

Can the ratio of metastatic to examined lymph nodes (N ratio) be used as an independent prognostic factor in patients with gastric cancer? Is the hypothetical TRM (tumor-ratio-metastasis) staging system an alternative to the TNM (tumor-node-metastasis) staging system?

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Prz Gastroenterol 2013; 8 (4): 247–256

DOI: 10.5114/pg.2013.37488

Key words: gastric cancer, ratio, hypothetical TRM staging.

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Abstract

Aim: Lymph node metastasis is the most important prognostic factor in patients with gastric cancer. However, lymph node classification is controversial. We reported the prognostic factors of gastric cancer and the impact of N ratio classification in predicting prognosis and the suitability of TRM classification as an alternative to TNM (tumor-node-metastasis) classification for lymph nodes to avoid stage migration in gastric cancer.

Material and methods: A total of 90 patients, who underwent R0 resection for gastric cancer, were analyzed. Independent variables of the study were age, gender, tumor site, type of surgery, lymph node dissection, tumor size, T stage, differentiation, total number of removed lymph nodes, number of metastatic lymph nodes, N ratio, N stage, and TNM stage. N ratio was used instead of N stage in the hypothetical TRM staging system. Dependent variables of the study were 2-year and 5-year survival rates.

Results: The N ratio cutoff points were 0, 0.10, and 0.25. The 2-year and 5-year survival rates were significantly higher in patients who had low T stages ($p < 0.001$, $p < 0.001$), N stages ($p < 0.001$, $p < 0.001$), N ratio ($p < 0.001$, $p < 0.001$), TNM stages ($p < 0.001$, $p < 0.001$), and underwent subtotal gastrectomy ($p = 0.006$, $p = 0.030$). When the TNM stages of the patients according to the UICC/AJCC TNM sixth and seventh edition staging system were compared to the TRM hypothetical staging system, stage migration phenomenon was observed at 36.6% and 8.8%, respectively.

Conclusions: N ratio classification can be used as an independent prognostic factor. The use of TRM hypothetical staging system for minimizing stage migration phenomenon requires further discussion.

Introduction

Gastric cancer is the fourth most common neoplasm in the world, with one million new cases every year [1]. *Helicobacter pylori* infection is an important factor increasing the risk of gastric cancer. There is a strong emphasis on the role of eradication of these infections in the prevention of gastric cancer [2]. Lymph node metastasis is one of the important indicators affecting

the prognosis in patients with gastric cancer. However, lymph node classification is controversial [3]. In radically resected gastric cancer patients, the number of metastatic lymph nodes and the depth of the primary tumor are reliable prognostic factors [4, 5]. In 1981, the Japanese Research Society for Gastric Carcinoma (JRS GC) adopted lymph node staging for gastric cancer, depending on the anatomical localization of metastatic lymph

nodes. This classification was revised by the Japanese Gastric Cancer Association in 1998 [6]. The International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) proposed a new classification for the N category, in 1997 and 2002, respectively, on the basis of the number of metastatic lymph nodes. This classification is now widely used throughout the world [7, 8]. In the TNM (tumor-node-metastasis) classification, there are many obvious differences in the prognosis within the same N category. The high-risk factors for recurrence are quite difficult to distinguish, especially in early gastric cancer [9]. The AJCC has published the seventh edition of the TNM classification for gastric cancer in recent years. However, there are still discussions about the zones of the N classification [10]. Some authors note that the UICC/AJCC TNM classification causes problems, such as the stage migration phenomenon [11–14]. In clinical practice, especially when considering adjuvant therapy, accurate staging of gastric cancer is crucial [15]. In addition, in the case of inadequate lymph node removal (less than 15), the patient's prognosis will be poorer than expected, when it is classified according to the UICC/AJCC N staging. For more accurate staging and a more reliable assessment of the prognosis, a new classification system was proposed, based on the ratio of the metastatic lymph nodes to the total number of lymph nodes (N ratio). The N ratio classification is advocated to avoid the stage migration phenomenon, and to be more effective in determining the prognosis, and thus it can be used instead of the N classification [1, 3, 13, 14, 16–23].

Material and methods

This is a retrospective cohort study, which included a total of 90 patients, who underwent R0 resection for gastric cancer at the Izmir Bozyaka Training and Research Hospital, in the First and the Second General Surgery Clinics, between 1997 and 2011. The exclusion criteria were metastatic disease, cancer at the anastomosis site, proximally or distally positive surgical margins, peritoneal implantation, R1 and R2 resection, extensive ascites, synchronous or metachronous tumors, patients who died within 30 days after surgery and patients who refused to have postoperative chemoradiotherapy. Patients with cardia cancer were excluded from the study because cardia cancer is a different clinical entity. Staging was done using the sixth edition of the UICC/AJCC TNM staging system (N0: no metastasis; N1: metastasis in 1–6 lymph nodes; N2: metastasis in 7–15 lymph nodes; N3: metastasis in more than 15 lymph nodes). All patients were evaluated by the Oncology Council and received the appropriate treatment. All of the cases had control visits every 3 months in the first 2 years, and once every 6 months afterwards.

The independent variables were age, gender, tumor location, type of surgery, type of lymph node dissection, tumor size, tumor stage, tumor differentiation grade, total number of removed lymph nodes, number of metastatic lymph nodes, the ratio of the number of removed lymph nodes to the number of metastatic lymph nodes (N ratio), N staging, and TNM staging. The N ratio values of 0%, 1–10%, 11–25% and above 25% were assigned as N ratio 0, N ratio 1, N ratio 2, and N ratio 3, respectively. The dependent variables are the 2-year and 5-year survival.

While creating the hypothetical TRM (tumor-ratio-metastasis) staging, the N ratio values (N ratio 0, N ratio 1, N ratio 2, and N ratio 3) were used instead of the N values (N0, N1, N2, and N3) of the sixth and the seventh editions of the UICC/AJCC TNM staging system. While evaluating the stage migration phenomenon, as there was no stage IV for the patients with stage M0 in the seventh edition, the cases with stage IIIc disease were assessed in the stage migration phenomenon. The patients with stage II A and II B were not included in evaluation in the stage migration phenomenon.

The data regarding the independent variables were obtained retrospectively from the patient records. The survival results were obtained from the medical files, the hospital death records, and by telephone calls to the patients.

Statistical analysis

The SPSS 15.0 package program was used for data analysis. The descriptive data were presented as the mean, standard deviation, and percentage distributions. The effect of independent variables on survival was analyzed using Kaplan-Meier survival analysis. A *p* value < 0.05 was considered statistically significant.

Results

The study included 34 (37.8%) females and 56 (62.2%) males, with a mean age of 61.3 ±12.2 years (range: 32–82 years). The tumor localizations were upper, middle, lower, and diffuse, at a rate of 7.8%, 38.9%, 45.5%, and 7.8%, respectively. Total gastrectomy was performed in 51.1% of the cases, whereas 48.9% underwent subtotal gastrectomy. D0, D1 and D2 lymph node dissection was performed in 3.3%, 70.0%, and 26.7% of the cases, respectively. The mean tumor diameter was 6.5 ±3.5 cm (range: 1–16 cm). T1, T2, T3 and T4 stages were 11.1%, 8.9%, 78.9%, and 1.1%, respectively. Differentiation was found to be good (G1), moderate (G2), poor (G3), undifferentiated (G4), and unknown at rates of 4.4%, 31.1%, 46.7%, 7.8% and 10.0%, respectively. The average number of removed lymph nodes was 24.6 ±14.4 (0–74), and the average number of metastatic lymph nodes was

7.9 ±10.8 (0–47). Of the patients with 15 or fewer removed lymph nodes, 12 (48.0%) were female, and 13 (52.0%) were male. Of the patients with more than 15 removed lymph nodes, 22 (33.8%) were female and 43 (66.2%) were male. N0, N1, N2 and N3 values were 30.0%, 31.1%, 21.1%, and 17.8%, respectively. N ratio 0, N ratio 1, N ratio 2, and N ratio 3 values were 30.0%, 12.2%, 12.2%, and 45.6%, respectively. TNM stages of IA, IB, II, IIIA, IIIB and IV were 10.0%, 5.5%, 18.9%, 26.7%, 20.0%, and 18.9%, respectively.

Of all the patients, 35 (38.9%) were alive, 41 (45.5%) were died, and 14 (15.6%) were lost to follow-up. The mean 5-year follow-up was 30.9 ±23.4 months (range: 2–60 months) for all patients, 12.9 ±10.2 months (range: 2–46 months) for patients who died, and 52.1 ±15.4 months (range: 7–60 months) for the surviving patients. The disease and the surgical characteristics of the patients are presented in Table I.

The 2-year and 5-year survival rates were significantly higher in patients with a lower T stage ($p < 0.001$ vs. $p < 0.001$), N stage ($p < 0.001$ vs. $p < 0.001$), N ratio ($p < 0.001$ vs. $p < 0.001$), and TNM stage ($p < 0.001$ vs. $p < 0.001$) and in patients who underwent subtotal resection ($p = 0.006$, $p = 0.030$). The 2-year and 5-year survival rates were highest in patients with gastric cancer located in the lower part of the stomach, whereas the 2-year survival was lowest in patients with gastric cancer located in the middle part of the stomach or diffusely, and this difference was significant ($p = 0.017$, $p = 0.028$) (Table II). The 2-year and 5-year survival curves according to the N ratio are presented in Figures 1 and 2.

The lower T stage ($p = 0.004$, $p = 0.001$), N stage ($p < 0.001$, $p < 0.001$), N ratio ($p < 0.001$, $p < 0.001$), and TNM stage ($p < 0.001$, $p < 0.001$) of the patients with 15 or fewer removed lymph nodes increased the 2-year and 5-year survival in this group (Table 3). In patients with more than 15 removed lymph nodes, of lower T stage ($p = 0.035$, $p = 0.012$), lower N stage ($p < 0.001$, $p < 0.001$), low N ratio ($p = 0.010$, $p < 0.001$) and low TNM stage ($p = 0.001$, $p < 0.001$) significantly increased the 2-year and 5-year survival. In this group, subtotal gastrectomy ($p = 0.045$) significantly increased 2-year survival (Table IV). The relationship of the N ratio values with the N values is presented in Table V.

In the comparison of the stages of the cases according to the sixth edition UICC/AJCC TNM staging system to the sixth edition of the hypothetical TRM staging, a stage migration of 36.6% (33/90) was found. When the staging was done according to the seventh edition UICC/AJCC TNM staging system, there was a stage migration of 30.0% (27/90), compared to the sixth edition UICC/AJCC TNM staging system. When the staging was

Table I. Distribution of patients according to disease and surgery

Variable	Number	Percentage
Site		
Upper	7	7.8
Middle	35	38.9
Lower	41	45.5
Diffuse	7	7.8
Type of dissection		
D0	3	3.3
D1	63	70.0
D2	24	26.7
Differentiation		
G1	4	4.4
G2	28	31.1
G3	42	46.7
G4	7	7.8
Unknown	9	10.0
T stage		
T1	10	11.1
T2	8	8.9
T3	71	78.9
T4	1	1.1
N stage		
N0	27	30.0
N1	28	31.1
N2	19	21.1
N3	16	17.8
N ratio		
N0	27	30.0
N1	11	12.2
N2	11	12.2
N3	41	45.6
6th edit. TNM stage		
IA	9	10.0
IB	5	5.5
II	17	18.9
IIIA	24	26.7
IIIB	18	20.0
IV	17	18.9
Number of retrieved lymph node		
≤ 15	25	27.8
> 15	65	72.2
Tumor size [cm]		
0–3	13	14.4
4–6	39	43.3
≥ 7	38	42.2
Surgery		
Total gastrectomy	46	51.1
Subtotal gastrectomy	44	48.9

Table II. Effect of the independent variables on 2-year and 5-year survival in all patients

Variable	Total <i>n</i>	2-Year			5-Year		
		Died patient, <i>n</i>	2-Year OS rate (%)	Value of <i>p</i>	Died patient, <i>n</i>	5-Year OS rate (%)	Value of <i>p</i>
Gender							
Female	30	17	43.3	0.138	19	36.7	0.181
Male	46	18	60.9		22	52.2	
Age							
≤ 60	33	12	63.6	0.127	15	54.5	0.147
> 60	43	23	46.5		26	39.5	
Site							
Upper	5	1	80.0	0.017	1	80.0	0.028
Middle-diffuse	37	23	37.8		25	32.4	
Lower	34	11	67.6		15	55.9	
Type of dissection							
D0	3	1	66.7	0.833	1	66.7	0.794
D1	55	25	54.5		31	43.6	
D2	18	9	50.0		9	50.0	
Differentiation							
G1	3	0	100.0	0.530	0	100.0	
G2	26	11	57.7		13	50.0	0.413
G3	37	18	51.4		21	43.2	
G4	3	1	66.7		2	33.3	
T stage							
T1	10	0	100.0	< 0.001	0	100.0	< 0.001
T2	8	1	87.5		1	87.5	
T3	57	33	42.1		39	31.6	
T4	1	1	0.0		1	0.0	
N stage							
N0	24	2	91.7	< 0.001	3	87.5	< 0.001
N1	23	10	56.5		12	47.8	
N2	16	12	25.0		14	12.5	
N3	13	11	15.4		12	7.7	
N ratio							
N0	24	2	91.7	< 0.001	3	87.5	< 0.001
N1	8	3	62.5		3	62.5	
N2	9	4	55.6		5	44.0	
N3	35	26	25.7		30	14.3	
6th edit. TNM stage							
IA	9	0	100.0	< 0.001	0	100.0	< 0.001
IB	5	0	100.0		0	100.0	
II	14	2	85.7		3	78.6	
IIIA	19	10	47.4		12	36.8	
IIIB	15	11	26.7		13	13.3	
IV	14	12	14.3		13	7.1	
Tumor size [cm]							
1-3	13	2	84.6	0.067	3	76.9	0.084
4-6	35	16	54.3		20	42.9	
≥ 7+	28	17	39.3		18	35.7	
Surgery							
Total	39	24	38.5	0.006	25	35.9	0.030
Subtotal	37	11	70.3		16	56.8	

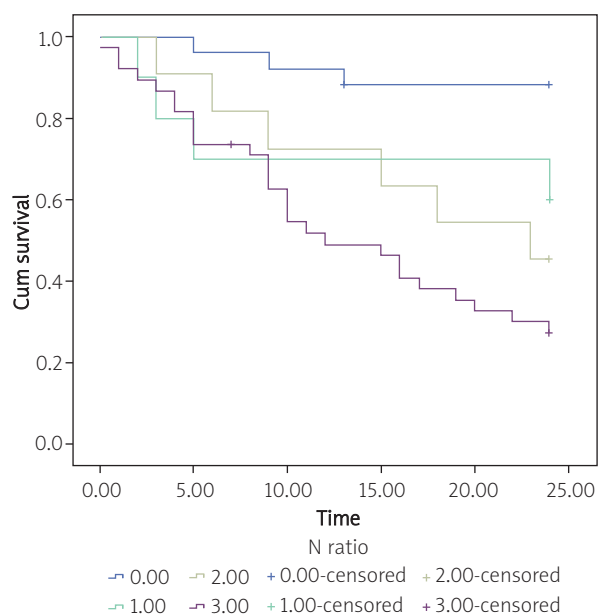


Fig. 1. Two-year survival curve according to the N ratio in all patients

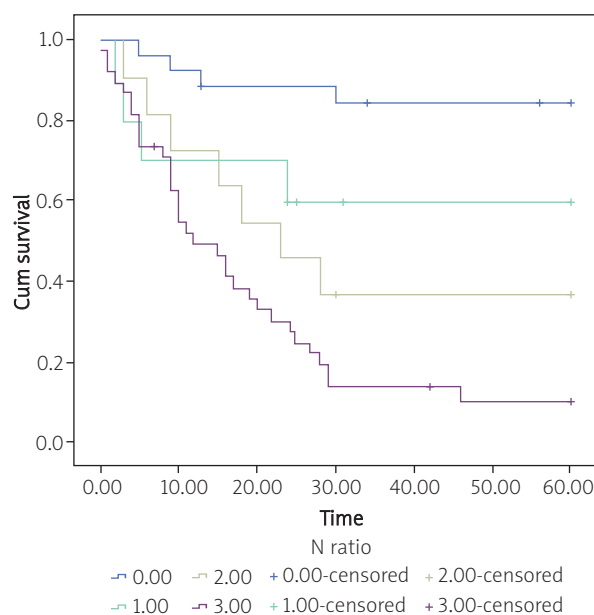


Fig. 2. Five-year survival curve according to the N ratio in all patients

done according to the seventh edition hypothetical TRM staging, there was a stage migration of 8.8% (8/90), compared to the seventh edition of the UICC/AJCC TNM staging. TNM and hypothetical TRM stages are presented in Table VI.

Discussion

In our study, 70.0% of patients underwent a D1 lymph node dissection, and 26.7% a D2 lymph node dissection. D2 lymph node dissection has been more frequently performed by surgeons interested in gastric surgery in recent years. In our series, there were 65 (72.2%) patients with removal of more than 15 lymph nodes, whereas 15 or fewer lymph nodes were removed in 25 (27.8%) patients. There was no significant difference in terms of 2-year and 5-year survival, with respect to the type of lymph node dissection ($p = 0.833$, $p = 0.794$). This is likely due to the small number of patients in the group with D2 lymph node dissection and the failure to perform a complete D2 lymph node dissection.

In patients with 15 or fewer removed lymph nodes, of advanced T stage, advanced N stage, advanced N ratio and advanced TNM stage significantly reduced the 2-year and 5-year survival rates. In patients with more than 15 removed lymph nodes, of advanced T stage, advanced N stage, advanced N ratio, and advanced TNM stage significantly reduced the 2-year and 5-year survival rates.

Various studies indicate that in cases with limited surgery, the N + patients have poorer 2-year and 5-year

outcomes compared to patients with the same N categories, who underwent adequate surgery. This is explained by the increased number of detected metastatic lymph nodes when an extensive lymph node dissection is performed, which changes the N category [14, 16, 18].

Due to the fact that some surgeons apply the D1 dissection routinely, it has been suggested that the N ratio classification can be used in routine clinical practice, regardless of the type of lymphadenectomy. Thus, it has been emphasized that the N ratio can be a strong prognostic factor in the staging system and can provide better staging and response to chemotherapy. In addition, the N ratio classification has been advocated to distinguish the prognostic categories not only in patients with removal of more than 15 lymph nodes, but also in patients with limited lymph node dissection, and in the case of N1 and N2 lymph node involvement [18].

The appropriate identification of the N ratio subgroups is controversial [17]. Different ratios have been used for cutoff points, such as 0, 0.20, 0.50 [22], 0, 0.30, 0.60 [1], 0, 0.10, 0.25 [16], 0, 0.30, 0.70 [24], 0, 0.15, 0.40 [25], 0, 0.10, 0.25 [18], 0, 0.25, 0.50 [13], 0, 0.10, 0.40 [21] and 0, 0.09, 0.25 [26]. This study used 0, 0.10 and 0.25 for cutoff points.

In most studies, N ratio classification has been used in cases with more than 15 removed lymph nodes. In a study of 906 patients, Xu D Zhi *et al.* also used the N ratio classification in cases with the removal of less than 15 lymph nodes [3]. They grouped the removed

Table III. Effect of the independent variables on 2-year and 5-year survival in patients with 15 or fewer removed lymph nodes

Variable	Total <i>n</i>	2-Year			5-Year		
		Died patient, <i>n</i>	2-Year OS rate (%)	Value of <i>p</i>	Died patient, <i>n</i>	5-Year OS rate (%)	Value of <i>p</i>
Gender							
Female	11	4	63.6	0.754	5	54.5	0.763
Male	10	3	70.0		4	60.0	
Age							
≤ 60	12	4	66.7	0.978	5	58.3	0.918
> 60	9	3	66.7		4	55.6	
Site							
Upper	1	0	100.0	0.542	0	100.0	0.683
Middle-diffuse	6	3	50.0		3	50.0	
Lower	14	4	71.4		6	57.1	
Type of dissection							
D0	3	1	66.7	0.913	1	66.7	0.710
D1	18	6	66.7		8	55.6	
D2	–	–	–		–	–	
Differentiation							
G1	1	0	100.0	0.631	0	100.0	0.729
G2	9	3	66.7		4	55.6	
G3	9	4	55.6		4	55.6	
G4	1	0	100.0		1	0.0	
T stage							
T1	6	0	100.0	0.004	0	100.0	0.001
T2	2	0	100.0		0	100.0	
T3	12	6	50.0		8	33.3	
T4	1	1	0.0		1	0.0	
N stage							
N0	11	0	100.0	< 0.001	1	90.9	< 0.001
N1	8	5	37.5		6	25.0	
N2	2	2	0.0		2	0.0	
N3	–	–	–		–	–	
N ratio							
N0	11	0	100.0	< 0.001	1	90.9	< 0.001
N1	2	0	100.0		0	100.0	
N2	1	1	0.0		1	0.0	
N3	7	6	14.3		7	0.0	
6th edit. TNM stage							
IA	6	0	100.0	< 0.001	0	100.0	< 0.001
IB	2	0	100.0		0	100.0	
II	3	0	100.0		1	66.7	
IIIA	7	4	42.9		5	28.6	
IIIB	2	2	0.0		2	0.0	
IV	1	1	0.0		1	0.0	
Surgery							
Total	3	2	33.3	0.186	2	33.3	0.291
Subtotal	18	5	72.2		7	61.1	

Table IV. Effect of the independent variables on 2-year and 5-year survival in patients with more than 15 removed lymph nodes

Variable	Total <i>n</i>	2-Year			5-Year		
		Died patient, <i>n</i>	2-Year OS rate (%)	Value of <i>p</i>	Died patient, <i>n</i>	5-Year OS rate (%)	Value of <i>p</i>
Gender							
Female	19	13	31.6	0.050	14	26.3	0.068
Male	36	15	58.3		18	50.0	
Age							
≤ 60	21	8	61.9	0.130	10	52.4	0.162
> 60	34	20	41.2		22	35.3	
Site							
Upper	4	1	75.0	0.060	1	75.0	0.067
Middle-diffuse	31	20	35.5		22	29.0	
Lower	20	7	65.0		9	55.0	
Type of dissection							
D0	–	–	–	0.989	–	–	0.720
D1	37	19	48.6		23	37.8	
D2	18	9	50.0		9	50.0	
Differentiation							
G1	2	0	100.0	0.695	0	100.0	0.604
G2	17	8	52.9		9	47.1	
G3	28	14	50.0		17	39.3	
G4	2	1	50.0		1	50.0	
T stage							
T1	4	0	100.0	0.035	0	100.0	0.012
T2	6	1	83.3		1	83.3	
T3	45	27	40.0		31	31.1	
T4	–	–	–		–	–	
N stage							
N0	13	2	84.6	< 0.001	2	84.6	< 0.001
N1	15	5	66.7		6	60.0	
N2	14	10	28.6		12	14.3	
N3	13	11	15.4		12	7.7	
N ratio							
N0	13	2	84.6	0.010	2	84.6	< 0.001
N1	6	3	50.0		3	50.0	
N2	8	3	62.5		4	50.0	
N3	28	20	28.6		23	17.9	
6th edit. TNM stage							
IA	3	0	100.0	0.001	0	100.0	< 0.001
IB	3	0	100.0		0	100.0	
II	11	2	81.8		2	81.8	
IIIA	12	6	50.0		7	41.7	
IIIB	13	9	30.8		11	15.4	
IV	13	11	15.4		12	7.7	
Surgery							
Total	36	22	38.9	0.045	23	36.1	0.151
Subtotal	19	6	68.4		9	52.6	

Table V. N ratio, N and TNM stage values in all patients

N ratio	N stage, n (%)				6 th edit. TNM stage th n (%)					
	N0	N1	N2	N3	IA	IB	II	IIIA	IIIB	IV
0	27 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (33.3)	4 (4.8)	14 (51.9)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	11 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (18.2)	9 (81.8)	0 (0.0)	0 (0.0)
2	0 (0.0)	10 (90.9)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	9 (81.8)	0 (0.0)	1 (9.1)
3	0 (0.0)	7 (17.1)	18 (43.9)	16 (39.0)	0 (0.0)	1 (2.4)	0 (0.0)	6 (14.6)	18 (43.9)	16 (39.0)

Table VI. TNM and hypothetical TRM stage values in all patients

Stage	6 th TNM, n (%)	6 hTRM, n (%)	7 th TNM, n (%)	7 hTRM, n (%)
IA	9 (10.0)	9 (10.0)	9 (10.0)	9 (10.0)
IB	5 (5.6)	5 (5.6)	5 (5.6)	5 (5.6)
II	17 (18.9)	16 (17.8)	–	–
IIA	–	–	3 (3.3)	2 (2.2)
IIB	–	–	14 (15.6)	16 (17.8)
IIIA	24 (26.6)	11 (12.2)	11 (12.2)	9 (10.0)
IIIB	18 (20.0)	8 (8.9)	12 (13.3)	8 (8.9)
IIIC	–	–	36 (40.0)	41 (45.5)
IV	17 (18.9)	41 (45.5)	–	–
Total	90 (100)	90 (100)	90 (100)	90 (100)

6th TNM – 6th edition UICC/AJCC TNM staging system, 6 hTRM – Hypothetical TRM staging system according to 6th edition UICC/AJCC TNM staging system, 7th TNM – 7th edition UICC/AJCC TNM staging system, 7 hTRM – Hypothetical TRM staging system according to 7th edition UICC/AJCC TNM staging system

lymph nodes as 1–3, 4–7, 8–11, and 12–15, and found no significant difference between the groups in regard to the prognostic value of the N ratio. The authors stated that a positive N ratio can be used as an independent prognostic factor in patients, regardless of the number of removed lymph nodes. In the multivariate analyses, the T stage and the N ratio remained statistically significant, while the N stage was not statistically significant. As a result, they concluded that a positive N ratio can prevent the stage migration phenomenon, and it is an acceptable method to predict the prognosis of gastric cancer.

In a study with 156 patients with early gastric cancer and lymph node metastases, Cheong *et al.* suggested that only the N ratio was associated with local recurrence and poor prognosis [9]. They stated that there are shortcomings of the current classification to determine the outcome according to the N staging, at least for early gastric cancer. They recommended a close follow-up of patients with early gastric cancer with an N ratio higher than 7%.

Although there are advocates of the superiority of the N ratio classification to the N classification, there are also

opposing views. In 96 patients who underwent D2 lymph node dissection due to gastric cancer with the removal of at least 16 lymph nodes, Espin *et al.* compared the MLNR (metastatic lymph node ratio) with the NMLN (number of metastatic lymph nodes) [27]. For the evaluation of the N ratio sub-groups, they used the cutoff points above 20% and below 20%, and for the assessment of the N classification they used the cutoff points of the affected lymph nodes of less than 5, and 5 and higher. The 5-year survival in the two groups was reported as 71.4%, 16.1%, and 73%, 15.6%, respectively. The authors indicated that the absolute number of metastatic lymph nodes was an important prognostic factor, and the N ratio classification revealed similar results without improving the prognosis. They reported that each positive lymph node decreased 5-year survival by 7.5%.

In the sixth edition UICC/AJCC TNM staging system, N3 classification cannot be completed in patients with the removal of less than 15 lymph nodes. In the seventh edition UICC/AJCC TNM staging system, since seven or more metastatic lymph nodes are classified as N3, it may prevent the stage migration phenomenon. Howev-

er, this issue is controversial. It is not yet known if the seventh edition of the UICC/AJCC TNM staging system will reduce the stage migration phenomenon [17].

The N ratio was also compared with the seventh edition UICC/AJCC TNM staging system. In their study of 1075 patients, Zhou *et al.* divided the N ratio sub-groups as 0%, 1–20%, 20–50%, and greater than 50% [15]. In this study, the UICC/AJCC N classification from 2009 was taken into account when evaluating the N classification (N0: 0 metastasis, N1: 1–2 metastases, N2: 3–6 metastases, N3a: 7–15 metastases, and N3b: more than 15 metastases). Compared to the N ratio classification, in the N classification, in patients with the removal of 15 or fewer lymph nodes, and more than 15 lymph nodes, a stage migration phenomenon of 14.6% and 23.3% was observed, respectively. In the current study, the comparison between the N ratio and the sixth edition UICC/AJCC N classification revealed a stage migration phenomenon of 36.6%. In the aforementioned study of Zhou *et al.*, in patients with the removal of more than 15 lymph nodes, a significant improvement in survival rates was observed compared to the patients with removal of 15 or fewer lymph nodes. Similarly, in the current study, the 2-year and the 5-year survival of N+ patients with the removal of 15 or fewer lymph nodes was poorer than the cases with removal of more than 15 lymph nodes in the same N category. (In patients with removal of 15 or fewer lymph nodes, the 2-year and the 5-year survival rates for N1 and N2 were 37.5% and 25.0%, 0.0 and 0.0; those of the patients with removal of more than 15 lymph nodes were 66.7% and 60.0%, 28.6% and 14.3%, respectively).

In their study of 1042 patients, Xiao *et al.* evaluated the N ratio sub-groups as 0%, 0–30%, 31–50%, and 51–100% [20]. They concluded that when more than 15 lymph nodes were removed, the seventh edition UICC/AJCC N classification was more appropriate than the sixth edition UICC/AJCC N classification. They also stated that when fewer lymph nodes were removed, there would be downstaging, while the removal of a large number of lymph nodes would mean upstaging. They advocated that the assessment of the presence of 7 to 15 metastatic lymph nodes as N3 in the seventh edition UICC/AJCC staging system could diminish the stage migration phenomenon; however, it is still not clear if the staging of the seventh edition UICC/AJCC N classification is optimal. They noted that in determining the risk profile of patients with gastric cancer, the seventh edition UICC/AJCC TNM staging system is superior to the sixth edition UICC/AJCC TNM staging system. However, they also indicated that the N ratio classification was superior to both the sixth and the seventh edition UICC/AJCC N classification.

In their study of 1343 patients, Wang *et al.* assessed the N ratio classification as an alternative to the seventh edition UICC/AJCC TNM staging [1]. They advocated the N ratio classification to be a very important prognostic tool for gastric cancer, and they stated that it has more advantages compared to the seventh edition UICC/AJCC TNM staging system. In the current study, when the staging was done according to the seventh edition UICC/AJCC TNM staging system, there was a stage migration phenomenon of 30.0%, compared to the sixth edition UICC/AJCC TNM staging system. When the staging was done according to the hypothetical TRM staging, there was a stage migration phenomenon of 8.8%, compared to the seventh edition UICC/AJCC TNM staging system.

Conclusions

The number of cases in our study is lower than that of the published series in the literature. However, many of our findings are consistent with the literature. In gastric cancer, tumor site, T stage, N stage, N ratio, and TNM stage greatly impact survival. Evaluated together with the literature, especially in cases of limited lymph node removal during surgery for gastric cancer, the prognostic power of the UICC/AJCC N classification is affected significantly. Although the seventh edition UICC/AJCC N classification has lowered the stage migration phenomenon compared to the sixth edition UICC/AJCC N classification, the proposed N ratio classification may be an alternative to the UICC/AJCC N classification. The global use of the hypothetical TRM classification based on the N ratio should be discussed in the near future, particularly in the assessment of the prognosis of patients with gastric cancer who will be scheduled for adjuvant therapy.

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