Original Article / *Özgün Araştırma*

DOI: 10.4274/haseki.galenos.2018.4514
Med Bull Haseki 2019;57:153-161

Evaluation of the Factors Affecting Survival in Patients with Gastric Cancer According to the 8th Edition of the Tumor, Node and Metastasis Classification

Mide Kanserli Hastalarda Sağkalımı Etkileyen Faktörlerin Tümör Nod ve Metastaz 8 Evreleme Sistemi ile Değerlendirilmesi

Mustafa Berkeşoğlu, Recep Çağlar, Aydemir Ölmez, Hakan Canbaz, Bahar Taşdelen*, Mustafa Musa Dirlik, Tuba Kara**

Mersin University Faculty of Medicine, Department of General Surgery, Mersin, Turkey
**Mersin University Faculty of Medicine, Department of Biostatistics and Medical Informatics, Mersin, Turkey*
***Mersin University Faculty of Medicine, Department of Pathology, Mersin, Turkey*

Abstract

Aim: We aimed to evaluate the effect of different parameters on survival in patients with gastric adenocarcinoma who underwent D2 lymph node dissection with more than 15 lymph nodes.

Methods: A total of 161 patients with gastric adenocarcinoma, who underwent curative gastrectomy and had more than 15 lymph nodes dissected between January 2001 and January 2015, were retrospectively evaluated. A hundred and forty-six patients were included in the study.

Results: The mean follow-up period was 24 (12-102) months and the mean survival time was 818.80±692.42 (66-3065) days. Gender, age, lymphovascular invasion and perineural invasion, tumor differentiation and histology were not found to have a statistically significant effect on overall survival. Length of hospital stay, tumor location, extent of surgery, chemotherapy, tumor stage (T category), total number of harvested lymph nodes, number of metastatic lymph nodes, lymph node status (N status), percentage of lymph node positivity, metastatic lymph node ratio and stage were found to have a statistically significant effect on overall survival.

Conclusion: Having distally located tumor, having chemotherapy, higher total number of harvested lymph node and lower N category were better prognostic factor for overall survival in gastric cancer patients having curative resection with more than 15 lymph nodes harvested.

Keywords: Gastrectomy, lymph nodes, prognosis, survival

Öz

Amaç: Mide adenokarsinomu nedeniyle 15'ten fazla lenf nodu çıkarılan ve D2 lenf nodu diseksiyonu yapılan hastalarda farklı parametrelerin sağkalıma olan etkisininin değerlendirmesi amaçlanmıştır.

Yöntemler: Ocak 2001 ve Ocak 2015 yılları arasında 3. basamak tedavi merkezimizde 15 lenf nodundan daha fazla lenf nodu çıkarılan küratif gastrektomi uygulanan 161 mide adenokarsinomalı hasta retrospektif olarak incelendi ve uygun 146 hasta detaylı olarak değerlendirildi.

Bulgular: Yüz kırk altı hastanın medyan takip süresi 24 (12-102) ay olarak saptanmıştır. Medyan sağkalım süresi 818,80±692,42 (66-3065) gün olarak saptanmıştır. Cinsiyet, yaş, lenfovasküler invazyon ve perinöral invazyon durumu, tümör derecesi ve histolojisi genel sağkalım bakımından istatistiksel olarak anlamlı bulunmamıştır. Hastanede yatış süresi, tümörün yerleşim yeri, yapılan cerrahinin genişliği, kemoterapi, T evresi, çıkarılan lenf nodu sayısı, metastatik lenf nodu sayısı, N evresi, PNP, MLR ve evre genel sağkalımda istatistiksel olarak anlamlı saptanmıştır.

Sonuç: On beş lenf nodundan daha fazla lenf nodu çıkarılan ve küratif rezeksiyon yapılan hastalarda, tümörün distal yerleşimli olması, adjuvan kemoterapi verilmiş olması, daha fazla lenf nodu çıkarılmış olması ve N evresinin düşük olması iyi prognostik faktör olarak saptanmıştır.

Anahtar Sözcükler: Gastrektomi, lenf nodları, prognoz, sağkalım

Address for Correspondence/Yazışma Adresi: Mustafa Berkeşoğlu
Mersin University Faculty of Medicine, Department of General Surgery, Mersin, Turkey
E-mail: berkesoglu@yahoo.com ORCID ID: orcid.org/0000-0002-5850-5592
Received/Geliş Tarihi: 26 June 2018 **Accepted/Kabul Tarihi:** 06 September 2018

Introduction

Lymph node status is an important indicator of survival in patients with gastric adenocarcinoma (GA) (1). Despite the fact that malignant cells are limited to mucosa and submucosa regardless of lymph node status in early gastric cancer, the predisposing factors for lymph node metastasis are still investigated for providing better outcome and survival rate (2). Since early GA has good prognosis, routine screening is not performed in most countries, therefore, GA is usually diagnosed at advanced stage. Surgical team is mostly unaware of the exact lymph node status in GA patients preoperatively despite imaging studies. Multiple factors, such as extent of node dissection and experience of the pathologist may affect the pathological lymph node status in patients with GA (1). Generally, dissection of 16 or more regional nodes is recommended to determine the correct nodal status, but this is not a strict surgical criterion (1). Some studies reported that D2 dissection, compared to D1 dissection, and dissecting more than 15 lymph nodes were favorable for optimal surgical outcome (3,4). Retrieval of less than 15 lymph nodes is considered an inadequate surgery and lymph node ratio is supplemental for nodal staging (3).

In this study; we aimed to evaluate the effect of different nodal systems on survival in patients with GA who underwent D2 lymph node dissection with more than 15 lymph nodes harvested.

Methods

The study was approved by Clinical Research Ethics Committee of Mersin University (no: 2016/185). Informed consent was not obtained from the patients due to the retrospective nature of the study. This retrospective study evaluated GA patients who underwent curative gastrectomy in our tertiary care center from January 2001 to January 2015. Only the resectable tumors arising from the gastric mucosa and tumors that arise from the first cranial 5 cm of gastric mucosa without crossing the esophagogastric junction were included. Patients with metastatic tumors, patients who underwent palliative interventions, patients having gastric cancer other than adenocarcinoma and patients with dissection of fewer than 16 lymph nodes were excluded from the study. One hundred and sixty-one patients who fulfilled the inclusion criteria were enrolled. Fifteen patients were also excluded from the study due to death within 30 days after surgery (5). The remaining 146 patients were evaluated in detail for survival. No patients had known metastatic disease, ascites and neoadjuvant chemoradiotherapy. All surgeries were performed by the same surgical team. Adjuvant chemotherapy indication (combination of 5-fluorouracil with cisplatin, docetaxel or none) was decided by the multidisciplinary council (department of general surgery, medical oncology, gastroenterology, pathology and radiology) for each patient.

Patients' data were collected from the database. The patients were evaluated with regard to age, gender, site and size of the tumor, extent of gastrectomy, complications of the surgery, stage and grade of the tumor, nodal staging according to different nodal evaluation systems, and presence of adjuvant chemotherapy. Effects of these variables on survival were investigated.

All the patients underwent endoscopy to determine the location of the tumor and pathological samples were collected preoperatively; either computed tomography scan or magnetic resonance imaging were mainly performed to determine the stage after the pathological diagnosis. Primary tumor site was defined as "distal 1/3", "middle 1/3", "proximal 1/3" and "linitis plastic". Extent of the surgery was decided according to tumor location; subtotal gastrectomy was performed with safety margin, especially for distal tumors. Total gastrectomy was mostly performed in all proximal-middle location tumors and linitis ones. Addition of "splenectomy" to the procedure was performed due to extent of surgery or iatrogenic laceration. The tumors were divided according to their grade and type into 3 categories: well-differentiated, moderately-differentiated and poorly differentiated/signet-ring cell type'. Status of lymphovascular invasion (LVI) and perineural invasion (PNI) were also evaluated. T stage was defined/redefined (6). For nodal evaluation, different lymph node staging systems were used. Total number of harvested lymph nodes and metastatic ones were calculated separately. N stage was defined according to the 8th edition of the Tumor, node and metastasis classification (6). Secondly, the number of metastatic lymph nodes and the total number of harvested lymph nodes were calculated and the ratio of metastatic to total retrieved nodes (MLR) was categorized as "MLR 0 (0%)", "MLR 1 (1-5%)", "MLR 2 (6-10%)", "MLR 3 (11-20%)", "MLR 4 (21-30%)" and "MLR 5 (>30%)" (7). Finally, percentage of node positivity (PNP) was defined as "PNP 0 (0%)", "PNP 1 (1-20%)", "PNP 2 (21-50%)" and "PNP 3 (>50%)" (3). Stage (1a, 1b, 2a, 2b, 3a, 3b and 3c) was also evaluated for survival analysis. Mortality information was confirmed via the Central Civil Registration System.

The patients were mainly evaluated by physical examination, chest X-ray (semi-annually), abdominal computed tomography (semi-annually) and upper endoscopy (annually) in the control visits. Follow-up visits were scheduled at three-month intervals for the first two years, six-month intervals for the third to fifth postoperative years, and once a year there after.

Statistical Analysis

Data were summarized as mean ± standard deviation, numbers (n), percent (%), minimum and maximum. Categorical variables were evaluated via a chi-square test and likelihood ratio. Student's t-test and the Mann-Whitney U test were used for continuous variables. We used Kaplan-Meier curves and log-rank test to estimate 1-year, 3-year and 5-year survival rates and Cox regression to investigate the univariate and multivariate effects of different parameters on overall survival time. Significant cut-off values for the total number of harvested lymph nodes and metastatic lymph nodes were obtained by calculating the ROC curve. Statistical 13.3 Software was used for statistical analysis. A p value of less than 0.05 was considered statistically significant.

Results

The operative mortality rate was 9.3% (15/161). The mean follow-up period for the 146 patients was 24 (12-102) months. Gender and age had no statistically significant effect on survival (Table 1). Parameters affecting survival are documented in detail in Table 1 and Table 2. Twenty-one (14.4%) patients had complication with prolonged hospital-stay due to mainly major wound infection, leakage, pulmonary disease and cardiac problems. Splenectomy was added to gastrectomy in 39 (26.7%) patients. Twenty-three (15.8%) patients had signet-cell histology. Signet-cell histology and poorly differentiated tumors were found in 68 (46.6%) patients. Both LVI and PNI positivity were seen in 103 (70.5%) patients. 108 (74%) patients had adjuvant chemotherapy. Most of the patients had advanced disease: T3-4 (71.9%), N2-3 (70.6%) and stage 3 (65.1%). The mean survival time was found to be 818.80±692.42 (66-3065) days. 1-year, 3-year and 5-year survival rates were 65.1%, 39.7% and 30.8%, respectively.

Overall Survival

Gender, age, differentiation of tumor and LVI and PNI statuses were not found to have a statistically significant effect on overall survival. In univariate analysis, it was observed that the total number of harvested lymph nodes and metastatic lymph nodes, length of hospital stay, tumor location, surgery type, preserving spleen, T staging, N staging, PNP, MLR, stage and adjuvant chemotherapy had a statistically significant effect on overall survival (Table 1). In multivariate analysis, having distal tumor, having chemotherapy, higher number of total harvested lymph nodes and lower N stage were found to have a statistically significant effect on overall survival (Table 2).

Discussion

In our study, we found that gender, age and differentiation of tumor were not found to have a statistically significant effect on survival (Table 1). In multivariate analysis, having distal tumor location, having adjuvant chemotherapy, higher number of the total harvested lymph nodes and lower N status were found to have a statistically significant effect on survival (Table 2).

Gastric cancer is the fifth most common malignancy and third-leading cause of cancer-related death worldwide (8). Surgery is the main treatment modality (8,9). Besides a successful surgery, some clinicopathologic factors, such as lymph node status and presence of advanced tumor were also found to take a role in long-term prognosis for GA (10). Lymph node status is one of the most important predictor of survival in GA, whereas a cut-off point for the total number of harvested lymph node during surgical dissection has not been found to estimate the postoperative prognosis in previous studies (1,8,9). Chen et al. (9) reported that the number of lymph nodes harvested was mainly dependent on the surgeon's technique and pathologist's experience; the main problem was staging of GA according to the number of harvested lymph nodes. Dissection of more than 15 lymph nodes is recommended to prevent the false down-staging (9). We included patients with at least 16 lymph nodes harvested in this study. We found that harvesting more than 33 lymph nodes had statistically significant effect on overall survival (Table 3).

Survival

When survival rates of GA were investigated in our study, we found 1-, 3- and 5-year survival rates of 65.1%, 39.7% and 30.8%, respectively. Kim et al. (10) declared that majority of deaths (70.5%) occurred within the first 2 years after gastrectomy and also declared that 1-, 3- and 5-year survival rates were 75.1, 48.1 and 37, respectively, similar with our results (10). Reported results demonstrated that there was a great variation for 5-year survival of GA, ranging from 5% to 90% depending on the extent of the disease, tumor and patient-related factors (10-18).

Tumor Location and Treatment

Patients with distal tumor location and subtotal gastrectomy had better prognosis in our study. Only five patients with distally located tumors had total gastrectomy to have negative margin, most of patients with distal tumor (94%) had subtotal gastrectomy. Distal tumor location and/or subtotal gastrectomy are still controversial prognostic factors for GA. Distal tumor location and resection with subtotal gastrectomy were similarly demonstrated to be better prognostic factors with our study results (1,9,19). In multivariate analysis, prognostic effect of having distal tumor location was

Table 1. Univariate analysis of prognostic factors in patients with gastric adenocarcinoma undergoing curative gastrectomy with harvested 16 and more lymph nodes

	n=146 (%)	Mean ± SD (range)	Hazard ratio	%95 CI	p value
Gender					
Male	98 (67.1)	-	1	-	0.893
Female	48 (32.9)	-	1.028	0.684-1.545	
Age (year)		62.57±12.14 (32-70)	1.005	0.988-1.022	0.536
Length of hospital stay (day)		11.45±6.95 (6-66)	1.049	1.022-1.077	<0.001
Location					
Distal 1/3	83 (56.8)	-	1		<0.001
Middle 1/3	46 (31.5)	-	0.616	0.255-1.488	
Proximal 1/3	13 (8.9)	-	1.879	0.975-3.624	
Linitis	4 (2.7)	-	8.429	2.977-23.871	
Surgery					
Subtotal gastrectomy	78 (53.4)	-	1	-	<0.001
Total gastrectomy	68 (46.6)	-	2.787	1.868-4.158	
Splenectomy					
Not performed	107 (73.3)	-	1	-	<0.001
Performed	39 (26.7)	-	2.140	1.412-3.243	
Grade and histology					
Well	25 (17.1)	-	1	-	0.994
Moderately	53 (36.3)	-	0.971	0.553-1.705	
Poor or signet cell	68 (46.6)	-	0.974	0.566-1.676	
LVI/PNI					
Both negative	23 (15.8)	-	1	-	0.266
LVI positivity	12 (8.2)	-	1.630	0.624-4.257	
PNI positivity	8 (5.5)	-	1.677	0.514-5.470	
Both positive	103 (70.5)	-	1.985	0.995-3.958	
Chemotherapy					
Yes	108 (74)	-	1	-	0.01
No	38 (26)	-	1.768	1.148-2.724	
T stage					
1	10 (6.8)	-	1	-	0.049
2	31 (21.2)	-	3.356	1.013-11.118	
3	70 (47.9)	-	3.412	1.065-10.928	
4a	15 (10.3)	-	3.559	1.132-13.315	
4b	20 (13.7)	-	3.672	1.161-17.412	
Total harvested lymph nodes (number)	-	31.14±13.41 (16-84)	0.972	0.954-0.990	0.002
Metastatic lymph nodes (number)	-	8.04±8.44 (0-39)	1.033	1.012-1.054	0.002
N stage					
0	25 (17.1)	-	1	-	0.006
1	18 (12.3)	-	1.100	0.442-2.736	
2	32 (21.9)	-	2.557	1.260-5.188	
3a	49 (33.6)	-	2.875	1.473-5.612	
3b	22 (15.1)	-	2.903	1.332-6.328	

Table 1. Continued

	n=146 (%)	Mean ± SD (range)	Hazard ratio	%95 CI	p value
PNP (%)					
0. 0	26 (17.8)	-	1	-	<0.001
1. 1-20	44 (30.1)	-	1.493	0.756-2.950	
2. 21-50	55 (37.7)	-	2.505	1.318-4.761	
3. >51	21 (14.4)	-	3.764	1.814-7.807	
MLR					
0. 0	26 (17.8)	-	1	-	<0.001
1. 0.01-0.05	13 (8.9)	-	0.875	0.308-2.487	
2. 0.06-0.10	9 (6.2)	-	0.629	0.177-2.228	
3. 0.11-0.20	22 (15.1)	-	2.467	1.191-5.110	
4. 0.21-0.30	26 (17.8)	-	2.149	1.059-4.359	
5. >0.30	50 (34.2)	-	3.473	1.808-6.670	
Stage					
1	12 (8.2)	-	1	-	0.015
2	39 (26.7)	-	2.536	0.884-7.272	
3	95 (65.1)	-	3.742	1.360-10.294	

LVI: Lymphovascular invasion, PNI: Perineural invasion, PNP: Percent of node positivity, MLR: Metastatic lymph node ratio, SD: Standard deviation, CI: Confidence interveral

more prominent than subtotal gastrectomy (p=0.018 vs 0.306). On the contrary, some studies claimed that organ preserving surgery had an unfavorable effect (20,21). Additional splenectomy during total/subtotal gastrectomy has been shown to have no effect on prognosis of GA (22,23). In this study, it was found that spleen-preserving surgery was associated with improved survival (Table 1). Poor prognosis due to adding splenectomy to the surgery may be associated with increased morbidity. However, preserving spleen had no prognostic effect on survival in multivariate analysis (Table 2). According to our study results, routine splenectomy was not necessary during gastrectomy unless the spleen is primarily affected by the tumor. The effect of chemotherapy on the GA prognosis remains controversial. Some studies reported that adjuvant chemotherapy had no effect on survival, whereas a recent literature review presented favorable effects of additional adjuvant chemotherapy (1,7,24,25). According to our study results, additional adjuvant chemotherapy seems to be a favorable prognostic factor for survival. Furthermore, chemotherapy was found to be a favorable prognostic factor in multivariate analysis.

Pathologic Features

Signet-cell histology and poorly-differentiated tumors were found in 68 (46.6%) patients. The results of the studies concerning the relationship between grade and survival of patients with GA are challenging. Chen et al. (9) and Kim et al. (10) reported that poorly-differentiated histology and signet-cell type were poor prognostic factors. Biondi et al. (1) reported lower survival rate in grade 3 (poorly differentiated) and linitis plastica groups (five-year survival rate 58.6 and 42.5%, respectively). On the contrary, we found no statistically significant relationship between tumor grade-histology and survival time, similar with some studies (7,19,21). When we evaluated in detail, patients with poorly-differentiated tumors and well-differentiated tumors had similar node-negativity rate (16.2% and 17.9%, respectively). However, patients with worse tumor histology had advanced N status (p=0.031), 31 of 78 (39.7%) patients with well or moderately differentiated tumors had N3 status, 40 of 68 (58.8%) patients with signet-cell histology and poorly differentiated tumors had N3 status. Taghavi et al. (26) declared that when adjusted for stage, signet ring cell did not portend a worse prognosis. The extensiveness of the tumor with lymph node metastasis may be a more important prognostic factor rather than tumor histology and grade according to our study results. LVI-PNI positivity was associated with survival in some studies (10,23,27). On the contrary, LVI-PNI positivity was not found to be associated with poor prognosis in our study.

Table 2. Multivariate analysis of prognostic factors (overall survival) in patients with gastric adenocarcinoma undergoing curative gastrectomy with harvested 16 and more lymph nodes

	n=146	Mean ± SD (range)	Wald statistic	df	Hazard ratio	%95 CI	p value
Length of hospital stay (day)	-	11.45±6.95 (6-66)	0.015	1	0.998	0.961-1.036	0.904
Location	-	-	10.118	3	-	-	
Distal 1/3	83 (56.8)	-	-	-	1	-	
Middle 1/3	46 (31.5)	-	-	-	0.369	0.132-1.031	0.018
Proximal 1/3	13 (8.9)	-	-	-	1.230	0.463-3.263	
Linitis	4 (2.7)	-	-	-	7.191	1.904-27.161	
Surgery	-	-	1.622	1	-	-	
Subtotal gastrectomy	78 (53.4)	-	-	-	1	-	0.203
Total gastrectomy	68 (46.6)	-		-	0.573	0.258-1.270	
Splenectomy	-	-	1.047	1	-	-	
Not performed	107 (73.3)	-	-	-	1	-	0.306
Performed	39 (26.7)				1.552	0.836-2.884	
Chemotherapy	-	-	21.525	1	-	-	
Yes	108 (74)			-	1	-	<0.001
No	38 (26)	-	-	-	3.781	2.192-6.523	
T stage	-	-	3.469	1	-	-	
1	10 (6.8)	-	-	-	1	-	
2	31 (21.2)	-	-	-	3.839	1.130-13.041	0.325
3	70 (47.9)	-		-	6.659	1.340-33.078	
4a	15 (10.3)	-	-	-	5.585	1.035-30.144	
4b	20 (13.7)	-	-	-	6.843	1.415-35.601	
Total harvested lymph nodes (number)	-	31.14±13.41 (16-84)	12.466	1	0.963	0.945-0.981	<0.001
Metastatic lymph nodes (number)	-	8.04±8.44 (0-39)	3.184	1	1.028	0.997-1.059	0.074
N stage	-	-	10.929	1	-	-	
0	25 (17.1)	-	-	-	1	-	
1	18 (12.3)	-	-	-	0.150	0.035-0.636	0.027
2	32 (21.9)	-		-	0.810	0.810-5.982	
3a	49 (33.6)	-	-	-	1.421	1.421-21.545	
3b	22 (15.1)	-	-	-	1.383	1.383-20.043	
Stage	-	-	2.367	2	-	-	
1	12 (8.2)	-	-	-	1	-	
2	39 (26.7)	-	-	-	0.707	0.164-3.048	0.306
3	95 (65.1)	-	-	-	0.337	0.045-2.528	

SD: Standard deviation, CI: Confidence interveral

Stage

In this study, lower stage was found to be associated with better survival (Figure 1). Stage and status of T and N were valuable parameters for survival (Table 1). Tumor detection in an early stage has been shown to be a very important prognostic factor (28). We also found the favorable prognostic effect of early stage on nodal status. The results of other studies demonstrated that patients with early stage tumors had statistically significantly higher survival rates, similar with our study results (7,23).

Nodal Status

In our study, we found that higher total number of harvested lymph nodes and lower number of metastatic lymph nodes had favorable effects on survival. Harvesting more than 33 lymph nodes provide beneficial effects on survival (Table 3). Some studies also reported that MLR was a determinant factor for survival (29). We included patients with more than 15 lymph nodes to prevent inaccurate surgery criticism or down-staging effect. In multivariate analyses, among the nodal parameters, higher total number of harvested lymph nodes and lower N stage were found to be favorable prognostic factors for survival (Table 2).

When we evaluated the effect of MLR and PNP on survival, we observed that higher MLR and higher PNP were statistically significantly worse prognostic factors for survival. Lee et al. (7) similarly reported that five-year survival decreased significantly with increasing MLR (7). Siewert et al. (30) declared significant deterioration of the prognosis on survival for stage II GA when more than 20% of the removed lymph nodes were metastatic. Most of the patients (63.2%) had MLR "0" in the study by Lee et al. (7), however, fewer patients (17.8%) had MLR "0" in our study. The reason for the different results may be related with different population features. One of the main differences between the two studies is no harvested lymph node cut-off in the study of Lee et al. (7) but >15 nodes was an inclusion criterion in our study (7). Shen et al. (8) reported that most patients (85%) had advanced tumors and harvesting more than 30 lymph nodes was associated with better survival for T3, T4, node-positive and stage 3-4 patients. In the present study, most of our patients (71.9% for T3-T4, 65.1% for stage 3) had also advanced tumors. Different cut-off values/systems may be used for lymph node ratio other than MLR. Harvesting more than 33 lymph nodes was associated with better survival in this study (Table 3). PNP level was also correlated with estimated results. Similar categorization values were found to be associated with reasonable predictive value in some studies (3). As well as adequate surgery, pathological evaluation is also important for lymph node ratio and survival (1,9).

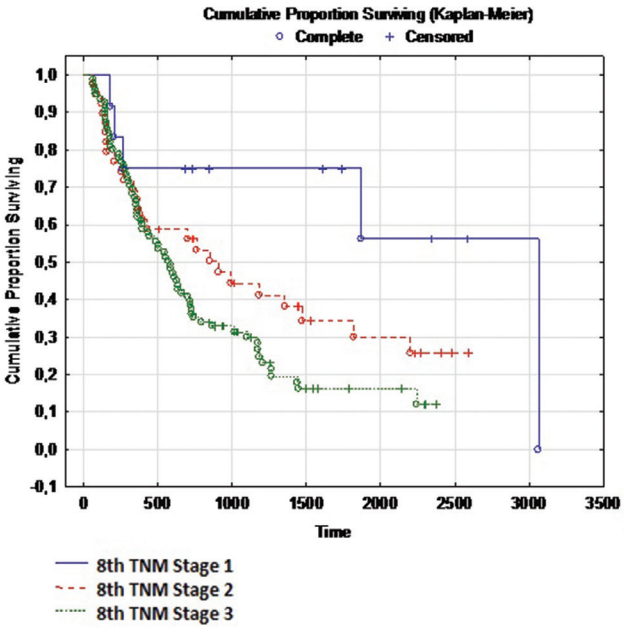

Figure 1. Lower stage was correlated with better survival

Study Limitations

This study had some limitations. Firstly, this is a retrospective study. Secondly, chemotherapy regimen was not unique and was not detailed. Small sample size was another limitation of the study. Further large-scale randomized controlled studies are needed. On the other hand, the study was based on new staging systems; the study population was homogenous, had at least 16 harvested lymph nodes and mostly had advanced-stage tumors.

Table 3. Cut-off value of total harvested lymph node numbers and metastatic lymph node numbers for prognostic significance on overall survival

	Cut-off value	Sensitivity	Specificity	AUC	95%CI for AUC	p
Metastatic lymph node numbers	>3	77.1	63.4	0.690	(0.608-0.764)	<0.001
Total harvested lymph node numbers	≤33	79.0	56.1	0.697	(0.615-0.770)	<0.001

CI: Confidence interveral, AUC: Area under the curve

Conclusion

When screening is not performed routinely, GA is usually diagnosed at advanced stage. Having distal tumor location, having adjuvant chemotherapy, higher total number of harvested lymph nodes and lower N status were found to be more important than grade-histological type of the tumor in survival rates in patients having advanced tumors.

Authorship Contributions

Surgical and Medical Practices: M.B., R.Ç., A.Ö., H.C., M.M.D., T.K. Concept: M.B., R.Ç., A.Ö., M.M.D. Design: M.B., R.Ç., A.Ö., H.C. Data Collection or Processing: M.B., A.Ö., H.C., B.T. Analysis or Interpretition: M.B., B.T. Literature Search: M.B. Writing: M.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Biondi A, D'Ugo D, Cananzi FC, et al. Does a minimum number of 16 retrieved nodes affect survival in curatively resected gastric cancer? Eur J Surg Oncol 2015;41:779-99.
2. Saragoni L. Upgrading the definition of early gastric cancer: better staging means more appropriate treatment. Cancer Biol Med 2015;12:355-61.
3. Kutlu OC, Watchell M, Dissanaike S. Metastatic lymph node ratio successfully predicts prognosis in western gastric cancer patients. Surg Oncol 2015;24:84-8.
4. Lavy R, Hershkovitz Y, Chikman B, et al. D1 versus D2 gastrectomy for gastric adenocarcinoma. Isr Med Assoc J 2015;17:735-38.
5. Lepage C, Sant M, Verdecchia A, Forman D, Esteve J, Faivre J. Operative mortality after gastric cancer resection and long-term survival differences across Europe. Br J Surg 2010;97:235-39.
6. Haejin I, Solsky I, Palis B, Langdon-Embry M, Ajani J, Sano T. Validation of the 8th Edition of the AJCC TNM Staging System for Gastric Cancer using the National Cancer Database. Ann Surg Oncol 2017;24: 3683-3091.
7. Lee SR, Kim HO, Son BH, Shin JH, Yoo CH. Prognostic significance of the metastatic lymph node ratio in patients with gastric cancer. World J Surg 2012;36:1096-101.
8. Shen Z, Ye Y, Xie Q, Liang B, Jiang K, Wang S. Effect of the number of lymph nodes harvested on the long-term survival of gastric cancer patients according to tumor stage and location: a 12-year study of 1,637 cases. Am J Surg 2015;210:431-40.
9. Chen S, Zhao BW, Li YF, et al. The prognostic value of harvested lymph nodes and the metastatic lymph node ratio for gastric cancer patients: results of a study of 1,101 patients. PLOS One 2012;7:e49424.
10. Kim Y, Ejaz A, Spolverato G, et al. Conditional survival after surgical resection of gastric cancer: a multi-institutional analysis of the US gastric cancer collaborative. Ann Surg Oncol 2015;22:557-64.
11. Arrington AK, Nelson R, Patel SS, et al. Timing of chemotherapy and survival in patients with resectable gastric adenocarcinoma. World J Gastrointest Surg 2013;5:321-28.
12. Degiuli M, Sasako M, Ponti A, et al. Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. Br J Surg 2014;101:23-31.
13. Miceli R, Tomasello G, Bregni G, Di Bartolomeo M, Pietrantonio F. Adjuvant chemotherapy for gastric cancer: current evidence and future challenges. World J Gastroenterol 2014;20;4516-25.
14. Markar SR, Karthikesalingam A, Jackson D, Hanna GB. Longterm survival after gastrectomy for cancer in randomized, controlled oncological trials: comparison between West and East. Ann Surg Oncol 2013;20:2328-38.
15. Kim JP, Lee JH, Kim SJ, Yu HJ, Yang HK. Clinicopathologic characteristics and prognostic factors in 10 783 patients with gastric cancer. Gastric Cancer 1998;1:125-33.
16. Isozaki H, Okajima K, Fujii K, et al. Effectiveness of paraaortic lymph node dissection for advanced gastric cancer. Hepatogastroenterology 1999;46:549-54.
17. Berardi R, Scartozzi M, Romagnoli E, Romagnoli E, Antognoli S, Cascinu S. Gastric cancer treatment: a systematic review. Oncol Rep 2004;11:911-16.
18. Dickson JL, Cunningham D. Systemic treatment of gastric cancer. Eur J Gastroenterol Hepatol 2004;16:255-63.
19. Alatengbaolide, Lin D, Li Y, et al. Lymph node ratio is an independent prognostic factor in gastric cancer after curative resection (R0) regardless of the examined number of lymph nodes. Am J Clin Oncol 2013;36:325-30.
20. Qiu MZ, Wang ZQ, Zhang DS, et al. Comparison of 6th and 7th AJCC TNM staging classification for carcinoma of the stomach in China. Ann Surg Oncol 2011;18:1869-76.
21. Strong VE, Wu AW, Selby LV, et al. Differences in gastric cancer survival between the US and China. J Surg Oncol 2015;112:31-7.
22. Wang F, Chang YC, Chen TH, et al. Prognostic significance of splenectomy for patients with gastric adenocarcinoma undergoing total gastrectomy: A retrospective cohort study. Int J Surg 2014;12:557-65.
23. Coimbra FJ, Costa WL, Montagnini AL, et al. The interaction between N-category and N-ratio as a new tool to improve lymph node metastasis staging in gastric cancer: results of a single cancer center in Brazil. Eur J Surg Oncol 2011;37:47-4.
24. Zhang M, Wang J, Shi W, et al. Prognostic significance of metastatic lymph nodes ratio in patients with gastric adenocarcinoma after curative gastrectomy. Chin Med J (Engl) 2014;127:1874-8.
25. Ilson DH. Current progress in the adjuvant treatment of gastric cancer. Surg Oncol Clin N Am 2017;26:225-39.

26. Taghavi S, Jayarajan SN, Davey A, Willis AI. Prognostic significance of signet ring gastric cancer. J Clin Oncol 2012;30:3493-8.
27. Sun Z, Wang ZN, Zhu Z, et al. Evaluation of the seventh edition of American Joint Committee on Cancer TNM staging system for gastric cancer: results from a Chinese monoinstitutional study. Ann Surg Oncol 2012;19:1918-27.
28. Saragoni L, Morgagni P, Gardini A, et al. Early gastric cancer: diagnosis, staging, and clinical impact. Evaluation of 530 patients. New elements for an updated definition and classification. Gastric Cancer 2013;16:549-54.
29. Dutta S, Crumley AB, Fullarton GM, Horgan PG, McMillan DC. Comparison of the prognostic value of tumour and patient related factors in patients undergoing potentially curative resection of gastric cancer. Am J Surg 2012;204:294-9.
30. Siewert JR, Böttcher K, Stein HJ, Roder JD. Relevant prognostic factors in gastric cancer ten-year results of the German gastric cancer study. Ann Surg 1998;228:449-61.