Metastatic/resected lymph nodes ratio-based classification in gastric cancer

Mide kanserinde metastatik/rezeke edilmiş lenf nodülü oranına dayalı sınıflama

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Background/aims: *Many studies have shown that the metastatic lymph node ratio, calculated by dividing the number of metastatic lymph nodes by the total number of lymph nodes, is an important prognostic factor in gastric cancer. In the present study, the applicability of the metastatic in the 1997 Tumor Node Metastasis system was investigated using our clinical data and discussed in light of the literature.* ***Methods:*** *The study was performed on the 166 patients with gastric cancer in whom R0 resection could be performed and more than 15 nodes were resected. The possible effects of age, gender, location, type of resection, number of resected lymph nodes, depth of invasion, number of involved lymph nodes, tumor grade and metastatic on survival were analyzed.* ***Results:*** *There was a direct correlation between the total number of nodes and the number of metastatic nodes (r: 0.319, p<0.0001). However, there was no correlation between metastatic and the total number of nodes (r: 0.0072, p: 0.354). Tumor location, size, depth of invasion, number of involved nodes and metastatic were found to be determinants of survival in univariate analysis. Cox regression analysis identified metastatic as the only independent prognostic factor.* ***Conclusions:*** *A new staging system based on metastatic will be resistant to stage migration and will include the surgical approach in staging. However, further studies are required to determine appropriate cutoff values and the best approach to patients with less than 15 resected nodes.*

Key words: Gastric cancer, staging, prognosis, metastatic lymph node ratio, lymphadenectomy

Amaç: *Bir çok çalışma metastatic lenf nodülü sayısının çıkartılan lenf nodülü sayısına bölünmesiyle elde edilen metastatik lenf nodu oranının mide kanserinde önemli bir prognostic factor olduğunu göstermiştir. Bu çalışmada 1997 Tümör Lenf Nodu Metastazı sınıflamasına metastatik uygulanabilirliği araştırılmış ve literatür verileri ışığında tartışılmıştır.* ***Yöntem:*** *Çalışma R0 rezeksiyon yapılmış ve en az 15 lenf nodülü çıkartılmış 166 mide kanser olgusu incelenerek yapılmıştır. Yaş, cinsiyet, lokalizasyon, rezeksiyon tipi, çıkartılan lenf nodülü sayısı, invazyon derinliği, tutulan lenf nodülü sayısı, grade ve metastatik sağkalım üzerine olan etkileri araştırılmıştır.* ***Bulgular:*** *Çıkartılan lenf nodülü sayısıyla, metastatik lenf nodülü sayısı arasında anlamlı bir korelasyon vardır (r: 0.319, p<0.0001). Ancak metastatik ve çıkartılan lenf nodülü sayısı arasında anlamlı fark bulunamamıştır (r: 0.0072, p: 0.354). Univaryans analizde tümör lokalizasyonu, çap, invazyon derinliği, metastatic lenf nodülü sayısı ve metastatik sağkalımı istatistiksel anlamlı etkileyen faktörler olarak bulunmuştur. Cox regresyon analizinde ise metastatik tek bağımsız prognostic faktör olarak saptanmıştır.* ***Sonuç:*** *metastatik dayalı yeni bir evreleme sistemi ever kayması sorununa daha dirençli olacak ve cerrahi yaklaşımı evreleme sitemine katacaktır. Bununla beraber 15'ten az lenf nodülü çıkarılmış olgular için metastatik uygun eşik değeri saptamak için yeni çalışmalara ihtiyaç vardır.*

Anahtar Kelimeler: Mide kanseri, evreleme, prognoz, metastatik lenf nodülü oranı, lenfadenektomi

INTRODUCTION

The two most important determinants of prognosis in gastric cancer are depth of tumor invasion and lymphatic involvement. The two available staging systems are based on these parameters. The classification developed by the Japanese Research Society for Gastric Cancer is not only a staging system but also a scheme that groups lymph nodes anatomically and also serves as a guide to surgery. It is a complex classification that requires expertise. The 1997 version of the Tumor Node Metastasis (TNM) system developed by the International Union Against Cancer (UICC) is used more frequently in western countries; it is based primarily on the depth of invasion and number of involved lymph nodes (1,2). In spite of its many positive aspects, the new TNM system has several weaknesses. Although the problem is ameliorated, stage migration is a persistent issue. Studies show that the higher the number of resected nodes, the higher the number of metastatic lymph nodes. A mi-

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nimum of 15 nodes are required for an adequate assessment but the number is actually 25 for a precise evaluation (3).

In Japan, Korea and many western countries, extended lymph node dissection is an integral part of gastric cancer surgery. Centers from Japan and Korea report low morbidity and mortality as well as higher survival rates with extended lymph node dissection. However, these successful results could not be replicated in western centers. Especially in the recently published Dutch study, D2 dissection increased mortality and morbidity but did not improve survival. Ten-year results of a subgroup showed low morbidity and mortality as well as increased survival if D2 dissection can be performed without pancreatectomy and splenectomy (4). In spite of these results, a large number of patients in western countries undergo DO dissection that yields less than 15 lymph nodes. Generally, D1 dissection is conducted (15-25 lymph nodes). D2 dissection (more than 25 nodes) is performed only in some centers (5).

Many studies have shown that the metastatic lymph node ratio (MLR), calculated by dividing the number of metastatic lymph nodes by the total number of lymph nodes, is an important prognostic factor. They have also shown that this parameter is less vulnerable to stage migration. The MLR may give more accurate prognostic information from the number of metastatic lymph nodes. Another important advantage is that it may reflect the efficacy of lymph node dissection (6-8). Studies from different countries are required to elucidate the issue further. In the present study, the applicability of the MLR in the 1997 TNM system was investigated using our clinical data and discussed in light of the literature.

MATERIALS AND METHODS

Between January 1991 and December 2004, 306 patients underwent surgery for gastric cancer in the Department of General Surgery of Uludağ University Faculty of Medicine. Patients who died in the early postoperative period or who were lost to follow-up were excluded from analysis. The study was performed on the 166 patients in whom R0 resection could be performed and more than 15 nodes were resected. The possible effects of age, gender, location, type of resection, number of resected lymph nodes, depth of invasion, number of involved lymph nodes, tumor grade and MLR on survival were analyzed.

The 1997 UICC/American Joint Committee on Cancer (AJCC) staging system was used for N classification. MLR was calculated by dividing the number of metastatic lymph nodes by the total number of lymph nodes. MLR was stratified into six groups, from 0 to 100% at 20% intervals. The log rank test was used to determine the best cutoff point of MLR. Considering that patients with no involved nodes should not to be included with those having nodal involvement and that the survival rate for categories 0.41-0.6, 0.61-0.8 and 0.81-1 were very similar, we graded the MLR into four groups as follows: N: 0, N1: 0-0.20, N2: 0.21-0.40 and N3: >0.40 according to results of this test.

The Kaplan-Meier method and the log rank test were used in survival analysis. Multivariate analysis was performed using the Cox proportional hazards model selected in forward stepwise regression. The relationships between the total number of lymph nodes, number of metastatic lymph nodes and the MLR were evaluated with the Pearson correlation test. Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) version 11.5 (SPSS, Chicago, IL).

RESULTS

The mean age (±SD) was 58.6 ± 12.7 years (range, 22-80 years). Fifty-nine patients were women and 107 were men. The mean number of resected lymph nodes was 30.1 ± 16 (range, 15-80) per patient. The mean number of metastatic lymph nodes was 9.47 ± 13.8 (range, 0-79) per patient. The mean MLR was 0.29 ± 0.32. The details of patient characteristics are presented in Table 1. The five-year survival rate was 35% (mean: 57.6, 95% CI: 46 to 69) for all patients. Survival curves with respect to N based on the number of metastatic nodes and N based on MLR are shown in Figure 1. The correlations between the total number of resected nodes, number of metastatic lymph nodes and MLR are shown in Figure 2. There was a direct correlation between the total number of nodes and the number of metastatic nodes (r: 0.319, $p<0.0001$). However, there was no correlation between MLR and the total number of nodes (r: 0.0072, p: 0.354).

Table 2 compares the observed five-year survival rates of the 1997 version of TNM pN subgroups separated according to the MLR. Among these subgroups, different survivals were found according to their MLR. Prognosis improved with a decrease in MLR. The best survival rates were noted in the patients in the pN1-N2/MLR less than 0.20 subgroups.

Table 1. Patient characteristics

Features	N (%)
Gender	
Male	107 (64.4)
Female	59 (35.6)
Age	
≤40	18 (11)
41-60	70 (42.2)
>60	78 (46.8)
Resection type	
Total	100 (60.2)
Subtotal	66 (39.8)
Tumor size	
≤5	48 (28.9)
6-10	97 (58.5)
>10	21 (12.6)
Depth of invasion	
pT1	14 (8.4)
pT2	21 (12.7)
pT3	121 (72.9)
pT4	10 (6)
Tumor location	
Lower third	67 (40.3)
Middle third	63 (38)
Upper third	27 (16.3)
Whole stomach	9 (5.4)
Tumor differentiation	
Good	13 (7.8)
Moderate	79 (47.6)
Poor	74 (44.6)
***Dissection type**	
D1	80 (48)
D2	86 (52)
Number of metastatic lymph nodes	
N0 (0)	52 (31.3)
N1 (1-6)	39 (23.4)
N2 (7-15)	42 (25.4)
N3 (≥16)	33 (19.9)
Metastatic lymph node ratio	
0	52 (31.3)
0.01-0.20	31 (18.7)
0.21-0.40	26 (15.7)
≥0.40	57 (34.3)

Tumor location, size, depth of invasion, number of involved nodes and MLR were found to be determinants of survival in univariate analysis (Table 3). Cox regression analysis identified MLR as the only independent prognostic factor (Table 4).

DISCUSSION

The objectives of staging systems are to predict prognosis, plan treatment, determine the probability of success and compare the results from different institutions. Resistance to stage migration is a much desired characteristic in gastric cancer staging. The objectives of this study were to investigate the prognostic significance of the MLR, to compare the effects of using the number of resected lymph nodes or the MLR on the sensitivity to stage migration, and to determine whether the MLR can replace the number of metastatic lymph nodes in the TNM classification. In the present report, multivariate analysis identified MLR as the only independent prognostic factor. Although there was a positive correlation between the total number of resected lymph nodes and the number of metastatic nodes, there was no such correlation with the MLR.

In the 1997 TNM staging system, the N classification is based on the number of metastatic nodes. It is a simple and reproducible staging method. Many studies have reported that the number of metastatic nodes is influenced by the number of resected lymph nodes. An extended lymph node dissection with careful examination for metastases allows more accurate number-based N staging, and this should be performed whenever feasible (4-9). Nevertheless, extended lymph node dissection is not a routine part of gastric cancer surgery in many western centers. In an overview on gastric cancer treatment in the United States, D2 dissection ranged from only 4% to 7% of cases (10). Therefore, when a limited lymphadenectomy is performed, patients classified as N1 stage might in fact have been determined as N2 or N3 stage if an extended lymphadenectomy had been performed because of presence of skipped metastases. This phenomenon is called stage migration. Our study results showed that there was a positive correlation between the number of resected nodes and the number of metastatic nodes, but there was no such correlation with the MLR. The clinical significance of this phenomenon is that stage migration is possible even if more than 15 nodes are resected; on the other hand, MLR is minimally confounded by stage migration. The reported vulnerability of

Table 2. The relationship between MLR and the number metastatic nodes in patients with lymph node involvement (Prognosis improved with a decrease in MLR; the best survival rates were noted in the patients in the pN1-N2/MLR less than 0.20 subgroups)

	<0.20	0.21-0.40	>0.40	P value
N1 (1-6) n: 39	43% (mean: 80 mos.) n: 29	11% (mean: 38 mos.) n: 9	0% n: 1	0.042
N2 (7-15) n: 42	50% (mean: 84 mos.) n:2	7.7% (mean: 30 mos.) n:13	0% (mean: 18 mos.) n: 27	0.013
N3 (>15) n: 33	(-)	0% (mean: 13 mos.) n: 4	0% (mean: 12 mos.) n: 29	0.654

Table 3. Results of significant prognostic factors in univariate analysis

Risk Factor	Number of Patients	5-Year Survival (%)	Median Survival (Months)	P Value
Invasion				
M, sm (T1)	14	100	72	0.0002
Mp (T2)	21	70	90	
Ss, S (T3)	121	26	54	
(T4)	10	0	20	
Nodal status				
N0	52	34	120	0.00..
N1 (1-6)	39	25	43	
N2 (7-15)	42	7	20	
N3 (>15)	33	0	11	
Location				
Distal	68	30	66	0.019
Midgastric	64	28	73	
Proximal	26	21	29	
Diffuse	8	0	11	
Size				
<5 cm	48	61	78	0.00..
5-10 cm	97	33	53	
>10 cm	21	5.3	20	
Ratio of met. node				
0	52	34	120	0.00.
0-0.20	31	35	60	
0.21-0.40	26	9	33	
≥0.40	57	0	14	
TOTAL	166	35	57	

met: Metastatic, M: Mucosa, sm: Submucosa, Mp: Muscularis propria, Ss: Subserosa, S: Serosa

the 1997 TNM classification to stage migration has led many investigators to include MLR in staging because it has emerged as a good alternative in preventing the problem.

Table 4. Cox regression analysis identified MLR as the only independent prognostic factor

Ratio	Relative risk*	95% CI	P value
<0.20	2.05	0.89 to 4.72	0.092
0.21-0.40	4.83	2.18 to 10.67	0.000..
>0.40	9.37	4.34 to 20.2	0.000..

* : vs patients who had ratio: 0, CI: Confidence interval.

Reports from many western and Japanese centers and our relatively small series show that MLR is a very powerful prognostic factor. In a study by Hyung et al. (11) on T3 patients who underwent D2 dissection, MLR was 10% in T3N1 patients and 25% in T3N2 patients. Use of MLR in patients with T3 tumors may provide a better prediction of prognosis. In a multi-center study by Siewert et al. (8), the 10-year results of 1654 patients were analyzed; the residual tumor status and the MLR (≤20% vs >20%) were identified as independent prognostic factors. That study confirmed that MLR may be used to assess the adequacy of lymphadenectomy. In a series of 865 patients who underwent D2 dissection, Yu et al. (12) defined three subgroups with respect to MLR (0: N0, 1-25%: N1, >25%: N2) and found significant differences between the three groups. In the study by Kodera et al. (13), four subgroups were defined: 0%, 1-19%, 20-60%, and >60%; MLR was found to be correlated with the number of metastatic nodes but not with the number of resected nodes. The authors recommended the use of MLR in the staging of patients who undergo D1 dissection. In Celen et al.'s (14) study, patients were

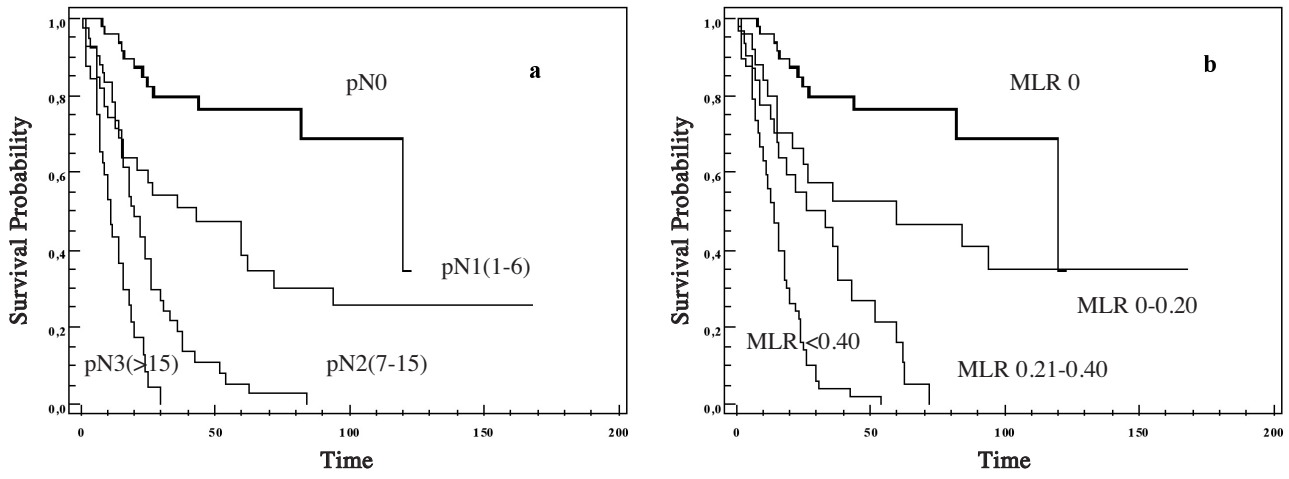

Figure 1. a) Survival with respect to the N stage based on the number of metastatic nodes: N0: 34% (median: 120 months), N1 (1-6): 25% (median: 43 months), N2 (7-15): 0% (median: 20 months), and N3 (>15): 0% (median: 11 months). **b)** Survival with respect to the N stage based on the MLR. N0: 34% (median: 120 months), N1 (0-0.20): 35% (median: 60 months), N2 (0.21-0.40): 0% (median: 33 months), and N3 (>0.40): 0% (median: 14 months).

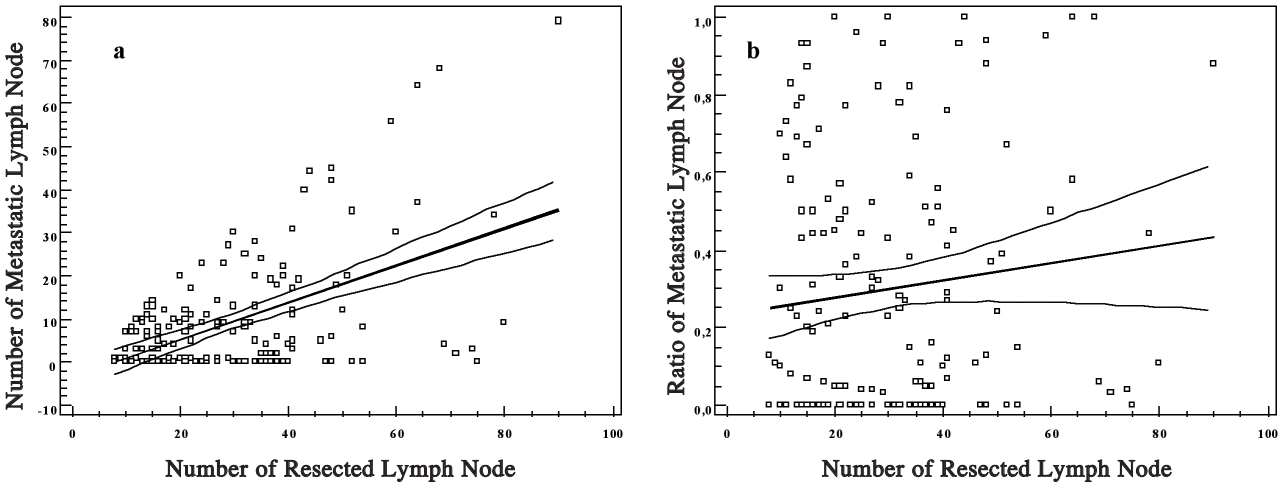

Figure 2. a) There was a positive correlation between the number of resected nodes and the number of metastatic nodes (r: 0.319, p<0.0001). **b)** There was no such correlation with the MLR (r: 0.072, p: 0.354). The clinical significance of this phenomenon is that stage migration is possible even if more than 15 nodes are resected; on the other hand, MLR is minimally confounded by stage migration.

divided into four ratio groups: 1-10%, 11-20%, 21-30%, and >30% according to MLR results, and overall survivals according to these groups were evaluated by log rank test. In that study, the best cutoff value was determined as 10% by using a receiver operating characteristic (ROC) analysis. They reported that MLR can be used as a reliable prognostic indicator. In a study from Italy, this ratio was determined by the best cutoff approach as follows: 1-9%, 10-25% and >25%. These authors noted that use of MLR for gastric cancer staging may improve the prognostic power of the current TNM staging system. It can be used in the selection of patients who may most benefit from adjuvant treatments (15). In the study by Bando et al. (6), the frequency of stage migration was 15% when the number of metastatic nodes was used for staging; the figure was only 7% with MLR. Other studies have also confirmed that this ratio is the most important prognostic factor and should be used in staging (16-18). The different cutoff values for MLR that have been reported in the literature may have been influenced by the number of patients. In our study, we established the cutoff points for MLR based on the statistical significance observed with increasing values of 20% as 0-0.20, 0.21-0.40 and >0.40 by using log rank test. These values are similar with other studies in the literature. However, there is no consensus on the appropriate cutoff value in the literature. Therefore, a consensus based on a greater number of patients should be established to determine more precise levels.

Lymph node involvement and depth of invasion are considered the main prognostic factors for patients with gastric cancer. In the present study, the tumor location, size, depth of invasion, number of involved nodes and MLR were found as statistically significant factors in univariate analysis. However, Cox regression analysis identified MLR as the only independent prognostic factor. Another study that included a similar number of patients from our country reported that the depth of invasion is not a prognostic factor in multivariate analysis (14). The most probable explanations for this conflicting data are the relatively lower number and higher ratio of our patients with T3.

The present study and the literature show that MLR is the most important prognostic factor and that its use is the most effective method for the prevention of stage migration. A new staging system based on MLR will be resistant to stage migration and will include the surgical approach in staging. However, further studies are required to determine appropriate cut-off values and the best approach in patients with less than 15 resected nodes.

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