

ORIGINAL ARTICLE

Clinicopathological characteristics, prognosis and survival outcome of gastric cancer in young patients: A large cohort retrospective study

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Summary

Purpose: To investigate the survival outcome of patients with gastric cancer ≤ 40 years of age and to compare them to older patients with gastric cancer.

Methods: The study included gastric cancer patients treated between 1990 and 2014. Patient demographics, tumor histopathological characteristics and outcome were registered. Patients were classified according to the International Classification of Diseases for Oncology. Two subgroups of patients were created based on age: group 1 (40 years and less at the time of diagnosis, and group 2 (patients older than 40 years). Categorical and continuous variables were analyzed with χ^2 and Mann-Whitney U tests, respectively. Overall survival (OS) rates were estimated by the Kaplan-Meier method.

Results: Diffuse adenocarcinoma was more common in the young group (48.9%) than in the older group (28.9%)

($p < 0.0001$). No statistically significant survival difference was noted between younger (11 months) and older patients (12 months) ($p = 0.79$). Early stage ($p < 0.0001$), absence of perineural invasion (PNI) ($p < 0.0001$), absence of lymphovascular invasion (LVI) ($p < 0.0001$), and non-cardia tumors ($p < 0.0001$) were associated with better OS rates in univariate analysis. Non-cardia tumors ($p = 0.016$) and stage ($p < 0.0001$) were independent prognostic factors of survival outcome in multivariate analysis.

Conclusions: This study demonstrated that young and older patients with gastric cancer have similar outcomes in terms of OS.

Key words: gastric cancer, younger patients, older patients, prognostic factors, survival, outcome

Introduction

Although decreased cancer incidence and mortality rates are observed in developed countries, it is estimated that cancer will be responsible for more deaths than cardiovascular diseases in the future [1-3].

Cancer incidence rates are increasing in Turkey due to improvement in the cancer screening system [4].

When analyzing the overall worldwide statistics of gastric cancer, which is still the fourth most common cancer and the second leading cause of cancer-related mortality, incidence and mortality rates are declining [5-7].

Additionally, gastric cancer tends to be more frequently diagnosed in elderly patients, particularly in United States and Japan [8,9]. The age-adjusted

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mortality rate of gastric cancer is increased with older age [10]. Previous studies demonstrated that 2-8% of patients with gastric cancer are younger than 40 years [11-13].

Following recent developments in cancer screening, the incidence of advanced gastric cancer shows a decrease in Japan. However, gastric cancer in adults remains a significant problem as people younger than 40 years of age are not included to routine gastric cancer screening in Japan. And also, gastric cancer is difficult to diagnose in young people without screening due to the asymptomatic nature of the disease even in advanced stages [13].

The prognosis of young patients with gastric cancer is uncertain, according to previous studies. Clinicopathological characteristics of gastric cancer are dealing with differences between young and older patients and the prognosis of gastric cancer is worse for young patients based on clinicopathological characteristics and delayed diagnosis [14-17]. However, some other studies demonstrated that prognosis and outcome of young patients with gastric cancer were similar to older patients [13,18-20]. Few studies have evaluated the clinicopathological characteristics, prognosis, and outcome of young and older patients with gastric cancer.

This large retrospective study aimed to investigate the clinicopathological characteristics, prognosis and survival outcome of patients with gastric cancer <40 years of age and also to compare them with older gastric cancer patients.

Methods

This study was approved by the local ethics committee and written informed consent was obtained from all participants before study entry.

Patients

The study included gastric cancer patients treated at tertiary hospital in Turkey between 1990 and 2014. We reviewed the demographics of the patients, histopathological characteristics of the tumors and outcome. Data on patients' clinicopathological characteristics were registered and included age, gender, patient symptoms at the time of diagnosis, tumor location, surgical procedures, histological type, LVI, PNI, depth of invasion, lymph node metastases and distant metastases.

Patients were classified according to the International Classification of Diseases for Oncology [21]. Considering age groups in Turkey, 85% of cancer patients are diagnosed when they are older than 40 years [4]. Moreover, in a previous study, Isobe et al. examined the distribution of gender frequency, undifferentiated cancer type, stage IV disease and 5-year OS to describe the suitable age groups for comparison. Demographic and clinicopathological characteristics tended to be different between the patients aged ≤ 40 years and >40 years

[13]. Therefore, two subgroups of patients were created based on age: group 1 consisted of patients 40 years and younger at the time of diagnosis, and group 2 consisted of patients older than 40 years. Patients were included when gastric cancer (adenocarcinoma) was histologically confirmed and survival data were available. Patients were excluded when a tumor other than adenocarcinoma was histologically identified.

In addition to age subgroups, we classified the cases into two subgroups based on anatomic localization:

- Group 1: Proximal stomach (cardia) and
- Group 2: Noncardia (gastric antrum, pylorus, lesser curvature and greater curvature of the stomach) [22].

Gastric adenocarcinoma stage was determined according to the 7th Edition of the International Union Against Cancer Guidelines.

Statistics

Categorical and continuous variables were summarized using descriptive statistics (e.g., median, range, frequency, and percentage) and compared with χ^2 and Mann-Whitney U tests, respectively. OS rates were estimated by the Kaplan-Meier method and compared with log-rank test. OS was calculated from the date of diagnosis until death from any cause or last date of patient known to be alive. All variables that were significant in univariate analysis were entered in multivariate analysis. All analyses were performed using the SPSS 15.0 (SPSS Inc., Chicago, IL, USA) software. The statistical level of significance was set at $p < 0.05$.

Results

The hospital-based registry included 866 cases of gastric adenocarcinoma treated between 1990 and 2014. Ninety-two (10.6%) patients belonged to the young group and the young patients rate from 1990 to 2002 was 10.8%, while it was practically identical (10.6%) from 2002 to 2014. This rate between the two periods was practically identical.

The median age in the young group was 37 years (range 22-40) and 60 years (range 41-75) in the older group. Young group contained higher proportion of female patients (42.4%) than older age group patients (28.6%) and this difference was statistically significant ($p = 0.008$).

There were no significant differences in tumor localization in the stomach (cardia/non-cardia), PNI, LVI, tumor stage, surgical procedures between younger and older groups. Diffuse adenocarcinoma was significantly more common in the young group (48.9%) than in the older group (28.9%) ($p < 0.0001$).

Details of demographic and histologic factors are shown in Table 1.

There was no statistically significant survival difference between patients younger than 40 years and older than 40 years.

Table 1. Details of demographic and histologic factors in younger and older patients with gastric cancer

<i>n</i> =866	>40 years of age (<i>n</i> =774) %	≤40 years of age (<i>n</i> =92) %	<i>p</i> value
Median age (range)	60 (41-75)	36 (22-40)	
Diagnosis			0.91
1990-2002	89.2	10.8	
2002-2014	89.4	10.6	
Sex			0.006
Male	71.4	57.6	
Female	28.6	42.4	
Location			0.95
Cardia	18.2	18.5	
Non-Cardia	81.8	81.5	
Antrum	44.7	48.9	0.1
Greater curvature	18.7	18.5	
Cardia	18.2	18.5	
Lesser curvature	14.7	13.0	
Pylorus	2.5	0	
Linitis plastica	1.2	1.1	
Symptoms			0.69
Dyspepsia	38.9	44.6	
Pain	24.7	23.9	
Nausea	16.3	13.0	
Anorexia	7.5	7.6	
Hemorrhage	6.7	6.5	
Acute abdomen	2.2	0	
Other	1.4	3.3	
Asymptomatic	2.4	1.1	
Operable			0.39
Yes	57.2	53.3	
No	42.8	46.7	
Surgical treatment			0.53
Total gastrectomy	33.6	34.8	
Subtotal gastrectomy	23.9	18.5	
Inoperable/palliative	42.8	46.7	
Histology			<0.001
Intestinal adenocarcinoma	68	42.4	
Diffuse adenocarcinoma	28.4	48.9	
Mixed adenocarcinoma	2.7	7.6	
Other	0.9	1.1	
T stage			0.26
T1	3.3	7.1	
T2	16.4	21.4	
T3	57.8	47.6	
T4	19.7	16.7	
Tx	2.7	7.1	
N stage			0.64
N0	22.7	26.2	
N1	38.1	31.0	
N2	21.1	19.0	
N3	14.1	16.7	
Nx	4.1	7.1	

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<i>n</i> =866	>40 years of age (<i>n</i> =774) %	≤40 years of age (<i>n</i> =92) %	<i>p</i> value
M stage			0.29
M0	48.9%	43.0	
M1	51.1%	57.0	
TNM stage			0.34
I	3.2	5.4	
II	5.9	4.3	
III	25.2	18.5	
IV	48.1	56.5	
Unknown	17.6	15.2	
Lymphovascular invasion			0.40
Positive	32.8	31.5	
Negative	6.6	10.9	
Unknown	60.6	57.6	
Perineural invasion			0.53
Positive	29.7	28.3	
Negative	9.7	14.1	
Unknown	60.9	57.6	

Table 2. Univariate analysis of prognostic factors for gastric cancer in young and older patients

<i>Subgroups</i>	<i>Median OS median±SD (95% CI)</i>	<i>p</i> value
All patients	12.00 ± 0.22 (11.56-12.44)	
Age, years		0.79
>40	12.00 ± 0.24 (11.53-12.47)	
≤40	11.00 ± 0.43 (10.15-11.85)	
Gender		0.26
Male	12.00 ± 0.26 (11.49-12.51)	
Female	12.00 ± 0.44 (11.14-12.86)	
Location		<0.001
Cardia	10.00 ± 0.33 (9.35-10.65)	
Non-Cardia	12.00 ± 0.43 (11.17-12.84)	
TNM stage		<0.001
I	not reached	
II	51.00 ± 10.67 (30.09-71.92)	
III	20.00 ± 1.46 (17.15-22.85)	
IV	10.00 ± 0.21 (9.59-10.41)	
unknown	15.00 ± 2.30 (10.50-19.50)	
LVI		<0.001
yes	20.00 ± 1.35 (17.36-22.64)	
no	29.00 ± 5.39 (18.43-39.57)	
unknown	10.00 ± 0.22 (9.57-10.43)	
PNI		<0.001
yes	20.00 ± 1.43 (17.19-22.81)	
no	28.00 ± 5.47 (17.27-38.73)	
unknown	10.00 ± 0.22 (9.57-10.43)	

The median patient OS was 12 months (range 11.5-12.4). The median OS in patients younger than 40 years was 11 months (10.1-11.8) and 12 months (11.5-12.4) in patients older than 40 years (*p*=0.70) (Figure 1).

Univariate analysis was conducted based on age subgroup, gender, PNI, LVI, disease stage (I, II, III, IV), histology subtype and tumor localization in the stomach (Table 2). Early stage cancer (*p*<0.0001), absence of PNI (*p*<0.0001), absence of LVI (*p*<0.0001), and non-cardia tumors (*p*<0.0001) were significantly associated with better OS rates. The OS curves are shown in Figure 1.

Based on these results, we performed multivariate analysis using Cox proportional hazard model. Non-cardia tumors (*p*=0.016) and stage (*p*<0.0001) were independent prognostic factors of survival outcome. The details of Cox regression analysis of OS are shown in Table 3.

Discussion

Gastric cancer is the fifth most commonly diagnosed malignancy [23], but its incidence is on decline worldwide [1-3,5,24-26]. Nonetheless, gastric cancer is the third leading cause of cancer-related mortality in men and fifth in women [23-26]. Actually, gastric cancer rates have increased among older people in the United States, Japan and Turkey [10, 25-28]. However, in the current study, the incidence of young patients with gastric cancer during 1990 to 2002 and from 2002 to 2014 was the same.

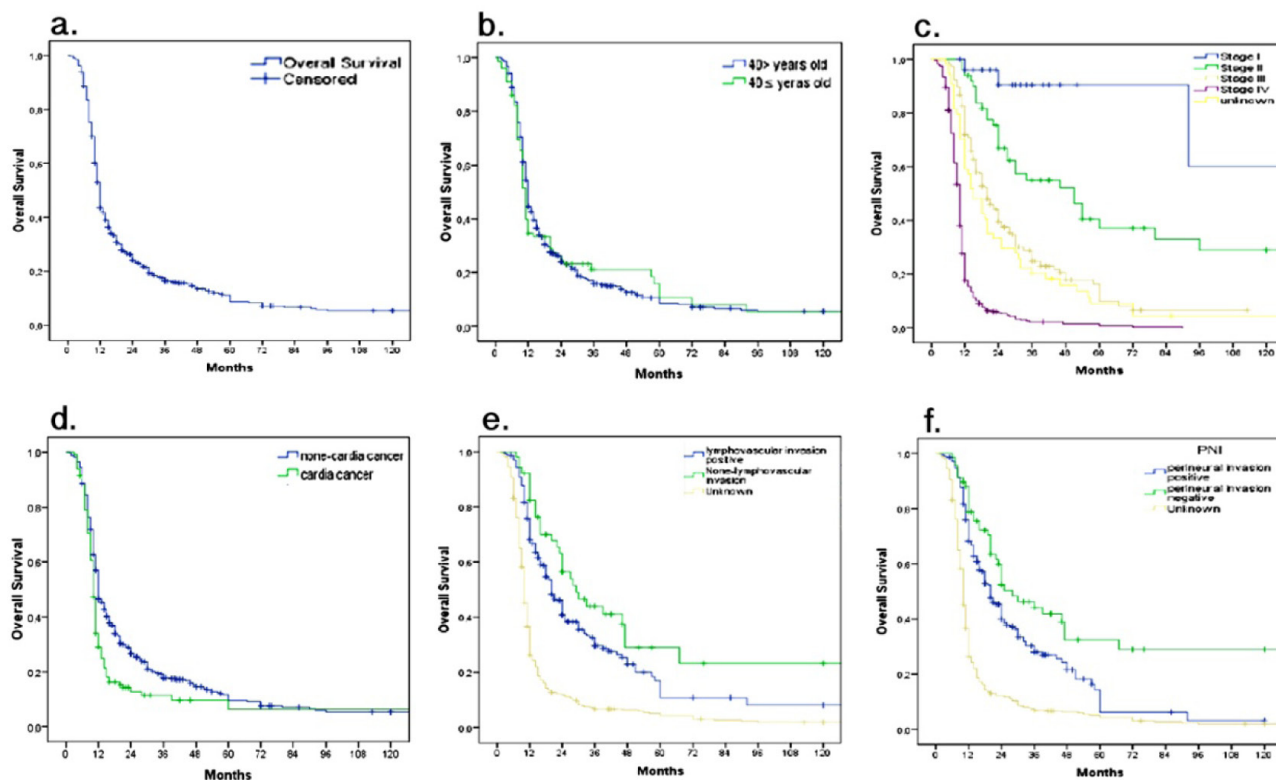


Figure 1. Kaplan-Meier curves of overall survival (OS) according to; **(a)** all patients with gastric cancer (blue line: all patients) OS:12mos (11.5-12.4); **(b)** younger and older patients with gastric cancer (blue line: <40-year-old patients) mOS:12mos (11.3-12.9) (green line: ≥40-year-old patients) mOS:11mos (10.1-11.8,) $p=0.70$; **(c)** stage (blue line: stage I, green line: stage II, brown line: stage III, purple line: stage IV, yellow line: stage unknown, $p<0.0001$); **(d)** cardiac vs. non-cardiac tumors (blue line: non-cardiac location, yellow line: cardiac location, $p=0.016$); **(e)** lymphovascular invasion (blue line: LVI positive, yellow line: LVI absent, brown line: LVI unknown, $p<0.0001$); **(f)** perineural invasion (blue line: PNI positive, green line: PNI negative, brown line: PNI unknown, $p<0.0001$). LVI:lymphovascular invasion, PNI:perineural invasion.

Table 3. Multivariate analysis of prognostic factors in young and older patients with gastric cancer

	Hazard ratio	95% Confidence Interval	p value
TNM stage			
I	0.10	0.03 - 0.33	<0.001
II	0.45	0.28 - 0.72	0.001
III	0.96	0.68 - 1.36	0.824
IV	2.64	1.94 - 3.60	<0.001
Location			
Cardia vs Non-cardia	1.30	1.05 - 1.60	0.016

The clinical outcome of young patients with gastric cancer remains controversial in prior studies. Some studies demonstrated poorer outcome in young patients [14-17]. Other studies demonstrated similar OS rate in young and older patients with gastric cancer [13,18-20].

Our large retrospective study demonstrated that young and older patients with gastric cancer had similar outcome in terms of OS.

The controversy over the outcome between studies can be explained with the fact that in some

studies power was insufficient based on patients' number and in some studies patients were not matched based on tumor stage. However, Isobe et al. found that young and elderly patients showed similar outcome when matched for tumor stage [13]. Our younger and older patient populations with gastric cancer had the same distribution in all stages.

In this study, we demonstrated that younger patients with gastric cancer were mainly female with diffuse-type gastric adenocarcinoma, as reported

in most previous studies [13-20]. The reasons for this increased frequency of females in young gastric cancer patients are still to be defined.

In a previous study, young gastric cancer patients (<40 years of age) had more metastatic disease than older patients [29].

Moreover, Dongyun et al. suggested that diffuse-type gastric adenocarcinoma was associated with poor outcome [30]. In the current study, young patients with gastric cancer had high incidence of diffuse-type gastric adenocarcinoma than older ones, but with the same outcome. This may be attributed to the fact that young patients have less comorbidities and good performance status. However, as a limitation of this study, patient comorbidity index and performance status were absent from their charts.

In the present study, independent poor prognostic factors were advanced stage, LVI, PNI and cardia tumor location and these factors were the same between young and older patients. The study results share similarities to a previous large study [29].

Conclusions

Our large retrospective study demonstrated that young and older patients with gastric cancer had similar outcome in terms of OS. We demonstrated that younger patients with gastric cancer were mainly female with diffuse-type gastric adenocarcinoma. Prognostic factors' effects on OS were similar between young and older patients with gastric cancer.

Authors' contributions

DT, MK, FS and AO collected patient data. MEG analyzed and interpreted the data of all patients and wrote the manuscript. DT and AZ were major contributors in writing the manuscript. KT, EA and SB revised the manuscript and prepared the final form. All authors read and approved the final manuscript.

Conflict of interests

The authors declare no conflict of interests.

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