ORIGINAL ARTICLE

A Five-Year Survival Analysis of Patients with Gastric Cancer in Kerman Province

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Abstract

Purpose: Gastric Adenocarcinoma (GAC) is the second most frequent cause of cancer-related deaths worldwide. Determining survival and its associated prognostic factors provides a basis for further interventions to prolong survival among patients with GAC. In this study, we aimed to perform a 5-year survival analysis among GAC patients in Kerman, Iran.

Materials and Methods: This retrospective multi-centric study was conducted on all patients with GAC who were referred to Afzalipour, Bahonar, and Shafa Hospitals in Kerman, Iran in 2009-2019. The 5-year survival rates were calculated based on prognostic factors, including age, histopathology, stage/grade of the tumor, metastatic status, and surgical procedures using the Kaplan-Meier analysis and log-rank test.

Results: The 5-year survival rate of GAC patients with total gastrectomy was higher than those with subtotal gastrectomy ($P = 0.03$). Also, the 5-year survival rate was substantially improved after lymph node dissection ($P < 0.001$). Overall survival has not been significantly different in terms of age, sex, grade, histological type, clinical T stage, lymphovascular invasion, and perineural invasion.

Conclusion: Overall survival was different for the two surgical procedures and lymph node dissection. Therefore, total gastrectomy and lymph node dissection are significant independent prognostic factors for overall survival in patients with GAC.

Keywords: Gastric Neoplasm; Survival; Prognosis.

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1. Introduction

Gastric Cancer (GC) is the fourth most commonly diagnosed malignancy and the second most fatal cancer worldwide [1]. The annual number of deaths attributed to GC was estimated to be approximately 720,000 in 2012, and over 950,000 new cases are diagnosed every year [1, 2]. The incidence of GC varies according to the region; a high incidence in East Asia and South America, while a low incidence in western countries [3].

There are three distinct subtypes of GC: distal intestinal-type GC, which is associated with chronic gastritis and Helicobacter pylori (H. pylori) infection; proximal intestinal-type gastroesophageal cancers, which are more severe; and diffuse signet-ring cell type cancers [4]. Generally, GC is more common in men than in women [5]. Gastric Adenocarcinoma (GAC), the focus of this paper, is the most common histological type (~95%) among all malignancies originating in the stomach. Although the incidence of GAC has decreased over the last 50 years to reach a plateau, GAC still imposes a significant health burden globally [6].

Two topographical subgroups are considered for GAC, including non-cardia and cardia, since these tumors have varying patterns of incidence, etiology, and prognosis [7]. The risk factors for GC include smoking, alcohol consumption, occupational and environmental exposures, H. pylori, blood type, age, sex, and chronic gastritis [8]. Overall, GAC has a weak prognosis; tumor stage, comorbidities, and age are the strongest prognostic factors but have a vast diversity around the world. The prognosis of non-cardia adenocarcinoma is, in general, better than that of cardia adenocarcinoma [7].

The survival time is used for investigating the impact of different treatments for gastric cancer. In order to analyze the survival time, the survival rates are calculated. Factors such as the tumor stage and the treatment type impact on the survival of patients suffering from GC. Given that GC is usually diagnosed at advanced stages, its survival rate is quite low. Only a small number of patients suffering from gastric cancer will survive for five or more years after the diagnosis [9]. Despite the improvements in diagnosis and treatment, the 5-year Overall Survival (OS) rate for advanced GC is still below 30% [10]. Five-year survival in European countries is between 10 and 30 percent [11]. Studies conducted in Iran have reported the 5-year survival to be about 11 to 18 percent [12-14].

In order to study the survival rates of the patients with GAC and its associated prognostic factors, we performed a survival analysis on the patients diagnosed with GAC in 2009-2019 in Kerman, Iran. Our research aimed to estimate the survival rates of patients according to different tumor stages, while also estimating the survival rates of the patients based on different treatment types.

2. Materials and Methods

2.1. Study Population and Data Extracted

This retrospective multi-centric study was conducted on all patients diagnosed with GAC who were referred to Afzalipour, Bahonar, and Shafa Hospitals in Kerman, Iran in 2009-2019. Data were retrieved from the computer database. Study variables included the date of the first hospital attendance, date of diagnosis, age, sex, tumor grade, histological type, type of surgery, lymph node involvement, and clinical T stage. Missing data were completed through a follow-up phone call; otherwise, the sample was excluded from the study.

2.2. Data Analysis

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) software for Windows (version 22.0. SPSS, Inc., Chicago, IL, USA). The categorical variables were described as frequency and percentage, and the continuous variables as mean (±SD). Survival rates were estimated from Kaplan-Meier survival probabilities. Log-rank test was conducted to compare the survival rates according to study variables. A p-value < 0.05 was considered statistically significant.

3. Results

A total of 149 patients with GAC were enrolled in the study. Of the total patients, 112 (75.2%) had passed away at the time of the study. Among the patients, 52 (34.9%) were female. The mean (±SD) age of all patients was 60.12 (±13.8) years. The mean (±SD) age of male and female patients were 62.8 (±12.4) and 60.1 (±13.8) years, respectively. The median 5-year survival rate of the patients was estimated to be 34

(95% CI, 37-41) months (Figure 1). Additionally, the median 5-year survival rates for men and women were 33 (95% CI, 31-44) and 34 (95% CI, 30 to 49) months, respectively.

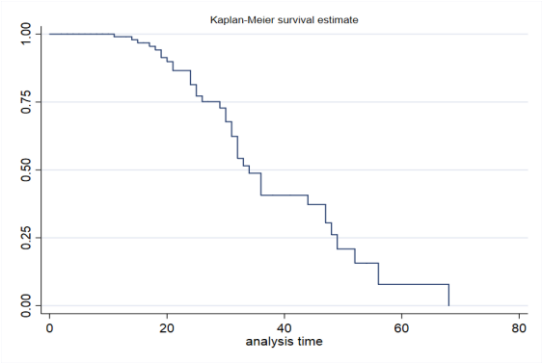

Figure 1. Survival curve of patients with gastric adenocarcinoma according to the Kaplan-Meier survival estimate

The survival rate of patients according to demographic and clinical variables is presented in Table 1. Accordingly, the 5-year survival rate of patients who underwent total gastrectomy was higher than the patients who had subtotal gastrectomy (P = 0.03). However, no significant difference was observed in the 5-year survival of patients according to the age group, sex, and stage of cancer. Furthermore, the 5-year survival of patients had no significant association with neoadjuvant or adjuvant Chemoradiotherapy (CRT). Similarly, the use of neoadjuvant or adjuvant chemotherapy (CTx) had no significant association with the 5-year survival. The 5-year survival of patients with Moderately-Differentiated (MD) grade did not differ from the patients with Poorly-Differentiated (PD) grade. Moreover, the 5-year survival of patients with metastatic lymph nodes had no significant difference compared to the patients with no metastasis. The 5-year survival of patients who were positive for Perineural Invasion (PNI) and Lymphovascular Invasion (LVI) was not significantly different compared to the PNI and LVI negative patients. There was no significant difference in the 5-year survival of patients based on the tumor location. One possible reason for the non-significant results was the small sample size since only 37 individuals were alive.

Out of 149 patients, 65 (43.6%) cases had undergone total gastrectomy and 62 (41.6%) had undergone partial gastrectomy. Overall, the survival rate was different for these two types of surgical procedures (P = 0.03). As depicted in Figure 2, the survival of patients who underwent total gastrectomy was better than that of other patients.

Of all patients, 32 (25.6%) were diagnosed with stage IIA, 37 (29.6%) had stage IIB tumors, 24 (19.2%) had stage IIIA tumors, 21 (16.8%) were diagnosed with stage IIIB, and 11 (8.8%) patients were diagnosed at other stages. The overall survival rate did not change significantly with the disease stage (P = 0.08). Additionally, 74 (53.24%) were diagnosed with moderately-differentiated grade and 65 (46.76%) had a poorly-differentiated grade. The overall survival rate did not differ significantly with the disease stage (P = 0.55) (Figure 3).

In the studied sample, 79 patients (62.2%) had a positive lymphovascular invasion. The overall survival rate did not differ significantly with the disease stage (P = 0.78). Similarly, perineural invasion was positive in 71 cases (55.9%) and the overall survival rate did not differ significantly with the disease stage (P = 0.55).

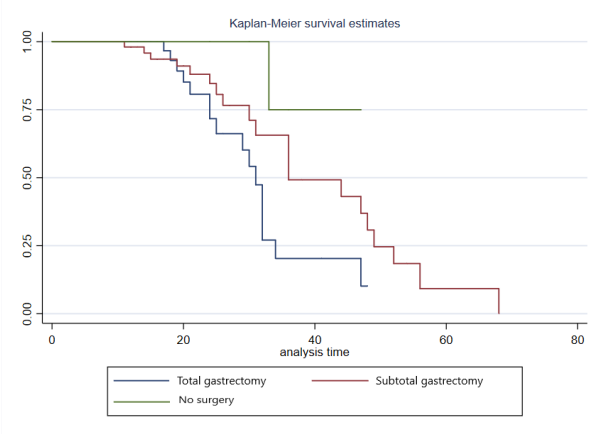

Figure 2. Survival curve of cancer patients according to the type of surgery

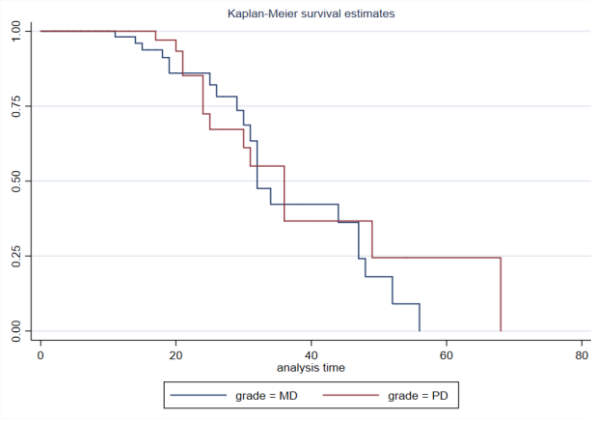

Figure 3. Survival curve of patients according to the disease grade

Table 1. Survival rate of patients with gastric adenocarcinoma based on demographic and clinicopathological characteristics

Variables		Frequency (%)	Median Survival (month)	5-year Survival Rate (%)	P-value Log Rank
Age group (years)	40 or lower	19 (12.7)	34	0.01	0.63
	Higher than 40	130 (87.25)	33	9	
Sex	Male	97 (65.1)	33	11	**0.48**
	Female	52 (34.9)	34	22	
Surgery	Total gastrectomy	65 (43.6)	31	10	0.03
	Subtotal gastrectomy	62 (41.6)	36	9	
	Without surgery	22 (14.77)	-	-	
Stage	II_A	32 (25.6)	36	0.01	0.08
	III_A	24 (19.2)	49	0.01	
	II_B	37 (29.6)	30	12	
	III_B	21 (16.8)	30	1	
	Others (IV_A, I_B, III_C)	11 (8.8)	32	-	
Grade	MD	74 (53.24)	32	0.01	0.55
	PD	65 (46.76)	36	0.01	
LVI	Yes	79 (62.2)	34	11	0.78
	No	48 (37.8)	32	13	
PNI	Yes	71 (55.9)	32	16	0.55
	No	56 (44.1)	34	10	
Margin	Yes	43 (33.6)	32	0.01	0.82
	No	85 (66.4)	32	0.01	
Neoadjuvant CTx	Yes	56 (37.6)	34	14	0.68
	No	93 (62.4)	36	16	
Adjuvant CTx	Yes	84 (64.6)	30	0.01	0.11
	No	46 (35.4)	34	0.01	
RTx	Yes	79 (53.7)	36	0.01	0.37
	No	68 (46.3)	33	0.01	
Neoadjuvant CRT	Yes	30 (20.1)	34	50	0.45
	No	119 (79.9)	33	8	
Adjuvant CRT	Yes	35 (27.1)	32	18	0.32
	No	94 (72.9)	34	8	
N	N0	24 (18.9)	44	20	0.8
	N1	40 (31.5)	32	15	
	N2	41 (32.3)	31	0.01	
	N3	22 (17.3)	31	0.01	
T	T2	31 (24.6)	34	12	0.63
	T3	76 (60.3)	31	10	
	Other (T1, T4, T4a, T4b)	19 (15.1)	36	21	
Tumor location	Cardia	45 (30.4)	33	21	0.24
	Antrum	22 (14.9)	48	19	
	Total	10 (6.8)	-	-	
	Body	30 (20.27)	32	19	
	Prepyloric	24 (16.2)	34	18	
	Pylorus	7 (4.73)	24	0.01	
	Fundus	10 (6.76)	31	0.01	

The type of treatment was neoadjuvant CTx in 56 (37.6%), adjuvant CTx in 84 (64.6%), radiotherapy in 79 (53.7%), neoadjuvant CRT in 30 (20.1%), and adjuvant CRT in 35 (27.1%) patients.

Adjuvant CTx was effective in improving the survival of cancer patients, but the difference in survival was not statistically significant (P = 0.11) (Figure 4). Moreover, neoadjuvant CTx was not effective in improving the survival of cancer patients and the difference was not statistically significant (P = 0.68) (Figure 5).

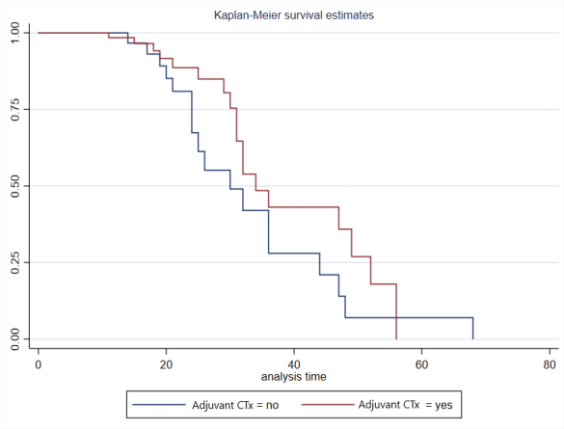

Figure 4. Survival curve for GC patients who underwent adjuvant chemotherapy and those without this treatment

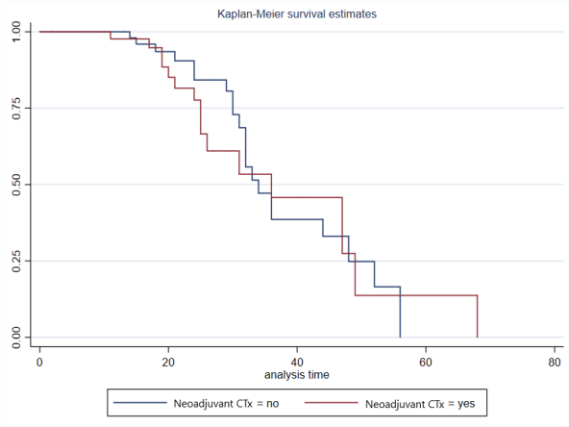

Figure 5. Survival curve for GC patients who underwent neoadjuvant chemotherapy and those without this treatment

Additionally, as demonstrated in Figure 6, twenty months after the treatment, the survival of patients who underwent neoadjuvant CRT was better than that of other patients, but this difference was not statistically significant (P = 0.45). Moreover, the survival of cancer patients who underwent adjuvant CRT was less than that of other patients, but this difference was not statistically significant (P = 0.32) (Figure 7).

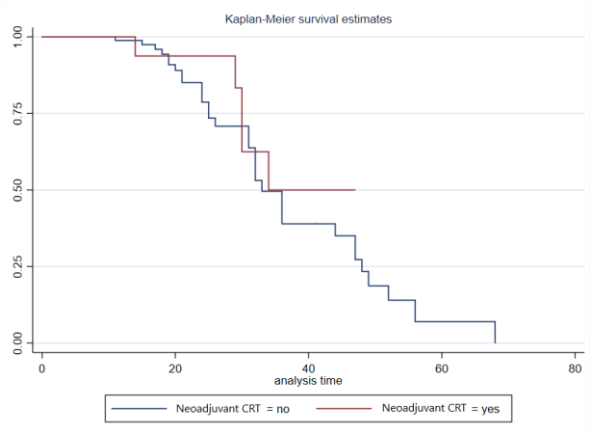

Figure 6. Survival curve for GC patients who underwent neoadjuvant chemoradiation and those without this treatment

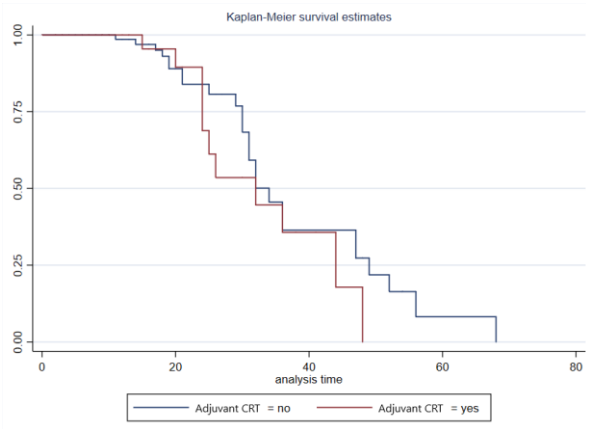

Figure 7. Survival curve for GC patients who underwent adjuvant chemoradiation and those without this treatment

Moreover, the 5-year survival rate was positively associated with the number of lymph nodes dissected (RR = 0.89, 95% CI: 0.85-0.93, P < 0.001), while inversely associated with the number of lymph nodes involved (RR = 1.15, 95% CI: 1.05-1.25, P=0.002) (Table 2).

Table 2. The five-year survival rate of the patients with gastric cancer according to the number of positive lymph nodes and number of lymph nodes removed

Variable	Relative risk	95% confidence limit	P Value
Number of lymph nodes removed	0.89	0.85-0.93	<0.001
Number of positive nodes	1.15	1.05-1.25	0.002

4. Discussion

Despite the developments in the diagnosis and treatment of GC, its prognosis is still poor with a 5-year overall survival of less than 30% in most countries. In China, for instance, GC is the second leading cause of cancer-related deaths, and the present 5-year cancer-specific survival is low due to the fact that over 80% of the patients are detected in an advanced stage [10]. Evaluation of key prognostic factors involved in GC could help clinicians better understand the disease progression and further improve treatment strategies.

Some investigations have used the cut-off age of 50 years for risk assessment, while others used 30 or 45 years [15-17]. In this study, we divided the GC patients into two groups of young (≤40) and elderly (>40) patients. Recently, some studies have proposed that young patients showed worse survival rates due to their characteristics and different tumor behaviors [18]. Song *et al.* [15] stated that the prognosis of GC was changed with age so younger patients had a higher survival rate following surgery as compared to older patients. In our study, 5-year survival was not different between young GC patients and elderly ones.

Our findings showed that 65.1% of the patients with GC were male which is compatible with the results of the studies by Biglarian *et al.* [19] and Ghadimi *et al.* [20]. This indicates the high incidence of gastric cancer in men. The 5-year survival probability following the diagnosis of gastric cancer in gender-specific terms was 11% in men and 22% in women. The results of our study are in agreement with those of Zaraati *et al.*, and Atoof *et al.* [21, 22]; they also showed higher 5-year survival in women as compared to men. These results also indicate that the five-year survival of patients with gastric cancer has been lower in Kerman province than that of other Iranian provinces as well as developing and developed countries. However, the log-rank test revealed no significant statistical difference.

In the present study, 44.8% of the patients had stage 3 and 4 cancer whereas in the study by Larizadeh, 65.9% of the patients had stage 3 and 4 tumors [23]. As can be seen, in our study, more patients were diagnosed at early stages, which can indicate an improvement in the screening program, increased endoscopic interventions, and enhanced patient awareness.

Some researchers have proposed that total gastrectomy had a lower relapse rate as compared to partial gastrectomy, concluding that it could have increased long-term survival [24-26]. Moreover, some studies found that subtotal and total gastrectomies had resembling postoperative complication rates and surgical outcomes; plus, total gastrectomies had the advantages of prolonged survival and symptomatic palliation [9, 27-29]. We suggest that although surgery can raise the 5-year survival rate of patients with cancer, total gastrectomy results in a better survival rate compared to partial gastrectomy for patients with gastric cancer.

The most widely used approach in East Asia is postoperative adjuvant CTx. According to a study, postoperative adjuvant therapy with S-1 (a fluoropyrimidine derivative) for 12 months enhanced 5-year survival and Relapse-Free Survival (RFS) in gastric adenocarcinoma patients with stage II/III who received D2 (lymphadenectomy) gastrectomy [30]. Studies comparing the postoperative adjuvant CRT in comparison with the surgery-alone group have demonstrated that the adjuvant CRT group had longer overall survival and RFS [31]. Preoperative treatment might contribute to improving the R0 resection rate, which is an independent predictive factor of 5-year overall survival [32]. Evidence shows that perioperative chemotherapy for resectable GAC could enhance cure rates [33]. Preoperative induction chemotherapy might be complementary to preoperative chemoradiotherapy since it could diminish the bulk of the primary tumor (in addition to treating micrometastatic cancer) and further improve the efficacy of chemoradiotherapy. It has been recently shown that preoperative chemotherapy prolongs overall survival and disease-free survival [34]. However, the current study did not show any significant difference between the preoperative and postoperative treatments, which can be due to the small sample size.

In the present study, similar to the study conducted by Ajani *et al.* [35], the baseline T and N stages were not associated with the survival rate. However, it may also be claimed that when surgery is the main treatment, the clinical stage can be more helpful and predictive, however, when the clinical stage (pretreatment pathologic stage) is changed as a result of preoperative therapy, the final pathologic stage becomes a predictive factor of patient outcome [35].

Tumors that are positioned in the gastric cardia had a worse prognosis compared to the ones found in other

areas of the stomach. Our study confirms previous reports from case series which state that the prognosis is poorer in cancer of the gastric cardia [36, 37]. This can be due to the fact that these tumors are generally diagnosed at a more advanced stage as compared to more distally positioned stomach tumors [38- 40].

It is established that PNI is a major route of spread for pancreatic, biliary tract, and colorectal cancers. Reportedly, it is an important route for the local spread of tumors which is associated with weak prognosis in head and neck, prostate, pancreas, and biliary tract cancers [41]. In this study, we assessed the positivity of PNI in patients with gastric adenocarcinoma and we found that 71 out of 149 patients (55.9%) were PNI positive. There was no statistical difference with respect to overall survival between PNI positive and negative patients. Selçukbiricik *et al.* demonstrated a significantly increased PNI in patients with gastric adenocarcinoma [41]. They reported that this can be an independent prognostic factor that is not affected by factors such as the tumor stage, lymph node metastases, and other classical ones. This discrepancy may be due to the fact that the patient population in each study had different tumor stages at the time of diagnosis, various clinicopathological features, and displayed different technical stained PNI [41].

Many authors have reported that LVI is an independent prognostic factor for lymph node metastasis and an independent prognostic factor in patients with gastric cancer [42-44]. In the present study, the prognostic value of LVI was evaluated in patients with GC and it was shown that 62.2% of the patients were LVI positive; however, no significant difference was seen in survival according to LVI. However, Lee *et al.* showed that LVI was an independent negative prognostic factor for node-negative patients [45].

In this study, 33.6% of the patients were positive for margins, and positivity of the margins did not affect the 5-years survival. Previous investigations have demonstrated that the existence of microscopic tumor at the resection margin (R1 status) is related to reduced survival; however, the adverse effect seems to depend on factors such as stage, T category/deeper wall penetration, N category/greater lymph node involvement, bigger tumor size (>5 cm), more extensive gastric involvement, Lauren diffuse pattern, high tumor grade/signet ring cell morphology, Borrmann type IV tumors, lymphatic vessel involvement, tumors in the proximal stomach, and total gastrecto [46-48].

The current findings demonstrated enhanced survival among patients with GC after removing a greater number of nodes. Consistently, Chen *et al.* documented a positive association between lymph node dissection and improved survival [49].

Overall, in the present study, the 5-year survival of patients who had total gastrectomy was better than that of patients who underwent subtotal gastrectomy. However, the 5-year survival of patients did not change significantly based on the tumor stage, undergoing neoadjuvant or adjuvant CRT, undergoing neoadjuvant or adjuvant CTx, MD grade as compared to PD, presence or absence of lymph node metastasis, sex, age group, presence of LVI and PNI, and the tumor location.

5. Conclusion

The findings of our study highlight that ascertaining the correct type of surgical procedure is an effective factor in the survival of gastric cancer. Although CRT and CTx did not significantly impact on the 5-year survival rate of patients, our results demonstrated that total gastrectomy and lymph node dissection were associated with a higher 5-year survival rate. Generally, the implementation of a program for early-stage diagnosis of cancer, through enhancement of patient awareness and increased access to screening programs in the regions where the prevalence of gastric cancer is high, seems necessary.

Acknowledgments

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