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Can Modified Dukes' Classification be Used in Gastric Cancer Staging?

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Aim: Dukes' staging system is a simple system used widely in the staging of colorectal cancer. This study was designed to analyze the applicability of the modified Dukes' classification system in gastric cancer cases.

Methods: The prognostic factors affecting survival in 139 gastric cancer cases who had had at least 15 lymph nodes removed were analyzed. Modified Dukes' and TNM classifications were investigated to correlate statistically significant prognostic factors. The investigated prognostic factors were age, tumor size, histological type, differentiation, localization and number of the lymph nodes removed, and the ratio of number of metastatic lymph nodes to the number of lymph nodes removed.

Results: Tumor size >10 cm, muscularis propria and serosa invasion, >6 invaded lymph nodes and metastatic lymph node ratio >0.29 were statistically significant poor prognostic factors in multivariate analysis. The two staging systems were in correlation with these poor prognostic factors. There was no statistical difference between receiver operating characteristics curves of the two systems. When the survival curves were examined, it was seen that Dukes' staging had a more stepwise curve than the TNM system.

Conclusion: Dukes' staging system is in correlation with prognostic factors in gastric cancer. It can be easily recalled. Dukes' A stage when applied to gastric cancer defines a good prognosis group. The reclassification of T2N0 tumors as early gastric cancer is an area of speculation which needs to be investigated separately.

Key Words: Gastric cancer, Dukes' classification, prognostic factors, staging systems

Modifiye Dukes Sınıflaması Mide Kanseri Evrelemesinde Kullanılabilir mi?

Amaç: Dukes evreleme sistemi kolorektal kanser evrelemesinde yaygın olarak kullanılan basit bir evreleme sistemidir. Bu çalışma modifiye Dukes sınıflamasının mide kanseri olgularında uygulanabilirliğini araştırmak amacıyla düzenlenmiştir.

Yöntemler: Cerrahi de en az 15 lenf nodülü çıkarılmış 139 mide kanserli olgunun yaşam sürelerine etkili faktörler analiz edildi. Modifiye Dukes ve TNM evrelerinin bu prognostic faktörlerle olan korelasyonu saptandı. Araştırılan faktörler yaş, tümor büyüklüğü, histolojik tip, diferansiasyon, lokalizasyon, çıkartılan lenf nodülü sayısı, metastatik lenf nodülü sayısı ve metastatik lenf nodülü sayısının çıkartılan lenf nodülü sayısına oranıdır.

Bulgular: Tümör çapının 10 cm'den büyük olması, muskularis propria and seroza invazyonu, metastatik lenf nodülü sayısının 6'dan büyük olması, metastatik lenf nodülü oranının 0.29'dan büyük olması çok yönlü analizde istatistiksel anlamlı kötü prognostic faktörler olarak bulundu. Her iki evreleme sistemi de bu faktörlerle korelasyon gösteriyordu. Receiver operating characteristics curves (ROC) analizinde her iki evreleme sistemi arasında istatistiksel fark yoktu. Sağ kalım eğrileri incelendiğinde Dukes evrelemesi TNM'ye gore daha basamaklı bir eğriye sahipti.

Sonuç: Dukes evreleme sistemi mide kanserindeki prognostic faktörlerle korelasyon göstermektedir. Kolayca akılda tutulabilir. Dukes A stage evresi iyi prognoza sahip bir grubu tanımlar. T2N0 hastaların erken mide kanseri olarak tanımlanması ayrıca incelenmesi gereken bir konudur.

Anahtar Sözcükler: Mide kanseri, Dukes sınıflaması, prognostik faktörler, evreleme sistemleri

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Introduction

A tumor case is staged in order to obtain information about the patient's prognosis and to compare it with other case series. It is also useful in arranging the treatment and evaluating success. Preferably, staging systems should be simple, easily applicable and understandable.

For gastric cancer the two major tumor-related prognostic factors are depth of invasion and lymphatic invasion. Two systems that are widely used in gastric cancer staging are also based on these variables. One of these systems is a Japanese staging system developed by the Japanese Research Society for Gastric Cancer and the other, which is more widely used in Western countries, is the TNM staging system developed by the International Union Against Cancer (IUCC). Aside from serving as a means of staging, the Japanese system anatomically separates the gastric lymphatic system into groups, and it can be used as a guide for surgery. It is quite complicated and requires expertise. The modified version of the TNM classification, developed in 1997, takes into consideration the depth of invasion and number of lymph nodes. It is more practical and easily applicable than the Japanese classification system and is more widely used in Western societies. However, more than one patient group is found in each stage, which can be confusing (1,2,3). In the West, the decrease in gastric cancer incidence has led to less frequent gastric cancer operations by surgeons (4). This can be a factor limiting the application of the TNM system in clinical practice.

The Dukes' staging system is a simple system used widely in the staging of colorectal cancer. Its applicability in gastric cancer was studied by Adachi et al. (5), and was shown to be a simple and easily applicable prognostic system. In their study, the Dukes' system used in colorectal cancer was modified according to the number of invaded lymph nodes. It was determined that this system was in correlation with other prognostic factors influential in gastric cancer (6). There are also studies concerning its use in esophagus cancer (7). Gastric cancer characteristics and survival results in Western societies show significant differences from the results of Japanese studies. Therefore, widespread applicability of such a system requires studies done in various countries. This study was designed to analyze the applicability of the modified Dukes' classification system, to compare it with the TNM system and to investigate the correlation with prognostic factors in gastric cancer cases with more than 15 lymph nodes removed.

Patients and Methods

In this study, 441 cases that were operated for gastric cancer between January 1992 and November 2002 in the General Surgery Department, Uludag University Faculty of Medicine, were retrospectively reviewed. Inclusion criteria included cases with total or subtotal gastric resection and more than 15 lymph nodes dissected. Cases with distant or peritoneal metastases, gastrointestinal stromal tumors, diagnosis of gastric lymphoma, inadequate records, unknown survival period, and those who died in hospital in 30 days were excluded from the study. Type I and II tumors of esophagogastric junction were excluded but Type III tumors were included. After evaluation of these criteria, 142 cases with interventions other than resections, 76 cases with insufficient lymph node numbers, 17 cases with lymphoma and stromal tumor diagnosis, 13 exitus cases and 54 cases with inadequate records were excluded and totally 139 cases were included in the study.

The postoperative survival times and the prognostic factors affecting survival for the 139 cases included in the study were analyzed. The correlation between the statistically significant prognostic factors and the modified Dukes' system was investigated. The investigated prognostic factors were age, tumor size, histological type, Borman classification (according to pathologic description), differentiation, localization and number of the lymph nodes removed and the ratio of number of metastatic lymph nodes to the number of the removed lymph nodes (mln/rln). For Dukes' classification, the modified Dukes'classification as suggested by Adachi et al., which involved invasion depth and number of lymph nodes saved, was used (5,6). In this system, there are three groups in accordance with the original system. Dukes' A cases were cases with invasion of mucosa, submucosa and muscularis propria without lymphatic invasion. Dukes' B cases had subserosal or serosal invasion without lymph node involvement. Dukes' C cases were divided into two subgroups according to the number of invaded lymph nodes. Dukes' Ca were cases with any level of invasion of wall with 1-6 lymph nodes involved. Dukes' Cb cases had any level of invasion of wall with at least 7 lymph nodes involved. In Figure 1,

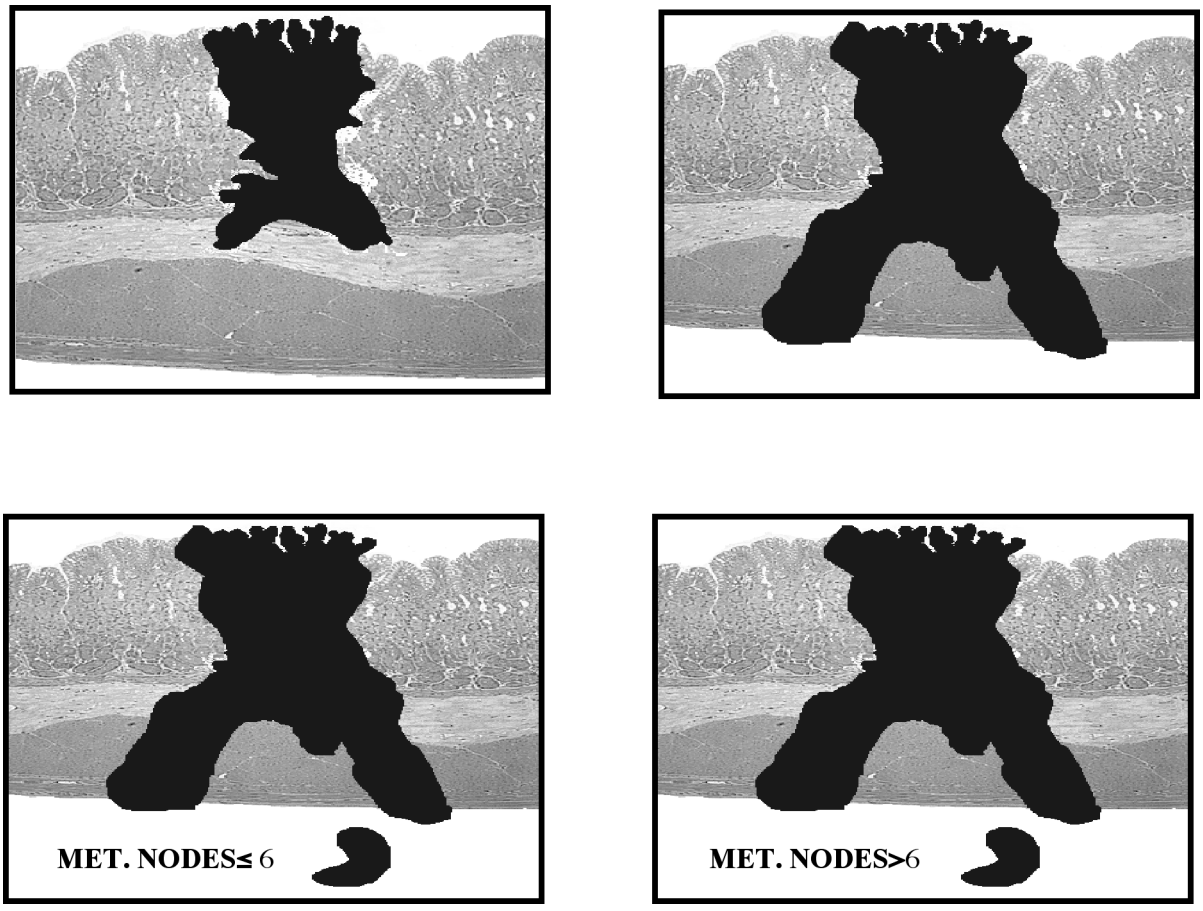


Figure 1. Modified Dukes' staging and corresponding TNM distribution.

modified Dukes' staging system and corresponding TNM distribution for each group is demonstrated.

The Statistical Package for Social Sciences (SPSS) version 10 (SPSS, Chicago, IL, USA) was used for all calculations. Fisher's exact and Mann-Whitney U tests were used for statistical comparisons of contingency tables and nonparametric values. Descriptive data were expressed as mean ± standard deviations. Pearson's correlation analysis was performed to describe the linear association between prognostic factors, Dukes' classification and TNM classification. Cut-off points were determined to class risk factors into two groups by the use of receiver operating characteristics (ROC). An ROC curve is simply a graph of sensitivity vs (1-specificity) for different values (which also change the sensitivity and specificity). The best value for balancing the sensitivity and specificity of the variable is the one represented by the point on the curve closest to the upper left-hand corner accepted cut-off. Comparison of ROC curves of Dukes'and TNM classification was performed. Survival curves were constructed by the Kaplan-Meier method. The significance of all investigated prognostic factors for postoperative survival was examined by log-rank test. In multivariate analysis of survival, Cox regression model was used to compare all prognostic factors found to be significant in univariate analysis in order to identify independent predictors of survival. A p value <0.05 was considered significant.

Results

Univariate analysis showed tumor size >10 cm, linitis plastica and proximal location, invasion depth, lymph node invasion, insufficient differentiation, and mln/rln ratio >0.29 to be significantly correlated with poor survival. The relationship between the investigated prognostic factors and survival are shown in Table 1.

Table 1. Results of univariate analysis (met: Metastatic. M: mucosa. sm: Submucosa. Mp: Muscularis propria. Ss: Subserosa, S: Serosa).

Risk Factor	Number of Patients	5-Year Survival (%)	Mean Survival (Month)	P Value
Invasion				
M,sm(T1)	8	100	65.1 ± 8.1	0.0002
Mp(T2)	17	61	93 ± 14	
Ss,S(T3)	103	22	57 ± 7.1	
(T4)	11	11	21 ± 9.8	
Nodal status				
N0	43	72	117 ± 10	0.00..
N1(1-6)	27	36	69 ± 16	
N2(7-15)	38	12	38 ± 7.2	
N3>15	31	6	13 ± 1.7	
Location				
Distal	56	34	67 ± 10	0.016
Midgastric	51	61	75 ± 9.6	
Proximal	25	0	32 ± 7.5	
Diffuse	7	0	11 ± 3.3	
Organ resection				
Present	49	25	39.7 ± 5.6	0.06
Absent	90	35	41.4 ± 5.32	
Size				
<5 cm	39	61	101 ± 12	0.00..
5-10 cm	74	27	59 ± 8.6	
>10 cm	26	0	23 ± 6.2	
Borman classification				
Type 1	5	20	26 ± 5.3	0.042
Type 2	16	78	123 ± 15	
Type 3	84	34	67 ± 8.5	
Type 4	34	14	37 ± 8.6	
Differentiation				
Good	7	50	85 ± 32	0.045
Moderate	43	28	71 ± 12	
Poor	89	30	52 ± 6.2	
No of met. lymp node				
<4	63	73	115 ± 8.8	0.00..
≥4	76	9	30 ± 4.6	
Ratio of met. node				
≤0.29	74	65	111 ± 8.6	0.000
>0.29	65	2	19 ± 2.2	
TOTAL	139	33	66.6 ± 6.47	

Prognostic factors significant in univariate analysis were investigated in multivariate analysis. In multivariate analysis, tumor size >10 cm (odds ratio: 4.69, p: 0.03), muscularis propria (odds ratio: 4.7, p: 0.029) and serosa invasion (odds ratio: 4.9, p: 0.026), number of invaded lymph nodes >6 (odds ratio: 3.7, p: 0.045) and mln/rln ratio >0.29 (odds ratio: 7.5, p: 0.006) were significant independent prognostic factors (Table 2). It was determined that the two staging systems were in correlation with these poor prognostic factors in correlation analysis.

Overall five-year survival rate was 33%; the mean overall survival was 66.6 months. In Figure 2, survival curve for all cases is shown. Sensitivity and specificity for both staging systems were investigated by ROC analysis. Cut-off points were determined as stage Ca for Dukes' staging and IIIA for TNM staging. For these cut-off points, sensitivity and specificity of Dukes'staging were 70% and 81.3% versus 71.6% and 79.3%, respectively, for TNM staging. There was no statistical difference between ROC curves of these two systems (p: 0.561). The results of ROC analysis are presented in Table 3.

Table 2. Results of multivariate analysis (Rate: Ratio of number of metastatic lymph nodes to number of the removed lymph nodes).

Factor	Odds Ratio	P Value
T2 Invasion	4.7	0.029
T3 Invasion	4.9	0.026
Size >10 cm	4.69	0.03
Positive Node >6	3.7	0.045
Rate > 0.29	7.5	0.006

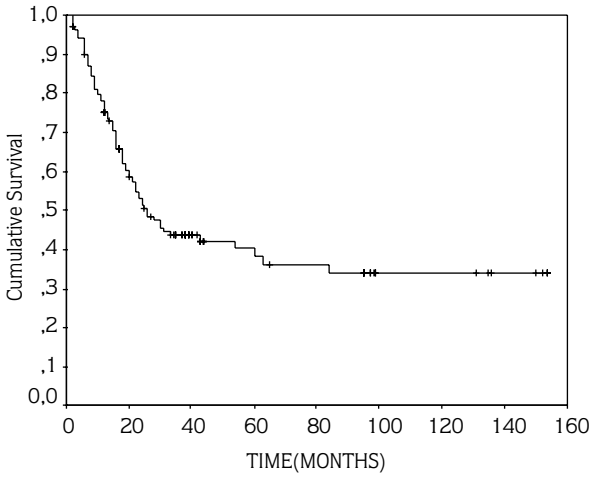
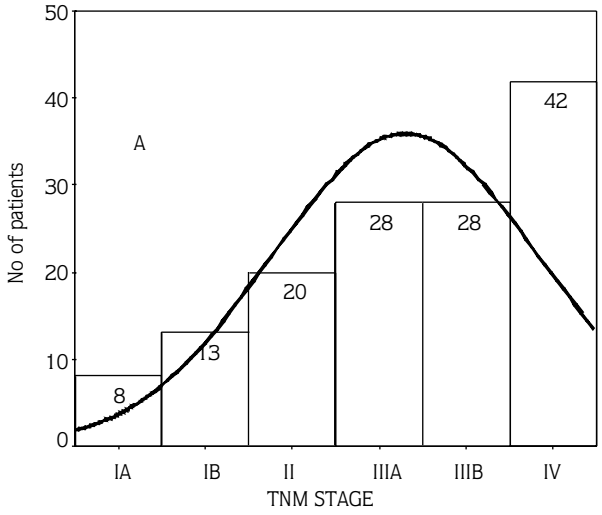


Figure 2. Kaplan-Meier survival curve for all patients. The five-year survival was 33% and mean survival time was 66.6 months.

Most of our cases were in advanced stages. Distribution of cases according to stage is shown in Figure 3. Five-year survival rates were 100% in Dukes' A stage, 84% in Dukes' B stage (mean survival: 131 months), 30% in Dukes' Ca stage (mean survival: 59 months), and 9% in Dukes' Cb stage (mean survival: 30.8 months). Excluding between Dukes' stages A and B, there were statistically significant differences in survival times between stages (p: 0.25 = Dukes' A vs B, p: 0.001 = Dukes' B vs Ca, p: 0.008 = Dukes' Ca vs Cb). According to TNM staging system, five-year survival in stage IA was 100% and in stage IB 87% (mean survival: 89 months), in stage II 85% (mean survival: 132 months), in stage IIIA 28% (mean survival: 58 months), in stage IIIB 12% (mean survival: 40 months) and in stage IV 7% (mean survival: 18 months). There were no statistically significant differences between stages IA, IB and II;

Table 3. The results of ROC analysis (CI: Confidence interval. AUC: Area under curve). There was no statistically significant difference between staging systems (p: 0.561).

Staging System	Criteria of cut-off point	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
Dukes staging	Ca	%70 (61.9–84.1)	81.3 (71.2–92.2)	0.844 (0.766–0.904)
TNM staging	IIIA	%71.60 (62.3–85.2)	79.3 (70.4–91.3)	0.865 (0.791–0.921)



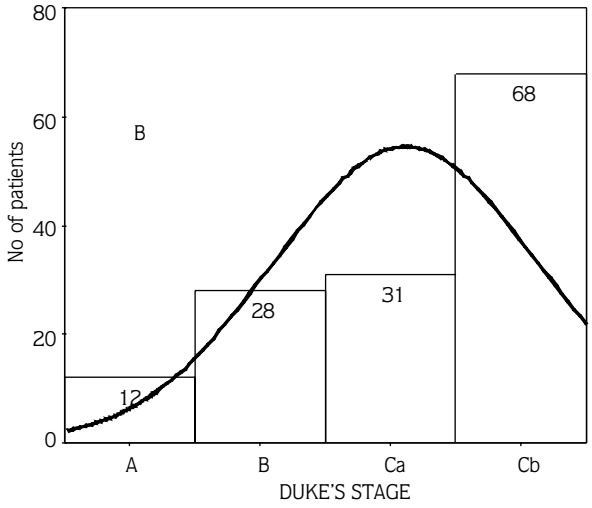
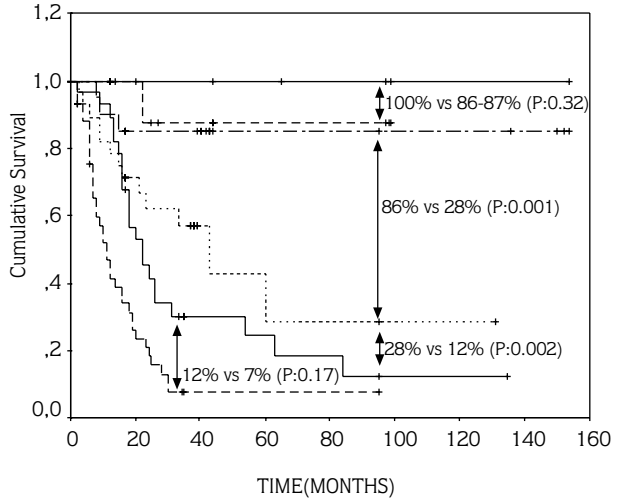


Figure 3. Distribution of cases according to stages for the two classification systems.



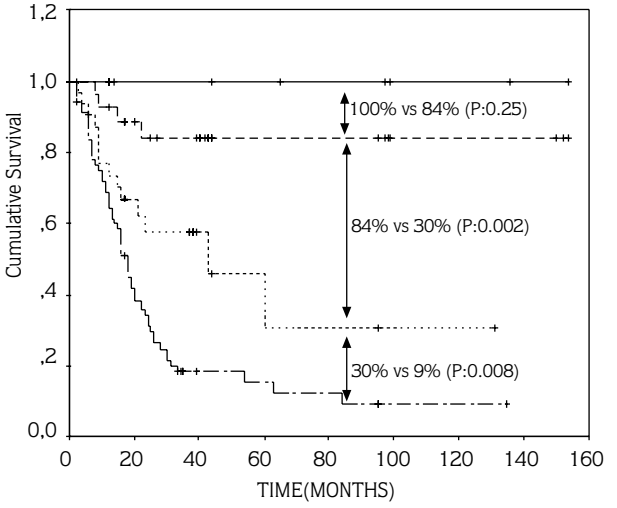


Figure 4. Survival analysis for both classification systems. There were statistically significant differences between Dukes'stages excluding between stages A and B. For TNM classification, there were no statistically significant differences between stages IA, IB and II, but difference started with stage IIIA. There was no significant difference between stage IIIB and IV.

statistically significant difference began after stage IIIA. There was no statistically significant difference between stage IIIB and IV (p: 0.32 = stage IA vs IB, p: 0.76 = stage IB vs II, p: 0.001 = stage II vs IIIA, p: 0.002 = stage IIIA vs. IIIB, p: 0.17 = stage IIIB vs. IV). Survival analysis results according to both systems are shown in Figure 4.

In the subgroup investigation of our cases, number of T1N0 cases was 8 and all were alive. There was only 1 T1N1 case. Only 1 of 13 cases in T2N0 was exitus (92%). There was no statistically significant difference for survival between the two groups (p: 0.68).

Discussion

There have been many studies in the literature that investigated various prognostic factors affecting survival in gastric cancer. Prognostic factors determined in our series were in agreement with most of them (8,9,10). According to results of the multivariate analysis, invasion depth, tumor size, positivity of lymph nodes and mln/rln ratio were found to be independent prognostic factors. Mln/rln ratio has been frequently used as a prognostic indicator,

especially in Western publications, and it is accepted to be an objective measure of the quality of lymph dissection (11,12,13). Although different ratios have been reported in the literature, ROC analysis in our study determined the highest sensitivity and specificity values at a level of 0.29. According to our results, a lower mln/rln ratio indicates better survival. In cases with lymph node involvement, it will be appropriate to achieve at least a 0.29 ratio. Dukes' staging system has been widely used for 60 years especially in colorectal cancer staging. This system is a simple and valuable staging system based on invasion depth and whether or not there is lymph node involvement. Adachi et al. was the first to apply it in gastric cancer staging (5). In this study, the C stage of the original Dukes' staging system was modified by dividing it into two stages according to number of metastatic lymph nodes as Ca (1-6 nodes) and Cb (>6 nodes). In gastric cancer staging, the modified Dukes' system was considered to be a simple and easily applicable staging system. One such study conducted by the same authors in recent years showed that this system was in correlation with prognostic factors, tumor progression and patient survival (6). In our study, all the prognostic factors obtained were in correlation with both TNM and the modified Dukes' staging system. The most significant characteristic of the modified Dukes' staging is that it emphasizes lymph node involvement. For this staging system, the cut-off point was found to be Ca in ROC analysis, and this point is the first stage of lymph node involvement. When the survival curves were examined, it was seen that Dukes' staging had a more stepwise curve than the TNM system.

Many studies have shown the efficiency of these widely used staging systems in survival analysis. The TNM system in particular has been widely accepted and is known to be an appropriate system to estimate survival (14,15). Is there a need for a new system in addition to these two in which prognostic values have been shown? We believe the answer is "yes" for two reasons. First, although the TNM system is not as complicated as the Japanese system, it can be difficult to recall in daily practice, especially in Western countries, because of the decreasing incidence in gastric cancer and the fall in operation numbers per surgeon per year (16,17). In the TNM system, one stage can include different types of tumors such as T1N2M0 and T2N1M0. Patients with these types of gastric cancer are accepted as stage II. The second reason is related to the early diagnosis of gastric cancer. The incidence of early gastric cancer is 35-60% in a Japanese series and 20-25% in Western countries, whereas this ratio is below 5% in developing countries (4). In our study, the incidence of early gatric cancer was 17/441 (3.8%) for all patients and 9/139 (6.4%) for patients included in the study. This indicates a major health problem in our country. In early gastric cancer cases, nodal invasion is the most important factor affecting prognosis (18,19). In many studies, although there is a significant survival difference between T1N0 and T1N1 cases, survival is fairly good in T2N0 cases. Similar findings were obtained in the study made by Kikuchi et al. (20), in which 848 early gastric cancer cases were investigated. Ten-year survival rate related to cancer was 87.2% for node-positive cases and 99.2% for -negative cases. In multivariate analysis, lymph node positivity has a 6.9-fold negative effect on survival. The difference between node-negative and -positive early gastric cancer prognosis increases especially in 10-year survivals. In the study in which Nogueira et al. (21) presented their 10-year experience in early gastric cancer, while it was found that presence of lymph node invasion is the most important factor affecting survival, invasion depth was not determined to relate with survival period. Adachi et al. (22) divided 217 patients into three groups as T1N0, T2N0 and T1N1 and determined 10-year survival rates in their study as 94.7%, 96.9% and 85.1%, respectively. In the T1N1 group, survival is statistically significantly less. Cases in Dukes' A may be defined as early gastric cancer (22,23,24,25). Our results also support these findings. In series in which the number of T1 cases is few, like ours, including T2N0 cases in this group will increase the number of patients in this series. This finding, especially in countries like Turkey where early gastric cancer cases are extremely low, calls to mind the need for a new definition for early gastric cancer.

There may be two points of criticism of the analysis of the series presented. First, 139 cases were included in the study from among 441 cases operated. Second, it was started not five but two years retrospectively. Though including 139 cases from 441 in our study can be seen as limiting the value of our results, the rate of cases excluded from the study because of lack of survival follow-up and inadequate records was only 12% (54/441). The main problem is the excessive number of cases with palliative surgical procedures and number of lymph nodes removed of <15, which were removed when resection was done. This situation can be seen as the case characteristic of our country and an indication of inadequate lymph gland dissection in our clinic. As our cases were mostly at

advanced stage, follow-up started two years later, which is a sufficient period for evaluating survival in these cases.

In conclusion, Dukes' staging system is in correlation with prognostic factors and can be easily recalled. This study, which is the first series outside Japan with respect to the applicability of the system, is in agreement with other studies. Application of Dukes' A stage in defining early gastric cancer is one of the other important results of our study and literature data. However, our case number is insufficient to make a definite interpretation.

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