

Factors affecting mortality in elderly patients who underwent surgery for gastric cancer



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Factors affecting mortality in elderly patients who underwent surgery for gastric cancer

AIM: *The aim of this study was to determine factors affecting overall mortality in patients over 60 years of age who underwent surgery for gastric cancer in our clinic.*

MATERIAL AND METHODS: *Data on histopathological diagnosis (tumor size, lymph node status, and number), pathological stage, serum albumin level, tumor markers, complete blood count, and demographic information of 109 patients over 60 years of age who had surgery for gastric cancer between January 2011 and July 2016 were obtained retrospectively from the patient files. In addition, the survival status of all patients were examined and recorded. Metastatic lymph node ratio (MLR), red cell distribution width platelet ratio (RPR), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and prognostic nutritional index (PNI) were calculated.*

RESULTS: *On univariate analysis of independent parameters, pathological LN number ($p = 0.001$), MLR ($p < 0.001$), T3 ($p = 0.001$) or T4 ($p = 0.006$) tumor stage according to TNM system, the presence of metastasis ($p = 0.063$), and male gender ($p = 0.066$) were found to affect overall mortality (OM). On multivariable Cox regression analysis of these results, MLR ($p = 0.005$) and T stage ($p = 0.006$) was determined to be a statistically significant and independent prognostic value.*

CONCLUSION: *In patients over 60 years of age who underwent surgery for gastric cancer, the factors affecting mortality were determined to be the presence of metastases, number of pathological lymph nodes, and male gender. Metastatic lymph node ratio and T1&T2 stage were determined to be independent prognostic factors.*

KEY WORDS: Elderly, Gastric cancer, Mortality, Prognostic factor

Introduction

The average life span of humans has gradually been increasing. The ratio of the population over 60 years of age is expected to rise from 12% to 22% between 2015

and 2050¹, and social and healthcare systems will inevitably face new difficulties. One of these difficulties is gastric cancer, which is common in the elderly. According to the American National Cancer Institute², the median age for gastric cancer diagnosis is 69 years. In 2016, 26,370 people are expected to receive a diagnosis of gastric cancer and 10,730 people are expected to die from gastric cancer². Well known factors which affect overall survival are tumor size, lymph node extension, type of surgery, and presence of severe complications³. The aim of our study was to determine the factors affecting overall mortality in the elderly for gastric cancer, which is also increasing in frequency in Japan because it mostly affects the elderly.

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Materials and Methods

Approval from the ethics committee was received for this study (Ethics Committee 16.11.2016/E-16-1100). Data on demographics (i.e., age and gender), surgical operation performed (total/subtotal gastrectomy), histopathological diagnosis (tumor size, lymph node status, and number), tumor grade, serum albumin level, tumor markers, and whole blood count in all patients over 60 years of age who underwent surgery for gastric cancer between January 2011 and July 2016 in Ankara Numune Research and Training Hospital, Department of General Surgery were examined and recorded. Metastatic lymph node ratio (MLR), RDW/ Platelet ratio (RPR), Prognostic Nutritional Index (PNI), neutrophil-lymphocyte ratio (NLR), and platelet/lymphocyte ratio (PLR) were calculated from these data. In addition, the survival status of all study patients was obtained via telephone interviews and population databases. These parameters represented the independent study variables. The end point of the study was identification of the prognostic factors that affected overall mortality.

Patients with missing or inaccessible data and those who are receiving neoadjuvant chemotherapy were excluded from the study. The Cancer Staging Manual of the American Joint Committee on Cancer was used for disease staging⁴. Patients with T1 and T2 tumor stages were grouped and compared with patients with T3 and T4 tumor stages. (Table I)

STATISTICAL ANALYSIS

The descriptive statistics of the data were given as median (minimum- maximum) and frequency (percentage) for continuous and categorical variables respectively. The comparisons across the groups were made by using the Mann Whitney U test, Chi-Square test and Fisher's Exact Test as appropriate. Independent risk factors of mortality were defined using Logistic regression analysis and any clinically plausible variable whose univariate logistic regression analysis had a p-value less than 0.25 was considered as a candidate risk factor and was included in the multiple logistic regression models. Backward likelihood ratio stepwise method was used for variable selection and the final model was obtained. p values less than 0.05 were considered to be significant. Due to variations of the definition of geriatric population an age subgroup was formed with patients equal to or above 65 years of age. Same analyses were carried out with the same endpoints within this age 65 subgroup.

Results

A total of 109 patient files were accessed. Of these, 69 patients were male and 40 were female. The mean age

was 70.88±6.76 years. It was observed that 72 patients (50 male, 22 female) died (%66.1) and 37 patients (19 male, 18 female) survived (%33.9). The mean age was 71.05±6.86 years for the patients who died and 70.56±6.64 years for those who survived. There were distant metastases in 13 patients. Only one of them was in the living patients group. Ninety-six patients were in early and local advanced disease stage and had curative resection (subtotal or total gastrectomy + D2 lymph node dissection). 19 out of 109 patients (17.4%) deceased in the postoperative 30 days period which was considered as operative mortality. All pathology was gastric adenocarcinoma. Descriptive data of the variables including T tumor stage and grade are listed in Table 1. Mean number of total lymph nodes was 19.93±11.80, whereas mean number of metastatic lymph nodes was 6.85±8.05. No metastatic lymph nodes were found in the specimens of 27 patients (24.8%). Mean number of total lymph node in this specific group of patients was found 17.26±12.83. On univariate analysis of independent parameters and overall mortality (OM), gender (p=0.066), T stage of tumor (p = 0.002), presence of metastasis (p=0.063), metastatic LN number (p=0.001), and MLR (p<0.001) were significant. None of the other variables were found significant on univariate analysis. On multivariate Cox regression analysis, MLR (p = 0.005) and T tumor stage (p = 0,006) were statistically significant independent prognostic variables (Table II).

There were patients aged 65 or older. Of these patients 35 (38.9%) were female and 55 (61.1%) were male. Mean age was 72.87±5.71. In this subgroup, T stage of tumor (p=0.003), metastatic LN number (p=0.001), and MLR (p<0.001) were significant on the univariate analysis. Number of patients without distant metastasis was inadequate to draw a related statistical outcome on univariate analysis. On multivariate Cox regression analysis MLR (p=0.002) and T tumor stage (p=0.014) were statistically significant.

Discussion

Cancer is considered to be the second most frequent cause of mortality after cardiovascular diseases in developed countries, and the third most frequent cause of mortality in developing countries⁵. In a recently published, large-scale study that assessed the utility of radical surgery in elderly patients with gastric cancer, being over 80 years in age and having a TNM stage of more than 2 were shown to be independent risk factors for both general mortality and disease-free survival (DFS)⁶. In another large-scale study with over 600 patients, elderly gastric cancer patients' overall survival was compared with young patients'. There was no significant difference regarding overall survival between two age groups⁷. In a comparative study of patients in the age range of 65-74 and 30-34 years by Wang et al., the male mortality

TABLE I - Descriptive statistics of the patients.

	Living	Deceased
Patients N (%)		37 (33.9)
Gender N (%)		72(66.1)
<i>Male</i>		19 (27.5)
<i>Female</i>		18 (45.0)
Age		
Median (Min-Max)	71 (60-90)	70 (60-90)
Mean \pm SD	70,57 \pm 6,64	71,06 \pm 6,86
Tumor T (%)		
<i>T1</i>	5 (71.4)	2 (28.6)
<i>T2</i>	10 (66.7)	5 (33.3)
<i>T3</i>	15 (24.6)	46 (75.4)
<i>T4</i>	7 (26.9)	19 (73.1)
Surgery (%)		
<i>Total Gastrectomy</i>	16 (29.6)	38 (70.4)
<i>Subtotal Gastrectomy</i>	20 (37.0)	34 (63.0)
Metastasis(%)	1 (2.7)	12 (16.7)
Tumor Differentiation (%)		
<i>Poorly differentiated</i>	15 (28.3)	38 (71.7)
<i>Moderately differentiated</i>	16 (41.0)	23 (59.0)
<i>Well differentiated</i>	3 (30.0)	7 (70.0)
Total Lymph Node Number		
Median (Min-Max)	17 (0 – 52)	20 (0-60)
Metastatic Lymph Node Number		
Median (Min-Max)	1 (0-30)	6 (0-31)
Albumin (g/dL)		
Median (Min-Max)	3,51 (0.33-4.80)	3,70 (1.96 -5.10)
Mean \pm SD	3,46 \pm 0,98	3,65 \pm 0,73
Carcinoembryonic Antigen (ng/mL)		
Median (Min-Max)	2,07 (0.94-23.23)	2,30 (0.41-1084.00)
Mean \pm SD	3,41 \pm 4,52	25,44 \pm 154,40
Carbohydrate Antigen 19.9 (μ g/mL)		
Median (Min-Max)	18,18 (0.80-299.70)	13,91 (0.60-1542.00)
Mean \pm SD	43,53 \pm 68,48	122,83 \pm 308,54
Alpha Fetoprotein (ng/mL)		
Median (Min-Max)	2,37 (0.60-10.29)	2,20 (0.67-57.75)
Mean \pm SD	2,84 \pm 2,16	4,78 \pm 9,83
Red cell Distribution Width (%)		
Median (Min-Max)	15,60 (1.95-28.00)	14,40 (12.20-30.00)
Mean \pm SD	16,71 \pm 4,16	16,23 \pm 3,98
Platelet Count ($\times 10^3/\mu$ L)		
Median (Min-Max)	266,50 (117-497)	255 (10-867)
Mean \pm SD	286,86 \pm 97,93	261,77 \pm 115,15
MLR		
Median (Min-Max)	0,04 (0-1)	0,39 (0-1)
Mean \pm SD	0,18 \pm 0,27	0,43 \pm 0,32
RPR		
Median (Min-Max)	0,06 (0.01-0.15)	0,06 (0.02-1.82)
Mean \pm SD	0,064 \pm 0,028	0,094 \pm 0,210
NLR		
Median (Min-Max)	2,76 (1.27-27.74)	2,81 (0.25-36.53)
Mean \pm SD	4,37 \pm 5,15	3,97 \pm 4,78
Prognostic Nutritional Index		
Median (Min-Max)		
Mean \pm SD	12,22 (6.77-19.35)12,04 \pm 3,23	11,80 (3.14-30.85)12,18 \pm 4,07
PLR		
Median (Min-Max)	166,19 (71.03-485.19)	157,07 (6.41-1382.35)
Mean \pm SD	187,96 \pm 96,47	202,43 \pm 193,08

N: Number, Min-Max: Minimum- Maximum, SD: Standard deviation, MLR: Metastatic lymph node ratio, RPR: Red cell distribution platelet ratio, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio

TABLE II - Results of the univariate and the multivariate logistic regression analysis.

Univariate	Multivariate			OR ^a	95% CI	p
	OR	95% CI	p			
Gender						0,066
<i>Female</i>	1,000					
<i>Male</i>	2,153	0,951-4,873				
Age (1 year increase)	1,011	0,953-1,073	0,720			
Tumor T Stage						0,002
<i>T1 - T2</i>	1,000			1,000		
<i>T3</i>	6,571	2,254-19,154	0,001	7,353	2,167-24,950	0,001
<i>T4</i>	5,816	1,671-20,247	0,006	4,244	1,020-17,663	0,047
Surgery						0,415
<i>Total Gastrectomy</i>	1,000	0,320-1,599				
<i>Subtotal Gastrectomy</i>	0,716	0,898-57,714	0,063			
Metastasis	7,200		0,432			
Tumor Grade						
<i>Poorly differentiated</i>	1,000					
<i>Moderately differentiated</i>	0,567	0,237-1,360	0,204			
<i>Well differentiated</i>	0,921	0,210-4,041	0,913			
Lymph Node Count (1 unit increase)	1,016	0,981-1,052	0,376			
Metastatic Lymph Node Count (1 unit increase)	1,159	1,058-1,270	0,001			
Albumin (g/dL - 1 unit increase)	1,327	0,815-2,163	0,256			
Carcinoembryonic Antigen (1 unit increase in ng/mL)	1,005	0,960-1,053	0,816			
Carbohydrate Antigen 19.9 (1 unit increase in µg/mL)	1,002	0,999-1,005	0,290			
Alpha Fetoprotein (1 unit increase in ng/mL)	1,051	0,925-1,195	0,447			
Red cell Distribution Width (1 unit increase in %)	0,971	0,879-1,072	0,559			
Platelet Count (1 unit increase)	0,998	0,994-1,002	0,272			
MLR (0,1 unit increase)	1,342	1,139-1,582	<0,001	1,289	1,079-1,540	0,005
RPR (0,1 unit increase)	1,667	0,417-6,749	0,467			
NLR (1 unit increase)	0,984	0,908-1,066	0,687			
Prognostic Nutritional Index (1 unit increase)	1,010	0,907-1,125	0,857			
PLR (1 unit increase)	1,001	0,998-1,003	0,673			

OR: Odds Ratio, CI: Confidence interval, MLR: Metastatic lymph node ratio, RPR: Red cell distribution platelet ratio, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio; ^a: Adjusted for Age

rate was 12 times higher in the 65-74 age group than the 30-34 age group. However, the female mortality rate was only 4.4 and 4.9 times in the age range of 65-69 and 70-74, respectively ⁸. Sakurai et al. compared patients over 80 years of age and between 60-69 years of age who underwent surgery for gastric cancer and found that less adjuvant therapy was required in the older group ⁹. Survival was found to be worse in the patients with stages 2 and 3 gastric cancer compared to the control group. Another study in our clinic on factors affecting mortality in 170 patients with gastric cancer found that age, neutrophil lymphocyte ratio, and MLR were independent risk factors ¹⁰. In this study, all patients over 60 years of age who had gastrectomy due to gastric cancer were evaluated; however, there was no statistically significant effect of age on mortality within our study populations.

The most important, salient finding of our study was that on multivariate analysis, MLR was identified as an independent variable affecting overall mortality in our elderly group of patients. MLR is considered to affect prognosis and mortality not only in elderly patients but also in all gastric cancers ¹⁰. Yamashita et al. concluded that MLR was better than lymph node stage in determining patient prognosis in advanced gastric cancer ¹¹. Komatsu et al. conducted large-scale study on patients who had curative resection for gastric cancer and showed that the ratio of lymph nodes contributed to prognosis ¹². In another broad study, MLR was observed to be a determining prognostic factor, especially in stage 3 gastric cancer patients who had undergone surgery ¹³. In a recent study by Cong et al., per-operative lymphocyte monocyte ratio was shown to affect prognosis in stage 2 or 3 patients over 75 years of age ¹⁴.

Another independent variable which was found to affect overall mortality was tumor T stage in our study. Due to inadequate number of patients with T1 or T2 tumors we evaluated all T1 and T2 stage patients in one group and compared their overall survival with patients with T3 and T4 tumors. Age adjusted odds ratios were found 7,353 and 4,244 in patients with T3 and T4 tumors, respectively. This expected finding can be considered as a proof of the survival advantage of the patients with early gastric cancer¹⁵.

In a 2016 study on patients over 70 years of age with gastric cancer, multivariate analysis showed that old age, male gender, low body mass index, low prognostic nutritional index, and high tumor grade had negative effects on overall mortality¹⁶. In our study, which was conducted in a similar patient group, age, prognostic nutritional index, and grade were not statistically significant even on univariate analysis. On the other hand, the increasing effect of male gender on mortality seemed to be significant on univariate analysis; however, it lost its effect on multivariate analysis that included age. In Cong's study, lymphocyte monocyte ratio was shown to affect prognosis in stage 2 or 3 patients over 75 years of age (14). Although, in a previous study of 170 patients with gastric cancer, we showed on multivariate analysis that lymphocyte-monocyte ratio and RDW/thrombocyte ratio affected mortality, it was not shown in this study of elderly subjects. This may be due to differences in hematological responses in the elderly group or inadequacy of sample size. In a study conducted by Hsu et al., low preoperative LMR was shown to be a poor prognostic factor in gastric cancer patients who had undergone surgery¹⁷.

Gastric cancer increases with age and is a very difficult disease in the elderly. Discussions on different ways to manage gastric cancer, which has a high mortality rate in the elderly and to evaluate non-surgical approaches are being conducted. In the study of Gong et al., two groups of patients over 80 years of age, who underwent curative resection and were treated conservatively, were compared. Apart from stage 4 patients, the resection cases showed a higher overall survival rate than conservatively treated patients. However, a survival effect of lymph node dissection in different stages was not observed¹⁸. In the study of Nashimoto et al., a positive contribution of surgery to survival was mentioned for female patients with advanced gastric cancer who were in the age range of 85-89 years. However, it is stated that the best strategy in advanced age groups of male patients with gastric cancer, in patients over 90 years old, or in patients with early gastric cancer was supportive care¹⁹. Mortality rates and factors affecting mortality will undoubtedly determine the management of gastric cancer in the elderly. In this study, MLR was found to be associated with increased mortality in the elderly group of patients. On the other hand, it is noteworthy that age, gender, tumor grade, and the number

of lymph nodes did not affect mortality. When evaluated together with data available in the literature, it is understood that the prognosis of patients with gastric cancer varies compared to the general population.

The definition of geriatric population is changing worldwide as World Health Organization pointed out²⁰. With this point of view, we defined a subgroup with patients aged 65 or older and run the same statistical analysis within this subgroup to provide more information. Our results were quite similar with the main study population with lesser values of significance due to smaller size of the subgroup population. Age remained insignificant as a predictor of mortality. On the other hand T tumor stage and MLR were found to be the main predictors of mortality. We were unable to analyze metastasis as a predictor due to inadequate number of patients in this subgroup.

Major weakness of this study is its retrospective design. A prospective study with a long term follow-up would provide better results. Another weak point of our study is that our study population only includes patients who underwent total or subtotal gastrectomy. As a result of this selection criterion, patients with preoperative diagnosis of distant metastasis became excluded unless palliative gastrectomy was required. This may have led to a selection bias especially in patients with higher stages of gastric cancer. One last weakness of this study is that data related with comorbidities

Conclusion

For patients over 60 years of age who underwent surgery for gastric cancer, on univariate analysis of independent factors that could influence mortality, presence of metastases, number of pathological lymph nodes, and male gender were found to be statistically significant. One multivariate analysis of these variables, metastatic lymph node ratio was found to be an independent prognostic factor. Broader, prospective, studies with long term follow up are still needed to clarify factors affecting mortality for elderly patients with gastric cancer

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