

Short-term Prognostic Value of Tumor Diameter in Stage 2 and 3 Gastric Cancer

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ABSTRACT

Objective: To investigate the prognostic value of tumor diameter in the short term of 3 and 5 years in patients operated for gastric cancer.

Study Design: A descriptive study.

Place and Duration of Study: Kartal Dr Lutfi Kirdar City Hospital, Istanbul, Turkey, from January 2014 to December 2018

Methodology: A total of 125 patients with stage 2 or 3 gastric cancer, followed up in the Department of General Surgery, were included. Demographic information, clinical, laboratory, and pathology reports were analysed in terms of postoperative 30-day mortality.

Results: The mean age of the patients was 63.9 ± 11.9 (31-88) years. Forty-four (35.2%) were in stage 2, and 81 (64.8%) were in stage 3 cancers. The mean tumor diameter was 6.5 ± 3.1 cm, and the mean metastatic lymph node rate was $35.6 \pm 29.8\%$. The mean follow-up period was 31.8 ± 21 months. The 3-year and 5-year survival rates were 39.8% and 17.6%, respectively. Tumor diameter was not directly related to survival, differentiation, number of resected lymph nodes, number of metastatic lymph nodes, and metastatic lymph node rate in stage 2 and 3 cases ($p > 0.05$ for each). The 5-year mortality risk was 1.2-fold higher in those with tumor diameter over 6.5 cm (95% CI 0.7-2.0; $p = 536$).

Conclusion: The tumor size did not have a direct effect on prognosis. It did not provide reliable data about short-term prognosis such as 3 and 5 years in stage 2 and 3 gastric cancer cases.

Key Words: Gastric cancer, Stage 2, Stage 3, Tumor size, Prognosis.

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INTRODUCTION

Gastric cancers are among the most common cancers, and the most common causes of death in the world. Generally, their prognosis is poor, and determining the prognosis is critical. Factors such as stage, invasion, metastasis, lymph node metastasis, and location, diameter and depth of the tumor are valuable in determining the prognosis in gastric cancer cases.¹⁻³

The longest diameter value of the primary tumor is important in planning the surgical operation method, and in determining the risk group in gastric cancer cases. In general, tumor diameter and number of metastatic lymph nodes can provide important information in predicting prognosis.³⁻⁷ However, in stage 2 and 3 cases, there are not much data on whether the tumor diameter and other prognostic parameters have value or whether they indicate an additional mortality risk.^{3,4}

In the present study, it was aimed to investigate whether the tumor diameter has a prognostic value and its relation with the number of lymph nodes resected during the operation, the number of metastatic lymph nodes and the rate of metastatic lymph nodes in patients with stage 2 and 3 gastric cancer.

METHODOLOGY

The present study was approved by the Local Ethics Committee (date: 30/12/2020; approval number: 514/192/40) and was planned retrospectively.

A total of 125 patients followed up after radical resection of gastric cancer at the Department of General Surgery, Kartal Dr Lutfi Kirdar City Hospital, Istanbul, Turkey, between January 2014 and December 2018, who were stage 2 or 3 as a result of pathological staging, were included in the study. The demographic information of the patients, the results of the pathological examinations of the tumor, and the survival time of the patients, were obtained from the hospital records. Patients who received neoadjuvant chemotherapy, those with liver, lung or other distant organ metastases, and those who underwent surgery other than total or subtotal radical gastrectomy, were excluded from the study.

All statistical analyses were performed using SPSS version 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data were given as mean \pm S.D, numbers and percentages.

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Table I: Distributions of the variables in terms of survival [n (%)].

	n (%)	3-year OS		5-year OS	
		Dead n=56 n (%)	Alive n=37 n (%)	Dead n=56 n (%)	Alive n=12 n (%)
Gender					
Male	74 (59.2)	33 (58.9)	24 (64.9)	33 (58.9)	7 (58.3)
Female	51 (40.8)	23 (41.1)	13 (35.1)	23 (41.1)	5 (41.7)
p		0.565		>0.999	
Age (years)					
≤60	45 (36.0)	24 (42.9)	10 (27.0)	24 (42.9)	2 (16.7)
>60	80 (64.0)	32 (57.1)	27 (73.0)	32 (57.1)	10 (83.3)
p		0.121		0.112	
Type of gastrectomy					
Total	83 (66.4)	30 (53.6)	26 (70.3)	30 (53.6)	9 (75.0)
Subtotal	42 (33.6)	26 (46.4)	11 (29.7)	26 (46.4)	3 (25.0)
p		0.107		0.173	
Differentiation					
Well differentiated	6 (4.8)	3 (5.4)	2 (5.4)	3 (5.4)	0 (0)
Moderately differentiated	49 (39.2)	23 (41.1)	11 (29.7)	23 (41.1)	6 (50.0)
Poorly differentiated	70 (56)	30 (53.6)	24 (64.9)	30 (53.6)	6 (50.0)
p		0.529		0.653	
Tumor diameter					
<6.5 cm	71(56.8)	34 (60.7)	22 (59.5)	34 (60.7)	7 (58.3)
>6.5 cm	54(43.2)	22 (39.3)	15 (40.5)	22 (39.3)	5 (41.7)
p		0.904		>0.999	
Tumor diameter					
<5.25 cm	51 (40.8)	27 (48.2)	13 (35.1)	27 (48.2)	7 (58.3)
>5.25 cm	74 (59.2)	29 (51.8)	24 (64.9)	29 (51.8)	5 (41.7)
p		0.212		0.525	
Number of resected lymph nodes					
<18.5	56 (44.8)	29 (51.8)	11 (29.7)	29 (51.8)	5 (41.7)
>18.5	69 (55.2)	27 (48.2)	26 (70.3)	27 (48.2)	7 (58.3)
p		0.035		0.525	
Number of metastatic lymph nodes					
<12.5	99 (79.2)	48 (85.7)	28 (75.7)	48 (85.7)	9 (75.0)
>12.5	26 (20.8)	8 (14.3)	9 (24.3)	8 (14.3)	3 (25.0)
p		0.220		0.395	
N ratio (%)					
≤52.3	86 (68.8)	42 (75.0)	25 (67.6)	42 (75.0)	8 (66.7)
>52.3	39 (31.2)	14 (25.0)	12 (32.4)	14 (25.0)	4 (33.3)
p		0.434		0.719	

Chi-square and Fisher's Exact tests were used. OS: Overall survival.

Comparisons between groups in terms of categorical variables were made using Pearson's Chi-Square test and Fisher's Exact test. Whether continuous variables were suitable for normal distribution was confirmed by Kolmogorov-Smirnov test. A kurtosis value between ± 1.0 is considered excellent for most psychometric purposes, but a value between ± 2.0 is in many cases also acceptable, depending on the particular application.⁸ Differences between groups in terms of continuous variables were analysed using Student's t-test, and comparisons of mean values between multiple groups were made using one-way analysis of variance. The relationship between continuous variables was evaluated using Spearman correlation analysis. The capacity of tumor diameter to predict 3-year and 5-year survival was analysed using receiver operating characteristic (ROC) curve analysis. ROC analysis was also used to determine the capacity of the number of lymph nodes resected during surgery, the number of lymph nodes found to be metastatic among them, and N ratio to predict 5-year survival. The 5-year mortality risks of the variables were determined using univariate Cox regression analysis. Results were evaluated at 95% confi-

dence interval, and $p < 0.05$ values were considered significant. Bonferroni correction was made where appropriate.

N ratio value was calculated as number of metastatic lymph nodes/number of lymph nodes resected during operation.⁷

RESULTS

The mean age of the patients was 63.9 ± 11.9 (min.-max: 31-88) years. The mean follow-up time was 31.8 ± 21 months, the mean 5-year survival time was 23.2 ± 20.1 months, and the mean 3-year survival time was 24.2 ± 13 months. The mean tumor diameter was 6.5 ± 3.1 cm, and the mean N ratio was $35.6 \pm 29.8\%$.

Of the patients, 59.2% were males, and 64% were over 60 years old. The 3-year and the 5-year survival rates were 39.8% and 17.6%, respectively. Total gastrectomy was applied to 66.4% of the patients. A total of 56% of the tumors were poorly differentiated, 43.2% were over 6.5 cm, and 59.2% were over 5.25 cm. The number of resected lymph nodes was 19 and above in 55.2% of the patients, and the metastatic lymph node number was 13 and above in 20.8%. N ratio was over 52.3% in 31.2% of the patients (Table I).

Table II: Comparisons between groups of certain variables by mean tumor diameter and mean 5-year survival time.

	Tumor diameter (cm) Mean±S.D	p-value	5-year OS (months) Mean±SD	p-value
5-year OS		0.669		-
Dead	6.0±2.8		-	
Alive	6.5±4.2		-	
3-year OS		0.179		-
Dead	6.0±2.8		-	
Alive	6.8±3.3		-	
Type of gastrectomy		0.001		0.868
Total	7.1±3.2		22.8±21.8	
Subtotal	5.2±2.6		23.6±17.9	
Differentiation		0.258		0.698
Well differentiated	5.9±1.6		14±6.1	
Moderately differentiated	6.0 ±2.4		24.4±21.3	
Poorly differentiated	6.9±3.5		22.9±20	
Number of resected lymph nodes		0.84		0.542
<18.5	6.4±3.5		21.7 ±19.2	
>18.5	6.5±2.7		24.7 ±21	
Number of metastatic lymph nodes		0.716		0.79
<12.5	6.4±3.2		22.9±19.6	
>12.5	6.7±2.8		24.6±23.2	
N ratio		0.08		0.738
52.3 or below	6.1±2.9		23.6±19.7	
over 52.3	7.2±3.3		21.8±21.7	
Stage		0.144		0.041
2A/2B	5.9±2.9		29.4±22.3	
3A/3B/3C	6.7±3.2		18.7±16.7	
Tumor diameter (cm)		-		0.625
<6.5	-		24.1±19.1	
>6.5	-		21.7±21.8	

Independent Samples' t Test and one-way ANOVA test were used.

The mean 3-year and 5-year survival rates were found to be similar between sex, age, gastrectomy type, differentiation degree, tumor diameter, number of resected and metastatic lymph nodes, and N ratio groups ($p>0.05$ for each, Table I).

The mean tumor size was significantly higher in patients, who underwent total gastrectomy compared to those who underwent subtotal gastrectomy ($p=0.001$). Three and five-year survival, differentiation, resected lymph nodes, number of metastatic lymph nodes, N ratio and stage groups were found to be similar in terms of the mean tumor diameter ($p>0.05$ for each). The mean survival time in stage 3 patients was found to be significantly higher than those in stage 2 ($p=0.041$). Tumor diameter, differentiation, number of resected lymph nodes, number of metastatic lymph nodes

and N ratio groups were found to be similar in terms of the mean 5-year survival time ($p>0.05$ for each) (Table II). Age, resected and metastatic lymph node numbers, N ratio and tumor diameter groups were similar in terms of the mean 5-year survival time ($p>0.05$ for each). Tumor diameter and age, 3-year survival time, 5-year survival time, number of resected lymph nodes, number of metastatic lymph nodes and N ratio ratios were not significantly correlated ($p>0.05$ for each).

In the univariate Cox regression analysis, it was determined that the 5-year mortality risk was 1.2-fold higher in those with tumor diameter over 6.5 cm (95% CI 0.7-2.0; $p=0.536$). It was found that the 5-year mortality risk increased 1.8-fold in stage 3 patients (95% CI 1.0-3.1; $p=0.043$) (Table III).

Table III: Univariate Cox regression analyzes.

	HR	95% CI	p
Age (years)			
≤60	1.2	0.7-2.1	0.479
>60	1		
Gender			
Male	1		
Female	0.8	0.5-1.5	0.546
Stage			
2	1		
3	1.8	1.0-3.1	0.043
Type of gastrectomy			
Total	1		
Subtotal	1	0.6-1.7	0.973
Differentiation			
Well differentiated	1		
Moderately differentiated	0.6	0.2-1.9	0.348
Poorly differentiated	0.6	0.2-2.0	0.41
Tumor diameter			
<6.5 cm	1		
>6.5 cm	1.2	0.7-2.0	0.536
Tumor diameter			
<5.25 cm	1		
>5.25 cm	1.2	0.7-2.1	0.419
Number of resected lymph nodes			
<18.5	1		
>18.5	0.9	0.5-1.5	0.57
Number of metastatic lymph nodes			
<12.5	1		
>12.5	0.9	0.4-1.8	0.716
N ratio (%)			
52.3 or below	1		
over 52.3	1.1	0.6-2.0	0.836

Univariate Cox regression analysis was used. HR: Hazard ratio, CI: Confidence interval, SII: Systemic immune-inflammation index.

In the ROC analyses, the sensitivity of the threshold value of 6.5 cm for tumor diameter to predict 5-year survival was 41.7%, and the specificity was 60.7% (AUC: 0.504; $p=0.968$; 95% CI: 0.301-0.706) and 5.25 cm had a sensitivity of 64.9% for predicting 3-year survival, and a specificity of 48.2% (AUC: 0.572; $p=0.239$; 95% CI: 0.456-0.689). The threshold value of 18.5 for the number of resected lymph nodes had a sensitivity of 58.3% for predicting 5-year survival, and a specificity of 51.8% (AUC: 0.565; $p=0.479$; 95% CI: 0.388-0.743). The threshold value of 12.5 for the number of metastatic lymph nodes had a sensitivity of 25% for predicting 5-year survival, and a specificity of 85.7% (AUC: 0.371; $p=0.164$; 95% CI: 0.158 - 0.585). The threshold value of 52.3% for N ratio had a sensitivity of 33.3% for predicting 5-year survival, and a specificity of 75% (AUC: 0.408; $p=0.322$; 95% CI: 0.205-0.612).

DISCUSSION

In gastric cancer cases, the location, size, depth and spread of the primary tumor are among the factors that critically determine the prognosis.⁹⁻¹² There have been not so much data on whether tumor diameter alone has a significant prognostic value in stage 2 and 3 cases. The present study data indicate that tumor diameter may not provide as valuable information as expected in terms of prognosis in these cases.

In gastric cancer cases, tumor size is known as an important parameter in terms of surgical evaluation of the patient, the type and course of the operation, and the prognosis.⁹⁻¹² Wang *et al.* investigated only patients with tumors in the distal third of the stomach and included stage 1B patients, and determined the tumor diameter threshold value as 4.8 cm in terms of prognosis, and reported that this value was 80% sensitive and 68% specific for predicting 5-year survival.¹⁰ However, in the ROC analysis performed in the present study in which only stage 2 and 3 cases were included, the sensitivity of the threshold value of 6.5 cm for the tumor diameter to predict 5-year survival was 41.7%, and the specificity was found to be 60.7%. In addition, the sensitivity of the threshold value of 5.25 cm for tumor diameter to predict 3-year survival is 64.9%, and the specificity was calculated as 48.2%. The sensitivity and specificity rates of these threshold values were below the acceptable levels in terms of predicting 3 and 5-year survival. These findings indicate that the prognostic value of tumor diameter is limited in stage 2 and 3 gastric cancers.

In gastric cancers, the mean survival time is reported to decrease as the tumor diameter increases.⁹⁻¹² Li *et al.* determined 10 cm, which is the 90th percentile tumor diameter, as the threshold value among advanced gastric cancer cases, and determined that the mortality risk in patients

with tumors over 10 cm increased 1.4 times.¹¹ However, it is noteworthy that the mortality risk did not increase significantly, although the threshold value obtained was very high. Kunisaki *et al.*⁹ accepted a tumor diameter of 10 cm as the threshold value in their study in which patients at all stages were included, and reported that the prognosis was poor in those with high tumor diameter. These researchers reported that the survival rate was significantly lower in patients with large tumor diameter according to this high threshold. Wang *et al.* included stage 1B cases in their studies in which only patients with tumors in the lower third of the stomach were examined, and they reported that the 5-year survival rate was significantly lower in those with tumors larger than 4.8 cm in diameter.¹⁰ Zu *et al.* reported that survival time decreased significantly in patients with tumor diameter greater than 5 cm in both stage 2 and stage 3 patients.¹² These researchers have extended the follow-up period up to 15 years in their studies. In their data, the decrease in survival time in patients with tumors above 5 cm in stage 2 and 3 patients was not very pronounced; however after 5 years, the negative decomposition on the graph was largely evident. However, in the present study, the mean 3-year and 5-year survival rates were similar between tumor size groups. No significant difference was found between patients with high and low tumor diameters in terms of the mean 5-year survival time. There was no significant correlation between tumor diameter and 3-year and 5-year survival times. All these findings show that the diameter of the tumor in stage 2 and 3 cases is not a direct determinant of the short-term prognosis such as 3 and 5 years.

Zu *et al.* reported that the diameter of the tumor increased the mortality risk 1.8 times.¹² In the univariate Cox regression analysis, performed in the present study, it was determined that the 5-year mortality risk was 1.2-fold higher in those with a tumor diameter greater than 6.5 cm compared to those with tumors below 6.5 cm. This finding shows that although tumor diameter does not have a direct effect on prognosis in stage 2 and 3 gastric cancer patients, tumors above 6.5 cm increase the risk in terms of mortality, albeit low. This indicates that there is a certain relationship between tumor size and prognosis in these stages.

In cases where the tumor diameter is higher than 5 cm, it has been reported that the tumor is aggressive in terms of clinical picture and prognosis.¹² Zu *et al.* reported that the prognosis worsened significantly in patients with tumors larger than 5 cm in their study, which included all gastric cancer stages.¹² In their data, it is seen that the majority of small tumors are in stage 1 cases, and the rate of large tumors is rapidly increasing in stage 2 and 3 cases. In the study of Wang *et al.*, it is observed that the proportion of patients with a large tumor diameter increases rapidly as the stage increases.¹⁰ In the present study, the mean tumor diameter was determined as 6.5 ± 3.1 cm, 59.2% above 5.25 cm, and 43.2% of the tumors were found above 6.5 cm. This

indicates that the tumor diameter is generally large in stage 2 and 3 gastric cancer cases. It is known that the prognosis is poor, and the mortality rate is high in these stages. In addition, the already large tumor diameter at these stages may indicate that a critical threshold value between tumor diameter and survival has already been exceeded, and there is no significant extra effect on prognosis after this point.

It has been stated that the number of lymph nodes resected during the operation is important in gastric cancer cases. It has been emphasized that the number of resected lymph nodes exceeding 16 is valuable for a healthier staging, and it has been noted that it is especially important to remove at least eight lymph nodes.¹³ In the study, the number of resected lymph nodes and survival-fold were not found to be significantly correlated, and in the Cox regression analysis, it was calculated that the mortality risk in those with 19 or more resected lymph nodes was similar to those with 18 or less nodes removed. All these findings show that the number of lymph nodes resected in stage 2 and 3 gastric cancer cases is not a direct determinant of survival and prognosis.

It has been reported that the number of lymph nodes found to be metastatic in gastric cancer cases is valuable in terms of prognosis.¹⁴ In the present study, the number of metastatic lymph nodes groups were found to be similar in terms of 3 and 5-year survival rates and 5-year mean survival. In addition, the mean number of metastatic lymph nodes was found to be similar between those who died and survived during the 5-year follow-up period. No significant correlation was found between the number of metastatic lymph nodes and both the 3-year and 5-year survival. All these findings show that the prognostic value of the number of metastatic lymph nodes in stage 2 and 3 gastric cancer cases is not significant.

In recent studies, it has been stated that the N ratio value can provide important information in terms of prognosis in gastric cancer cases.^{7,15} In the present study, the mean 3-year and 5-year survival rates and the mean 5-year survival time were found to be similar between the N ratio groups. In addition, the mean N ratio was found to be similar between those who died and survived at the 5-year follow-up duration. N ratio was not significantly correlated with both the 3-year and 5-year survival times. All these findings show that N ratio is not directly related to prognosis in stage 2 and 3 cases, and does not provide reliable data for prognosis.

The facts that the number of the patients was not so high and that the study did not cover the long-term survival, were the limitations.

CONCLUSION

The findings of the present study show that the number of resected and metastatic lymph nodes, especially the tumor diameter, or the N ratio value do not have a direct effect on the prognosis in stage 2 and 3 cases, and that they do not

provide reliable data about the short-term prognosis such as 3-year and 5-year in stage 2 and 3 cases.

ETHICAL APPROVAL:

This retrospective cohort study was performed at the Department of General Surgery, Kartal Dr Lütfi Kırdar City Hospital, Istanbul, Turkey. Local Ethics Committee approval (date: 30/12/2020; approval number: 514/192/40).

CONFLICT OF INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

HU: Conception and design, analysis and interpretation of data, drafting of the manuscript, advices and final approval.

SK: Analysis and interpretation of data, conception and design, reviewed the paper, and final approval.

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