepwise manner at a unit of the number of metastatic lymph nodes of 1 between cases which were classified as TanyN3M0 according to the 7th edition and TanyNanyM1, the difference in the survival rate reached no statistical significance when the number of metastatic lymph nodes was greater than 33. This phenomenon was also observed in stage IIIb patients whose number of metastatic lymph nodes was greater than 28 and stage IIIc patients whose number of metastatic lymph nodes was greater than 29. Of the N3 patients, however, there were only three patients with stage IIb or stage IIIa whose number of metastatic lymph nodes was greater than 24. Accordingly in these cases, a statistical analysis could not be performed. Based on the results of the above analysis, in cases which were classified as N3 according to the 7th edition, further efforts are needed to obtain the optimal cut-off value for the number of metastatic lymph nodes. This should be followed by subclassification system. Thus, efforts should be made to differentiate these TNM stages.

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