ORIGINAL ARTICLE

Influential Factors on Survival in Gastric Cancer: A Single-center Study

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Background: Gastric cancer (GC) is one of the conspicuous causes of cancer-related death worldwide. Considering the mounting incidence of this cancer in developing countries such as Iran, determining the influential factors on the survival of involved patients is noteworthy. Hence, we aimed to ascertain the survival rates and the prognostic factors in our GC patients. **Materials and Methods:** In this retrospective cohort study, data of 314 patients with GC in a referral cancer center in Hamadan province of Iran were studied. The outcome of our study was survival time and the influential factors were gender, age at diagnosis, tumor history, tumor grade, surgery history, radiotherapy history, stage of disease, metastasis history, and lymph node involvement. Kaplan – Meier method and log-rank test were used for the calculation and comparing the survival curves and Cox-proportional hazard model was used for the multivariable analysis of prognostic factors. **Results:** In a total of 314 GC patients, the median age at the diagnosis was 63 years (range: 21–92) with most patients (74.84%) being males. The median follow-up time was 2.42 years, and the median survival time was 2 years. The multivariable cox analysis of overall survival (OS) indicated that having distant metastasis increased the hazard of death by about 2.5 times ($P < 0.0001$, heart rates [HR]: 2.53, 95% confidence interval [CI]: [1.71, 3.75]), and receiving surgery as treatment, decreased the hazard of death up to 36% ($P = 0.02$, HR: 0.64, 95%CI: [0.46–0.89]). The other variables did not have any significant effects on the OS. **Conclusion:** The results of this study showed that lower survival (greater hazard of death) strongly and significantly associated with having distant metastasis in patients with GC and receiving surgery could significantly decrease the hazard of death in these patients instead.

Key words: Cox analysis, distant metastasis, gastric cancer, multivariable, overall survival

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INTRODUCTION

Gastric cancer (GC) is the fifth most common malignancy and one of the main causes of death due to malignancies worldwide.[1,2] There is substantial geographic variation in the mortality rates of GC, with the highest rates in developing countries.[3] In the last decade, studies have reported that survival rates in Iran are consistent with those in other developing countries, estimated to be about 12 per 100,000 population.[4] Population-based data on survival rates in gastrointestinal malignancies facilitate precise assessment of the disease impact on community health and aids health-care planning in future. On the other hand, as a life span similar to the general population is anticipated in the surviving cancer patients 5 years after diagnosis,[5] estimation of the 1, 3, and 5-year survival rates could be decisive for assessing and establishing the initial treatment, follow-up duration, and point of therapy termination. Moreover, clinicopathological properties of GC as the main

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prognostic factors including the WHO histopathological type, size of the tumor, pathologic grade, invasion through the gastric wall, vascular invasion, and lymph node involvement, could guide the oncologists for treatment plan designing.[6] Besides, regional factors seem to influence prognosis in GC, so reporting the prognostic factors from different geographical regions could positively add in to the literature. Hence, in this study, we have considered a cohort of patients with GC in Hamadan province of Iran and reported their 1-, 3-, and 5-years overall survival (OS) rates. In addition, we have used univariable and multivariable analyses to assess the prognostic potential of clinicopathological properties of the tumor on survival probability in this population.

MATERIALS AND METHODS

This study was conducted in Imam Khomeini cancer clinic (a referral cancer clinic affiliated by Hamadan University of Medical Sciences, Hamadan, Iran). We retrospectively tracked all cases of GC referred to our clinic in a 10-year period, from March 2009 to March 2019. All the data were fully anonymized in our data bank, and all patients were followed until the end of 2019 to update their survival status. Data regarding to the contributing factors including gender, age at diagnosis, tumor history, tumor grade, surgery history, radiotherapy history, stage of disease, metastasis history, lymph node involvement, survival status, and survival time were extracted. All influential factors were categorical by their nature except the age at the diagnosis that we categorized it based on the expert opinions. OS time measured from the time of diagnosis to the time of death, or the last contact in surviving patients. The inclusion criteria included definitive pathological diagnosis of GC and being native to Hamadan province. Lack of cooperation to complete survival information and major defects in the patient's medical record considered as exclusion criteria. Furthermore, all patients with two primary cancers simultaneously were excluded from the study. The primary cases were 350 that only 314 included in the study based on the mentioned criteria.

This research was approved by the Ethics Committee of Hamadan University of Medical Sciences.

Ethical considerations

The general (and not personal) information on the patients has been used in this study. The study protocol was approved by the institutional review board of Hamadan University of Medical Sciences (IR.UMSHA.REC.1399.456).

Statistical analysis

The data were analyzed retrospectively. Patients who were followed beyond 5 years were censored to improve the comparison between different groups as significant differences between follow-up periods could seriously bias the results. The Chi-squared test was used to compare the categorical variables between dead and alive patients. OS was measured from the time of diagnosis to the time of death, or the last visit/contact in surviving patients. Kaplan – Meier method was derived to calculate the OS and the log-rank Chi-squared test was used to compare the OS among different categories of each predictors. The median follow-up time was calculated using reverse Kaplan – Meier method. We did not have any documented data about patients' disease recurrence, so we were unable to determine the disease-free survival.

The effects of covariates on OS were analyzed through cox proportional hazard model. Variables with a $P < 0.2$ in univariable models were entered the multivariable analysis. Because of the strong association between metastasis and disease stage (causing collinearity in Cox PH modeling), we fitted the multivariable Cox model with metastasis as we believe it is the more important than disease stage. Nonetheless, we showed the univariable analysis of disease stage. The assumption of hazard proportionality was checked through Schoenfeld residuals (results not shown).

All analyses were done using STATA version 11.2 (StataCorp. College Station, TX, USA). $P < 0.05$ was considered significant in all statistical analyses.

RESULTS

Patient characteristics

We retrospectively analyzed 314 cases of GC in our cohort. The median age at diagnosis was 63 years (range, 21–92 years) with most patients (74.84%) being males.

Regarding to the pathological classification, 284 (90.45%) patients had adenocarcinoma, and 175 (77.43%) patients were detected at the clinical stage IV.

Overall, 42.36% of patients received surgical resection, and 100% of patients received at least one cycle of chemotherapy in our clinic and 79.62% received radiotherapy. In general, about half of the whole patients (48.73%) were died up to the end of study which is 5th year of follow-up, but among 176 patients who were metastatic at diagnosis, 110 (62.5%) patients had died ($P < 0.001$). Among 77 patients who had lymph node involvement at diagnosis, 45 (58.44%) had died ($P = 0.05$). The characteristics of patients are presented in Table 1.

Survival analyses

In this study, the median follow-up time was 2.42 years (95% confidence interval [CI]: 2.08–3.17), and the median survival time was 2 years (95% CI: 1.58–2.58). Table 2 summarizes the 1-, 3-, and 5-year rates of OS, and Table 3

Table 1: Demographic and clinical characteristics of gastric cancer patients

Variable	Subgroup	Alive: 161 (51.27%) (%)	Dead: 153 (48.73%) (%)	P*
Sex	Female	47 (29.2)	32 (20.9)	0.09
	Male	114 (70.8)	121 (79.1)	
Age	≤50	31 (19.25)	27 (17.7)	0.065
	51-75	119 (73.9)	103 (67.3)	
	>75	11 (6.85)	23 (15)	
Tumor	Without	15 (9.3)	15 (9.8)	0.83
	With	146 (90.7)	138 (90.2)	
Tumor grade	I	16 (10)	12 (7.8)	0.36
	II	39 (24.2)	29 (18.9)	
	III	33 (20.5)	38 (24.9)	
	Missing	73 (45.3)	72 (48.4)	
Surgery	No	85 (52.8)	96 (62.75)	0.07
	Yes	76 (47.2)	57 (37.25)	
Radiotherapy	No	123 (76.4)	127 (83.01)	0.146
	Yes	38 (23.6)	26 (16.99)	
Stage of disease	I|II	16 (10)	3 (2)	<0.001
	III	20 (12.4)	12 (7.8)	
	IV	66 (41)	109 (71.2)	
	Missing	59 (36.6)	29 (19)	
Metastasis	No	95 (59.01)	43 (28.1)	<0.001
	Yes	66 (40.99)	110 (71.9)	
Lymph node	Not involved	129 (80.1)	108 (70.6)	0.05
	Involved	32 (19.9)	45 (29.4)	

*The *P* values are based on Chi-squared test. Note: 1. Eighty-two patients have died (232 alive) at the end of first year of follow up and this number increased to 141 patients (173 alive) at the third year of follow up while 153 patients died totally (161 alive) at the last year of follow up which is 5 years

reveals the association of different variables with OS by univariable and multivariable analyses. The whole patients' OS curve portrayed in Figure 1a. Of note, the univariable and multivariable analyses limited to those patients who had tumor. This means that those 30 patients without any tumor excluded from these sets of modeling. The factors bearing significant association with increased survival in univariable analyses included receiving surgery ($P = 0.001$) and radiotherapy ($P = 0.009$). Higher clinical stage of the disease, aged more than 75 compared to 50 or less at diagnosis ($P = 0.04$), and having metastasis at diagnosis were associated with significantly decreased OS ($P < 0.0001$). Among other variables, sex and lymph node involvement also entered the multivariable model as they have $P < 0.2$.

On the multivariable analysis, as the two variables including disease stage and metastasis, not only had significant effect in the univariable analysis, but also had a high association with each other ($P < 0.001$), in order to hinder the problem of collinearity, we only entered distant metastasis (considering its importance) in the multivariable analysis and ignored the disease stage accordingly. The multivariable Cox regression analysis of OS indicated that having distant metastasis increased the hazard of death by about 2.5 times ($P < 0.0001$, heart rates [HR]: 2.53, 95% CI: [1.71, 3.75]), and receiving surgery as treatment, decreased the hazard of death up to 36% ($P = 0.02$, HR: 0.64, 95%CI: [0.46–0.89]). The other variables did not have any significant effects on the OS at the 0.05 level of significance. Figure 1b shows the adjusted OS of patients in the multivariable Cox model, indicating that the adjusted median survival of patients with metastasis was 1.08 years while the adjusted median survival of patients without metastasis was more than three times (i.e., 3.25 years). Figure 1c also shows the adjusted median survival of patients who had not had surgery is a bit more than 3 years while the adjusted median survival of patients who had surgery was exactly 5 years.

DISCUSSION

GC is remained to be a major public health issue worldwide and has been one of the main causes of mortality due to cancer in the 21st century.[7] The prognosis in this type of cancer is poor, and its 5-year survival rate is reported to be 10%–40% in most countries, and about 20% in developing countries. Cancer survival rates could be used as indicators for assessing the prerequisites of cancer management in the health-care system. Moreover, pointing out the pathoclinical characteristics affecting the survival rates in GC patients could assist specialists in the process of treatment planning. This study reports the OS of GC patients and evaluates the association between their survival rates and the potential prognostic factors such as age at diagnosis, sex, tumor grade, clinical stage, lymph node involvement, and distant metastasis. In Iran, the reported 5-year survival is about 28%.[8] In our study, the 5-year OS was 32.21%, which is higher than what it was reported in other studies.[9-11] In some studies,[12,13] female patients are reported to have better survival rates; however, in our study, although women had better 5-years OS, the difference of their OS with male patients was not significant. The highest survival rate is observed in patients aged <50 years of age.[10,14] Advanced age at the diagnosis is a significant prognostic factor and our findings were similar to the previous reports indicating worse survival for older patients.[15] Delay in the diagnosis of older patients could be an explanation for the lower survival in advanced age. In our study, comparable to other studies, the histologic type in most patients was adenocarcinoma. In the study by Safari M *et al.*,[16] adenocarcinoma was detected in 89.6% of patients and in the study by Akhondi-Meybodi *et al.*,[14] 94% had adenocarcinoma. Most studies agree that survival rate for adenocarcinoma is lower than other histologic types,[17] which was also confirmed by our results. Our study showed that the advanced clinical stage of tumor was a significant factor which affected the survival probability of patients in both univariable and multivariable analysis. This finding was similar to other studies which also pointed out a higher hazard of death for patients with advanced stage of the tumor.[12,17,18] Distant metastasis is an

Table 2: One, three and five years overall survival rates in patients

Variable	Group	1 year	P§	3 years	P§	5 years	P§
Total	All patients	73.10 (67.52-77.88)	-	40.28 (33.53-46.93)	-	32.21 (24.94-39.67)	-
Sex	Female	73.91 (61.84-82.69)	0.810	49.21 (35.23-61.75)	0.245	41.09 (25.76-55.81)	0.149
	Male	72.83 (66.33-78.29)		37.33 (29.64-44.99)		29.26 (21.17-37.8)	
Age	≤50	66.67 (52.43-77.52)	0.500	49.77 (34.79-63.06)	0.291	40.29 (23.93-56.11)	0.094
	51-75	75.70 (69.09-81.09)		39.26 (30.92-47.48)		33.21 (24.45-42.19)	
	>75	75.70 (69.09-81.09)		39.26 (30.92-47.48)		33.21 (24.45-42.19)	
Tumor	Without	58.49 (37.71-74.46)	0.720	36.21 (16.78-56.10)	0.719	36.21 (16.78-56.10)	0.366
	With	74.61 (68.81-79.49)		40.74 (33.61-47.73)		31.80 (24.12-39.73)	
Tumor Grade	I	80.77 (59.81-91.51)	0.820	39.26 (15.34-62.74)	0.388	-	0.343
	II	80.17 (67.72-88.21)		51.40 (36.45-64.47)		43.90 (28.19-58.55)	
	III	73.64 (61.08-82.71)		32.30 (19.36-45.94)		32.30 (19.36-45.94)	
Surgery	No	64.49 (56.56-71.34)	0.001	32.81 (24.33-41.53)	0.001	25.12 (16.25-34.97)	0.001
	Yes	84.43 (76.68-89.77)		49.77 (39.06-59.59)		41.04 (29.4-52.32)	
Radiotherapy	No	69.40 (62.93-74.97)	0.007	38.44 (31.00-45.81)	0.016	29.76 (21.51-38.44)	0.009
	Yes	87.72 (75.96-93.95)		49.11 (33.41-63.05)		41.83 (25.99-56.91)	
Stage of Disease	I|II	93.55 (62.27-99.07)	<0.0001	73.85 (37.80-90.99)	<0.0001	-	<0.0001
	III	93.22 (75.52-98.26)		55.54 (32.52-73.51)		41.78 (19.31-62.92)	
	IV	64.20 (56.3-71.04)		27.54 (19.85-35.77)		17.81 (10.07-27.34)	
Metastasis	No	85.71 (78.03-90.87)	<0.0001	58.15 (46.61-68.04)	<0.0001	51.30 (38.70-62.53)	<0.0001
	Yes	63.91 (56.05-70.75)		27.93 (20.27-36.08)		18.74 (11.03-28.04)	
Lymph Node	Not involved	75.24 (68.82-80.53)	0.283	43.39 (35.45-51.04)	0.1205	35.64 (27.14-44.21)	0.082
	Involved	66.90 (54.80-76.43)		31.10 (18.86-44.15)		21.17 (8.78-37.12)	

§The *P* values are based on log-rank tests

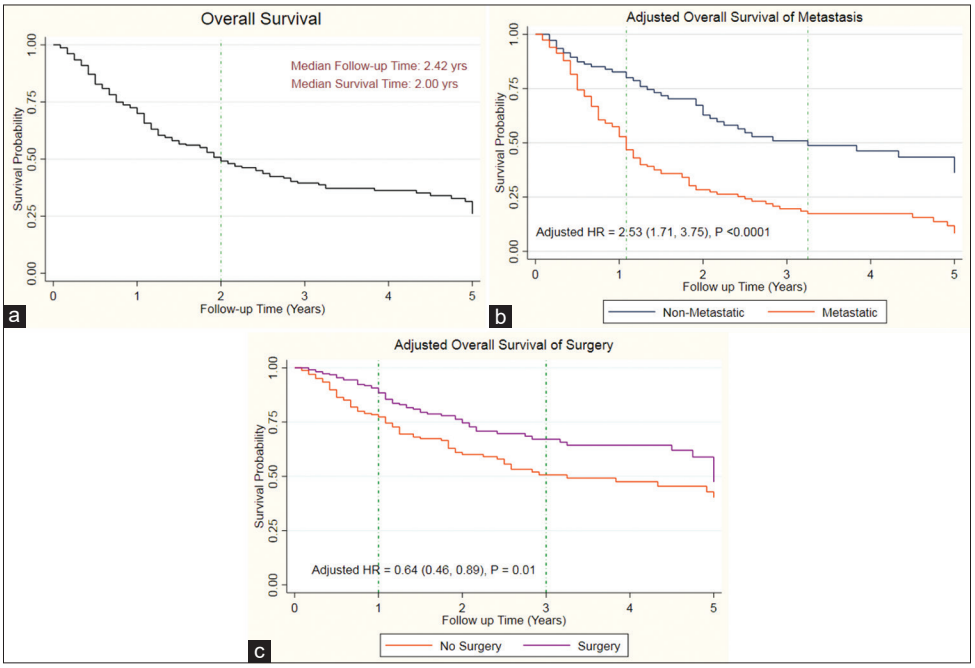

Figure 1: (a) Overall survival of all patients, (b) adjusted overall survival of all patients based on metastasis status and (c) adjusted overall survival of all patients based on surgery

important prognostic factor and many studies have shown that survival depends on the presence of metastasis.[11,19-21]

The results in both univariable and multivariable analyses in our study indicated a higher risk of death and a lower survival rate in patients with distant metastasis.

Surgery is the back bone treatment for GC, offering the best chance of cure, with 5-year survival of 50%–70%.[22] In our study, 5-year survival rate was significantly higher in patients who had undergone surgery compared to those receiving no surgical management. Surgery was reported to increase the 5-year survival rate from 47% to 54% in some studies.[23]

Table 3: Univariable and multivariable cox regression of prognostic factors

Covariates	Univariable		Multivariable	
	HR (CI %)	*P*	HR (CI %)	*P*
Sex				
Female	Ref.[ψ]	0.16	Ref.	0.60
Male	1.32 (0.90-1.96)		1.11 (0.75-1.65)	
Age at diagnosis				
≤50	Ref.	-	Ref.	-
51-75	1.19 (0.78-1.83)	0.41	1.10 (0.71-1.69)	0.67
>75	1.80 (1.03-3.14)	0.04	1.60 (0.90-2.83)	0.11
Tumor grade				
I	Ref.	-	Ref.	-
II	0.72 (0.37-1.44)	0.36	-	-
III	1.12 (0.58-2.15)	0.73	-	-
Surgery				
No	Ref.	0.002	Ref.	0.01
Yes	0.59 (0.42-0.82)		0.64 (0.46-0.89)	
Radiotherapy				
No	Ref.	0.01	Ref.	0.19
Yes	0.58 (0.38-0.88)		0.75 (0.48-1.15)	
Stage of disease				
I|II	Ref.	-	Ref.	-
III	1.45 (0.41-5.16)	0.57	-	-
IV	3.87 (1.23-12.2)	0.02	-	-
Distant metastasis				
Absent	Ref.	<0.0001	Ref.	<0.0001
Present	2.52 (1.77-3.6)		2.53 (1.71-3.75)	
Lymph node metastasis				
Absent	Ref.	0.08	Ref.	0.51
Present	1.36 (0.96-1.92)		0.88 (0.60-1.29)	

[ψ]Every "Ref." term in the table is the abbreviation of reference and shows the reference category in the estimation of HR for other categories of each variable. Note: 1. The univariable and multivariable analyses limited to those patients who had tumor. This means that those 30 patients without any tumor excluded from these sets of modeling. 2. Only covariates with *P*<0.2 in univariable analyses entered the multivariable analysis. 3. Stage of disease has not entered the multivariable model due to its collinearity with distant metastasis. 4. Eighty-two patients have died (232 alive) at the end of first year of follow up and this number increased to 141 patients (173 alive) at the third year of follow up while 153 patients died totally (161 alive) at the last year of follow up which is 5 years. 5. The results of this table is based on the 5 years of follow up. CI=Confidence interval; HR=Hazard ratio

In our study, this raise was from 25% to 40%, this could be explained by the fact that can be explained by the fact that those who underwent surgery had been in lower stages; however, in multivariable analysis, we demonstrated that receiving surgery as a treatment could decreased the hazard of death up to 36%. On the other hand, in our patients, the 5-year survival rate was also significantly influenced by receiving radiotherapy, this was dissimilar to the findings of other studies. Akhondi-Meybodi *et al*. reported that the 5-year survival rate by radiotherapy was 9% compared with 19% in patients not receiving radiotherapy as their treatment.[14] This lower survival rate was explicated by the toxicity of radiotherapy. Some research have shown no significant association between radiotherapy and survival rate.[24-27] Conversely, in our patients, radiotherapy increased the 5-year survival rate 10%.

The advantage of the present study is having a great number of follow-up population, but its limitations are being a retrospective study in a single institution, and not having a prespecified protocol before conducting the exploratory analyses. Therefore, we certainly suggest further research for clarifying the relationship between the clinicopathological markers and their prognostic effect on the survival of GC patients.

CONCLUSION

The results of this study showed that lower survival (greater hazard of death) is strongly and significantly associated with having distant metastasis in patients with GC adjusting for other patients characteristics and receiving surgery could significantly improve the survival (decrease the hazard of death) in these patients instead all over again adjusting for other patients characteristics.

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Conflicts of interest
There are no conflicts of interest.

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