

Comparison of five staging systems of lymph node metastasis in the gastric carcinoma

Ali Chehrei, Sakineh Amoueiian¹, Jamshid Ansari², Mehdi Montazer¹, Mohammad Hossein Sanei³

Department of Pathology, Thyroid Research Center, Arak University of Medical Science, Arak, Iran, ¹Department of Pathology, Mashhad University of Medical Science, Mashhad, Iran, ²Department of Oncology, Arak University of Medical Science, Arak, Iran, ³Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran

Background: The presence of metastatic lymph nodes is the most important prognostic factor for gastric carcinoma; however, the optimal system for the accurate staging of lymph node metastasis for patients with gastric cancer remains controversial. This study was designed to compare five systems in relation to the N classification of gastric carcinoma. **Materials and Methods:** This multicentric historical cohort study was conducted on 148 patients with M0 gastric adenocarcinoma who underwent gastrectomy in five referral hospitals in Iran. Lymph nodes were sectioned, stained with hematoxylin and eosin. The lymph node status was classified according to the five systems which are: The number of involved lymph nodes (TNM staging), metastatic lymph node ratio (N ratio), and the largest involved lymph node size, largest metastatic nest size and largest metastatic nest to lymph node size ratio. **Results:** Patients were classified into significant prognostic groups by the five N classification method including the TNM method, N ratio (0, ≤ 0.15 , 0.15-0.4, > 0.4), largest involved lymph node size (0, ≤ 5 , 5-11, > 11 mm), Largest metastatic nest size (≤ 1 , 1-7.5, > 7.5 mm) and largest metastatic nest to lymph node size ratio (≤ 0.3 , 0.3-0.9, > 0.9). All of the above systems remained as independently significant prognostic factors in terms of overall and disease free survival time. **Conclusion:** Among the N staging systems we recommend the metastatic lymph node ratio and largest metastatic nest to lymph node size systems, since they are reproducible, simple, have good survival applicability, have prognostic value and include less stage migration especially in patients whom fewer than 15 lymph nodes are dissected.

Key words: Gastric carcinoma, lymph node metastasis, metastatic nest, staging, TNM system

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INTRODUCTION

Gastric cancer is a universally common cancer^[1] and the second most common cause of cancer related death.^[2] Lymph node metastasis is reported to be one of the most important prognostic factors for gastric carcinoma.^[3-6]

The Tumor-Node-Metastasis staging method (TNM) staging system is a widely accepted method for the determination of prognosis and therapeutic plan.^[4] This system has been affected by increase of lymph node dissection and the pathologist's accuracy in finding the number of lymph nodes in the gastrectomy specimen.^[5,7] Furthermore, extended lymphadenectomy can cause stage migration due to increase in the number of metastatic lymph nodes.^[5,6,8] Many authors suggest that the lymph node staging system based on TNM classification will not be affected by the extent of lymph node dissection.^[1,5,9-15] Some authors have shown that staging based on the metastatic lymph node ratio (N ratio), which is calculated by dividing the number of metastatic lymph nodes by the total number of nodes

is an independent and easy-to-assess prognostic factor for patients with gastric cancer.^[6,8,16-19]

Recent findings about esophageal and colon cancer patients suggest that largest involved lymph node size is a more important prognostic factor in these patients than the number of lymph nodes involved,^[20-23] but in the case of gastric carcinoma there is a little evidence to show that lymph node size and metastatic nest size are prognostic factors.^[8,9,24]

In this study, we compare five methods of N classification of gastric carcinoma including TNM, N ratio, largest involved lymph node size, largest metastatic nest size, and the largest metastatic nest to lymph node size ratio for the prediction of survival and disease free survival time (DFS).

MATERIALS AND METHODS

This multicentric historical cohort study was conducted on 148 patients with M0 gastric adenocarcinoma who underwent surgery during 2002-2010: In Valiasr, Emam

Address for correspondence: Dr. Mohammad Hossein Sanei, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: sanei@med.mui.ac.ir

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Khomeini, Ghods (Arak, Iran), Alzahra (Isfahan, Iran) and Emam-Reza Hospitals (Mashhad, Iran). All patients were included if they underwent curative total or partial gastrectomy for M0 primary gastric adenocarcinoma. They were excluded if they had undergone surgery for lymphoma, gastrointestinal stromal tumor, peptic ulcer, and other diseases. Patients without lymph node metastasis and patients who had distant or peritoneal metastasis were also excluded. In all cases, diagnosis had been confirmed at least 1 year before the beginning of our study.

All dissected lymph nodes cut along their longest axis and fixed in formalin, embedded in paraffin, three micron section were prepared and the slides were stained with hematoxylin and eosin.

All the slides were reviewed by two pathologists and a consensus meeting was held in case of discrepancy. These pathologists had no information regarding the patients' prognosis (including survival or recurrence).

Important microscopic features were recorded, these include: Type of Adenocarcinoma (signet, intestinal), grade (poorly, moderately, and well-differentiated), stage, number of dissected and involved lymph nodes, largest size of involved the lymph nodes, largest metastatic nest diameter, and largest metastatic nest to lymph node diameter ratio.

The five systems were explained as bellow;

First: the node ratio (N ratio); the ratio of the number of involved lymph node to the total number of harvesting lymph nodes.

Second: the largest involve lymph node size; among involve lymph node the size of largest one was selected.

Third: the largest metastatic nest size; involve lymph nodes nest were mark under 40 magnifications. Then by microscopic ruler the size was measured and the largest one was selected. In case of multiple nests in one lymph node the sum of diameter of all were considered.

Forth: the largest metastatic nest to lymph node size ratio; for every involved lymph node the ratio of metastatic nest size to diameter of lymph node was calculated then among them the biggest ratio was selected.

Fifth: the well-known TNM system.

Table 1 shows each classification method.

Then, the survival rate and recurrence rate and disease free survival period of patients were determined. These patients

Table 1: Methods of lymph node status classification

Methods	N0	N1	N2	N3
TNM*	None	1-6	7-15	>15
N ratio**	None	≤0.15	0.15-0.4	>0.4
LLS	None	≤5	5-11	>11
LNS	None	≤1	1-7.5	>7.5
LNL ratio	None	≤0.3	0.3-0.9	>0.9

*According to count of involved lymph nodes; **the number of metastatic lymph nodes divided to the total number of dissected lymph nodes; LLS=Largest lymph nodes size (mm); LNS=Largest metastatic I nest size (mm); LNLratio=Largest metastatic I nest to lymph node ratio; TNM=Tumor-Node-metastasis

were visited by an oncologist or surgeon and survival and recurrence rates were determined.

Then, we determined the optimal cut off points of the N ratio, the largest involved lymph node size, the largest metastatic nest size and the largest metastatic nest to lymph node size ratio, which can predict prognosis (including survival time and DFS).

Finally, survival and DFS in the subgroups of each method were compared.

All data were analyzed by spss software (spss Inc., Chicago IL, VSA, version 16).

Simple descriptive techniques were used to describe the variables among the participants. The K-S and levene's test were applied to verify normal distribution and equality of variances. According to the results of the tests, mentioned above, we used the student *t*-test or Mann-withney U test for the comparison of the quantitative data in grouping variables. The Chi square test was used to find the relationship between the qualitative data. Receiver operating characteristic curves and sensitivity analysis were used to determine the optimal cut-off value of the N ratio, largest involved lymph node size, largest metastatic nest size, largest Metastatic to lymph node size ratio. Actuarial and Kaplan-Meier methods were used to estimate the survival function. Survival functions were compared by using the log-rank test between the subgroups.

All procedures were performed according to the principle of the Ethical Standards Committee of Arak (Iran) University of Medical Sciences.

RESULT

A total of 148 cases of gastric cancer in the time interval ranging from 2002 to 2010 reported in five hospitals in Iran were evaluated. The patients included 106 men (71.6%) and 42 women (28.4%). The mean age was 63.09 years (range = 27-85). Lymph node metastasis was observed in 114 cases. (77.02%)

The number of dissected lymph nodes per patient varied widely (1-48), with mean of 9.26. The mean primary tumor size was 5.7 cm (5.26-6.15). The 5-year overall survival rate was 16% [Figure 1] and the median of overall survival time were 16 months. (10.72-21.27). The median of overall DFS was 12 months (8.46-15.53). 102 (68.91%) patients were died by the end of follow-up. The results of the comparative analysis of demographics clinical and pathological features are shown in Table 2.

Median survival times were not significantly different between the subgroups of the clinicopathological parameters including sex, age, and site of tumor, type of gastrectomy, histological type, and grade of adenocarcinoma.

The numbers of patients in each nodal group is shown in Table 3. The comparative analysis of survival and DFS in each nodal group according to the five nodal classification systems is presented in Table 4 and Figures 2-6.

DISCUSSION

Lymph node metastasis is one of the most important prognostic factors of gastric cancer.^[25-28] At present, the classification of lymph node involvement in gastric cancer is still under extensive evaluation; there are some objectives for tumor staging: Assisting in the definition of clinical treatment, simplicity, surgical applicability, and providing some prognostic information for patients. To accomplish these objectives, every lymph node metastasis classification system should be simple, accurate, reproducible and prognostic relevance without stage migration.^[6,8] Reproducibility is crucial for post-treatment pathological classification, inter, and intra observer variability has to be low.^[6] According to each lymph node

metastasis classification, the prognosis can be estimated and determine the therapeutic strategy planning.^[4,6,28]

It has been suggested that the number of metastasis lymph nodes (TNM staging) is a widely accepted, convenience, reproducible method with good assessing potential for the prognosis of gastric cancer.^[4,5,29-31] This staging system is influenced by the number of the resected and examined lymph node. Although N classification is recommended the

Table 2: Comparative analysis of demographic, clinical and pathological features in-patient with gastric carcinoma

Factor	N (%)	Median survival (months)	95% CI Lower	95% CI Upper	Sig.
Sex					
Female	42 (28.4)	15	12.96	17.04	0.7
Male	106 (71.6)	19	12.14	25.85	
Age (years)*					
<60	50 (33.8)	21	8.23	33.76	0.3
>=60	93 (62.8)	16	10.31	21.68	
Site					
Cardia	31 (20.9)	10	5.63	14.36	0.5
Body	57 (38.5)	16	4.89	27.10	
Antrum	57 (38.5)	21	13.33	28.66	
Type of gastrectomy					
Total	73 (49.3)	12	6.21	17.78	0.1
Subtotal	75 (50.7)	23	13.80	32.19	
Histological type					
Intestinal	108 (73)	16	9.66	22.34	0.5
Signet	32 (21.6)	16	8.69	23.30	
Mucinous	8 (5.4)	27	0	69.76	
Stage (TNM)					
I	21 (14.2)	63	11.67	114.32	<0.001
II	57 (38.5)	14	8.83	19.16	
III	66 (44.6)	15	10.55	19.44	
IV**	4 (2.7)	2	-	-	
Grade					
Poorly	42 (28.4)	12	8.59	15.40	0.6
Moderately	43 (29.1)	16	1.83	30.1	
Well	63 (42.6)	23	0.74	28.25	

*There are five missing data in age; **According to > 15 lymph nodes involved (There are not distant metastasis); TNM=Tumor-Node-metastasis

Table 3: Number of patient in each nodal group according to five staging system (N=148)

System	N0	N1	N2	N3
TNM*	34	82	28	4
N ratio**	34	14	36	64
LLS	34	17	62	35
LNS	34	15	63	36
LNL ratio	34	16	61	37

*According to count of involved lymph nodes; ** the number of metastatic lymph nodes divided to the total number of dissected lymph nodes; LLS=Largest lymph nodes size (mm); LNS=Largest metastatic I nest size (mm); LNL ratio=Largest metastatic I nest to lymph node ratio

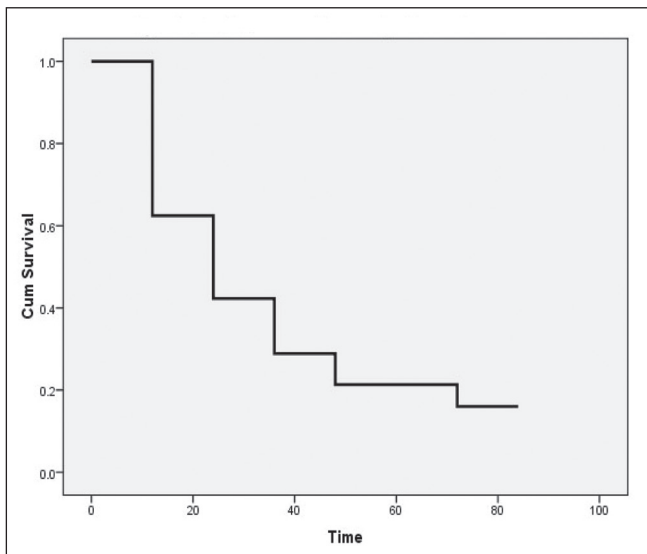


Figure 1: Survival function of all cases of gastric carcinoma

Table 4: Result analysis of survival and DFS between subgroups of each N classification system

System	Median of survival (month)	95% CI of survival		Sig.	Median of DFS*(month)	95% CI of DFS		Sig.
		Lower	Upper			Lower	Upper	
TNM								
N0	43	15.19	70.80		30	17.95	42.04	
N1	14	9.21	18.78		10	6.32	13.67	
N2	12	8.75	15.24		10	6.32	13.67	
N3	2	-		<0.001	1	-		<0.001
N ratio								
N0	43	15.19	70.80		30	17.95	42.04	
N1	10	0	30.30		8	0	24.90	
N2	15	8.80	21.19		10	5.48	14.51	
N3	12	9.23	14.76	<0.001	8	4.86	11.13	<0.002
LLS								
N0	43	15.19	70.80		30	17.95	42.04	
N1	24	13.34	34.64		18	10.51	25.48	
N2	13	10.10	15.89		10	6.80	13.19	
N3	10	7.52	12.47	<0.001	7	4.82	9.17	<0.001
LNS								
N0	43	15.19	70.80		30	17.95	42.04	
N1	24	5.29	42.70		20	0.94	39.05	
N2	13	7.01	18.99		10	6.96	13.03	
N3	10	7.06	12.93	<0.001	7	4.06	9.93	<0.001
LNLratio								
N0	43	15.19	70.80		30	17.95	42.04	
N1	24	3.57	44.43		12	0	32.16	
N2	13	8.01	17.98		10	6.20	13.79	
N3	12	9.70	14.29	<0.001	8	5.52	10.47	<0.001

DFS=Disease free survival time; LLS=Largest lymph nodes size (mm); LNS=Largest metastatic I nest size mm); LNL ratio=Largest metastatic I nest to lymph node ratio; TNM=Tumor-node-metastasis

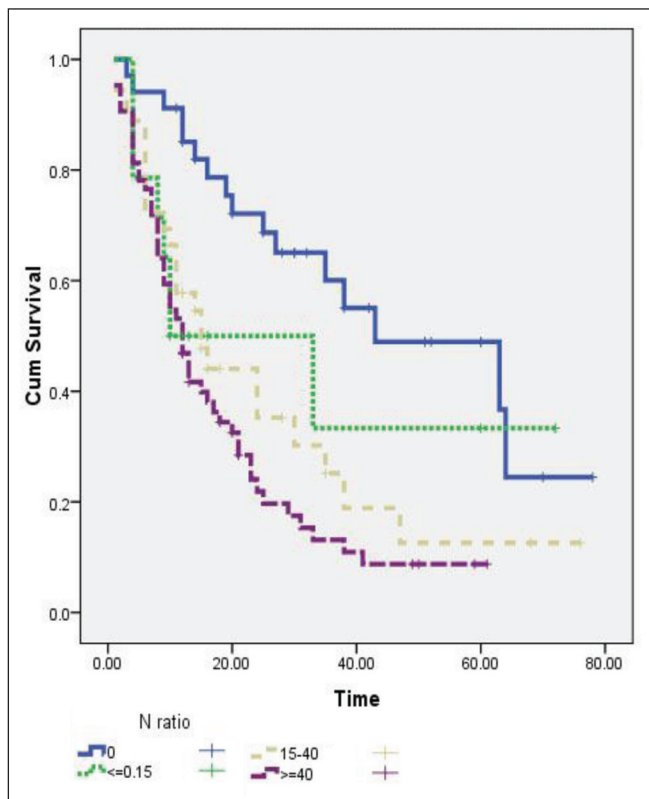


Figure 2: Survival functions of gastric carcinoma according to II ratio classification

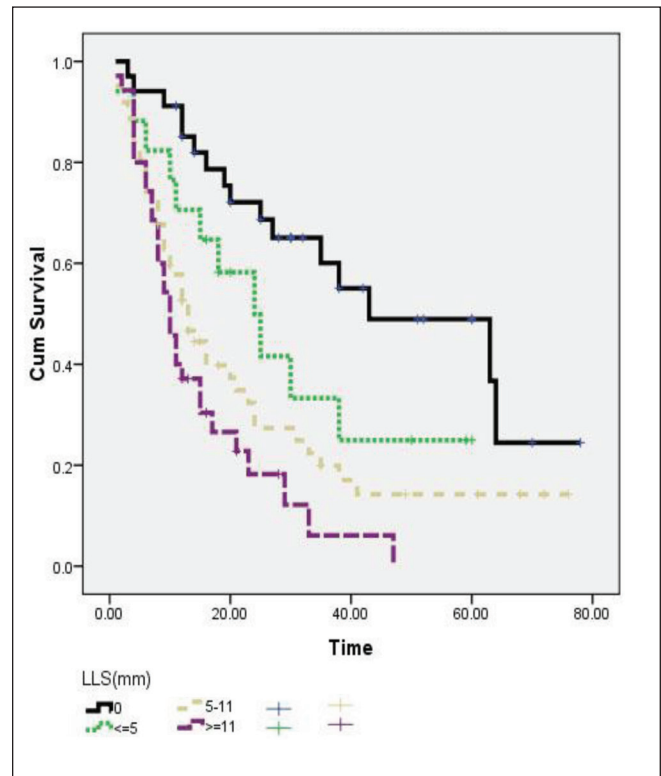


Figure 3: Survival functions of gastric carcinoma according to largest lymph node size classification

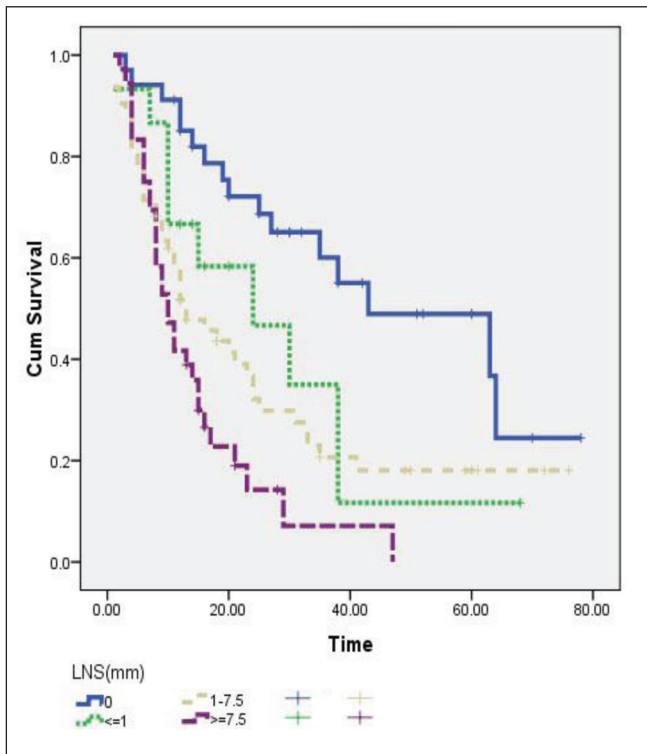


Figure 4: Survival functions of gastric carcinoma according to the largest metastatic nest size

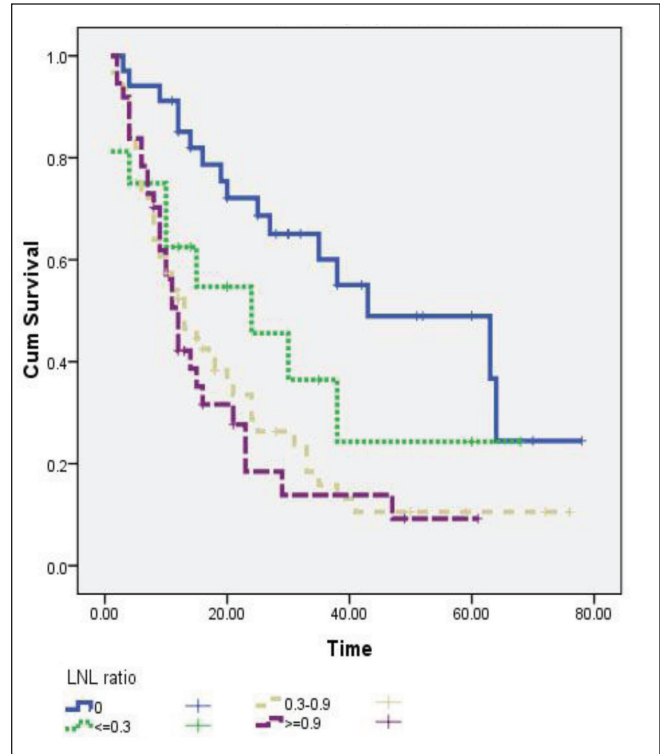


Figure 5: Survival functions of gastric carcinoma according to largest metastatic nest to lymph node size ratio

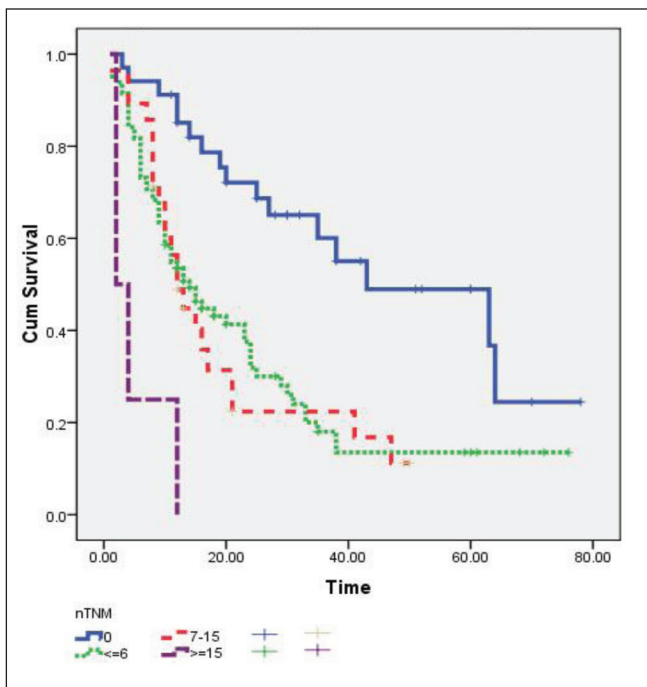


Figure 6: Survival functions of gastric carcinoma according to TNM classification

15 or more lymph nodes should be examined for accurate staging of gastric carcinoma,^[32] the number of metastatic lymph nodes increases in proportion to the number of dissected nodes, suggesting that the patient classified as N1 after limited lymph node dissection may be classified

as N2 or N3 after extensive lymphadenectomy. On the other hand, the N classification may be changed by adding or reducing one or more positive lymph nodes.^[8,13,14] This phenomenon is the so called stage migration error. Stage migration occurs in 5-15% of gastric cancer cases, after extensive lymphadenectomy.^[9,15] In addition, when fewer than 15 lymph nodes are detected, the probability of stage migration rises.

Another method for N classification in gastric cancer is N ratio, which is calculated by dividing the number of metastatic lymph nodes by the total number of nodes harvested. This factor reflects both tumor characteristics: The number of metastatic lymph nodes and the extent of lymphadenectomy.^[8] This system is convenient, reproducible and has surgical applicability, high ability to predict survival and reduced stage migration. In addition, the N ratio system is applicable in patients when fewer than 15 lymph nodes are dissected.^[10,15-19]

There has been no consensus about N ratio cut-off value for the classification of the N status in gastric carcinoma and the definition of the significant prognostic cut-off point varies.^[8-10,13,15,19,33-35] Many authors have shown a significant deterioration in prognosis when 25% of the removed lymph nodes were positive and in some studies three (<10%, 10-25%, >25%) or four (0, <10%, 10-25%, >25%) subgroups of cases with different survival time

were identified.^[8,9,13,18,29,34] In the present study, four subgroups of patients with remarkably different median survival time were identified: 0, <15%, 15-40% and >40%. We also tried to analyze the median of survival time and DFS of our cases and classify them with other cut-off points including 10% and 25%, but in the present study cut off points of 0, 15%, and 40% have the best significant different median of survival time between the subgroups. Lim *et al.* in the same study reported a significantly difference in survival rate when more than 40% of removed lymph nodes were invaded.^[33] Persiani *et al.* reported three subgroups of patients with significantly different 5-year survival rates by 2 cut-off points 15 and 40% (N1: Ratio <15%, N2: Ratio 15-40%, N3: Ratio >40%)^[5] we stratified the patients into four N ratio groups with three cut-off points (0, 15, 40%) rather than three N ratio groups with two cut-off points (15 and 40%); based on the hypothesis that gastric cancer with no nodal involvement should not be grouped with gastric cancer with nodal involvement. The cut-off point of zero was determined in the present study. In the literature review, other authors confirm the above hypothesis.^[8,13,14,36]

The N ratio system for the classification of gastric cancer N staging is a simple, accurate and reproducible method, but routine hematoxylin and eosin staining may not exactly reflect the lymph node metastasis due to lymph node micro-metastasis.^[14]

Others methods examined in this study for N classification of gastric cancer depend on the size of the lymph node and metastatic nest. There are several reports that the largest involved lymph node size may be useful for N classification in esophageal and colon cancer,^[20-23] however, attention to the largest involved lymph node size in N classification of gastric carcinoma has been rare.

Two previous study divided patients into two groups: Lymph node size <2 cm, >= 2 cm and found that this method was an independent prognostic factor.^[8,14] Dhar *et al.* in another study suggested a 7 mm or less cut-off point in the n classification of a number of patients who were then assigned to group N1, a second group that is group N2 had a 8 mm or more cut-off point.^[24] These above methods stratified patients into three groups (N0, N1, N2) with 2 cut-off points (7, 20 mm), but we stratified patients into 4 groups (N0, N1, N2, N3) with three cut-off points (0, 5, 11 mm). Since our classification is divided into four groups, this method is comparable with other classifications. Furthermore, it seems that both the size of lymph node and the size of the metastatic nest have theoretical value in the classification of N groups. Our study showed that the largest metastatic nest size was an independent prognostic factor in terms of overall and DFS.

It seems, in a theoretical approach, two factors that is metastatic nest size and lymph node size are important in the N classification of gastric carcinoma according to size; We described a factor for the classification of gastric cancer N groups according to the above two factors, we named this factor the largest metastatic nest to lymph node size ratio (MLS ratio). In this study, metastatic nest to lymph node diameter ratio was calculated for each lymph node and the largest ratio selected. MLS ratio is an independent prognostic factor in terms of overall and disease free survival rate. This method for gastric cancer N classification is a simple technique and needs only a standard microscopic ruler. This method is applicable especially in patients with fewer than 15 lymph nodes removed during surgery.

CONCLUSION

From among the N staging system we recommend the metastatic lymph node ratio and the largest metastatic nest to lymph node size systems, since they are reproducible, simple, have good survival applicability, have prognostic value and include less stage migration specially in patients whom fewer than 15 lymph nodes are dissected.

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