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Safety of prolonged wait time for gastrectomy in clinical stage I gastric cancer

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ABSTRACT

Background: Patients with stage I gastric cancer tend to wait for surgery. Although the cancer may progress during such a delay, effects of wait time for surgery on survival remain inconsistent. Here, we evaluated the safety of surgical wait time on survival of patients with clinical stage I gastric cancer.
Methods: The outcomes of 556 patients who underwent gastrectomy for clinical stage I gastric cancer between January 2007 and December 2011 were retrospectively evaluated. Patients were stratified into three groups based on wait time: short- (<61 days, n = 185), intermediate- (61–90 days, n = 218), and long-wait (91–180 days, n = 153) groups. Clinicopathological findings and survival were compared among the groups.
Results: The median wait time was 72 days. Age and comorbidities differed among the groups, but clinical and pathological cancer stages did not. Overall survival was comparable; the 5-year overall survival was 90.2%, 93.6%, and 88.8% in the short-, intermediate-, and long-wait groups, respectively. Multivariate analysis revealed that wait time was not an independent prognostic factor for overall survival. Adjusted hazard ratios (HRs) were 0.69 ($p = 0.262$) and 1.03 ($p = 0.926$) in the intermediate- and long-wait groups, respectively, with short wait time as the reference. Relapse-free survival was comparable among the groups (intermediate-wait HR = 0.80, $p = 0.476$; long-wait HR = 1.10, $p = 0.740$).
Conclusion: A half-year wait time for surgery was not independently associated with survival of patients with clinical stage I gastric cancer and may therefore be acceptable.

1. Introduction

Gastrectomy is a standard treatment for gastric cancer and is ideally performed soon after diagnosis. However, a delay until surgery is occasionally unavoidable. High-volume centers are known for long delays or wait times [1]. Moreover, such delays in diagnosis and treatment are more common among the elderly and patients with comorbidities [2,3]. In addition, because of high priority to treatment of patients with advanced stage cancer, patients with early stage cancer may experience delays [4]. Thus, wait time unfortunately exists in the real world.

Wait time until surgery has been associated with survival in various cancers [1,5]. Disease progression that occurs while awaiting surgery may worsen survival [3]; however, there is a wait-time paradox that patients with a long wait time show good survival because they have less advanced disease compared with those with a short wait time [6]. In addition, several previous studies have found that delays in diagnosis are not associated with cancer outcomes in patients with breast and pancreas cancers [7,8]. However, results of these studies should be interpreted with caution because it included patients with cancers of various stages without adjustments for confounding factors. Hence, effects of surgical wait time on cancer survival is not clear.

Our previous study revealed that preoperative wait time of up to 90 days did not affect survival in clinical stage II/III gastric cancer [9]. Because stage I gastric cancer is considered to develop slower than advanced stage cancer, we hypothesized that safe wait time that does not affect survival will be long. If a safe wait time for stage

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I gastric cancer is defined, treatment for comorbidities, preoperative rehabilitation, and nutritional intervention could be possible. These preoperative interventions may contribute in decreasing postoperative complications and improving survival. Therefore, determining the acceptable wait time in stage I gastric cancer is valuable. Hence, in this study, we investigated the impact of wait time from diagnosis to surgery on long-term survival of patients with clinical stage I gastric cancer.

2. Methods

2.1. Patients

We retrospectively evaluated 915 consecutive patients with clinical stage IA (T1[M, SM]N0) or IB (T1N1, T2[MP]N0) gastric cancer with gastrectomy at the Shizuoka Cancer Center between January 2007 and December 2011. The study excluded 218 patients with endoscopic submucosal dissection, two with preoperative chemotherapy, 95 with multiple active cancers, two who waited more than 180 days from diagnosis to surgery, and 42 for whom the date of preoperative initial esophagogastroduodenoscopy (EGD) was unknown. The remaining 556 patients were included. The institutional review board of Shizuoka Cancer Center (Approval no. 28-J171-28-1-3) approved this study.

Pathological tumor depth, nodal status, and curability of surgery were determined by the criteria of the International Union against Cancer (UICC) TNM Classification of Malignant Tumors [10]. Histological grading followed the Japanese Gastric Cancer Association classification [11]. Gastrectomy and lymph node dissection followed the Japanese gastric cancer treatment guidelines [12]. The surgeons who performed or supervised the procedures were board-certified by the Japanese Society of Gastroenterological Surgery.

2.2. Definition of wait time

Wait time was defined as the number of days from macroscopic diagnosis using EGD to gastrectomy. The initial endoscopies were performed at a clinic or at a regional hospital. Adenocarcinoma was preoperatively confirmed in gastric tumor biopsy specimens. Patients were stratified into three monthly unit groups based on wait time, short- (<61 days), intermediate- (61–90 days), or long-wait (91–180 days) groups, as the number of patients in these three groups were similar.

2.3. Evaluation

The clinicopathological characteristics and surgical procedures in each group were compared. Overall survival (OS) and relapse-free survival (RFS) were calculated in each group from the date of EGD diagnosis and were compared. The follow-up schedule followed the Japanese gastric cancer treatment guidelines [12].

2.4. Statistical analysis

Continuous variables were reported as medians and 25th and 75th percentiles and compared using Fisher's exact and Kruskal–Wallis tests. Cumulative survival was estimated by the Kaplan–Meier method. Independent prognostic factors were identified by univariate and multivariate analyses using the Cox proportional hazards model. A two-sided p-value of <0.05 was considered significant. The statistical analysis was performed using R Statistics version 3.2.0 (R Foundation, Vienna, Austria).

3. Results

3.1. Wait time

Fig. 1 shows the wait times from initial EGD to surgery. The median wait time was 72 days. There were 185 patients in the short-wait group (33.3%), with a median of 48 days; 218 patients in the intermediate-wait group (39.2%), with a median of 75 days; and 153 patients in the long-wait group (27.5%), with a median of 105 days. The median referral wait time from EGD in the clinic or other hospital to initial examination in the Division of Gastric Surgery at Shizuoka Cancer Center was 18 days; 13 days in the short-wait, 19 days in the intermediate-wait, and 28 days in the long-wait groups.

3.2. Patient characteristics

Table 1 summarizes the clinical characteristics. There were significant differences in age and comorbidity among the groups, but preoperative clinical stage did not differ. Table 2 shows the surgical and pathological characteristics. The surgical approach and procedure, pathological tumor depth, regional lymph node metastasis, and cancer stage in the three groups did not differ significantly. One pathological stage IV patient was found in the long-wait group. R0 resection was performed in most patients; however, R1 resection was performed in four patients. Of these patients, there were positive microscopic resection margins for

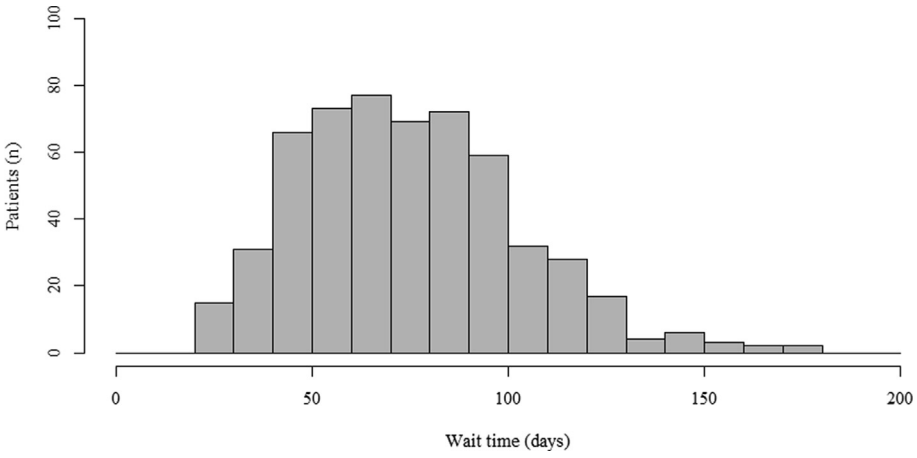

Fig. 1. Wait time from endoscopic diagnosis to surgery.

Table 1
Clinical characteristics of patients in the short- intermediate-, and long-wait groups.

	Wait time			p
	Short	Intermediate	Long	
	($n = 185$) [%]	($n = 218$) [%]	($n = 153$) [%]	
Age (years)				<0.001
Median (IQR)	62 (53–70)	64 (57–71)	67 (60–75)	
Sex				0.288
Male	111 [60]	146 [67.0]	102 [66.7]	
Female	74 [40]	72 [33.0]	51 [33.3]	
Body mass index (kg/m^2)				0.110
Median (IQR)	22.5 (20.4–24.6)	22.9 (21.0–25.3)	22.5 (20.5–24.5)	
ECOG performance status				0.275
0 or 1	185 [100]	218 [100]	152 [99.3]	
2 or 3	0	0	1 [0.7]	
Comorbidity				0.003
	59 [31.9]	66 [30.3]	71 [46.4]	
Clinical stage				0.102
cIA	146 [78.9]	183 [83.9]	134 [87.6]	
cIB	39 [21.1]	35 [16.1]	19 [12.4]	

IQR: interquartile range.
ECOG: Eastern Cooperative Oncology Group.

permanent specimens in three and positive peritoneal lavage cytology in one. Three patients with positive margins were in the short- and intermediate-wait group, and results of intraoperative frozen biopsy were negative for cancer. Additional surgery was performed in two patients; however, recurrence was noted. One patient was followed up without surgery, and no recurrence was noted. One patient with positive cytology in the long-wait group showed no distant metastases. Therefore, distal gastrectomy with D2 lymphadenectomy and S-1 adjuvant chemotherapy for 1 year were performed, and no recurrence was noted.

Table 2
Surgical and pathological characteristics of patients in the short- intermediate-, and long-wait groups.

	Wait time			p
	Short	Intermediate	Long	
	($n = 185$) [%]	($n = 218$) [%]	($n = 153$) [%]	
Surgical approach				0.517
Open	151 [81.6]	168 [77.1]	120 [78.4]	
Laparoscopy	34 [18.4]	50 [22.9]	33 [21.6]	
Surgical procedure				0.609
Distal gastrectomy	145 [78.4]	167 [76.6]	109 [71.2]	
Total gastrectomy	30 [16.2]	40 [18.4]	33 [21.6]	
Proximal gastrectomy	10 [5.4]	11 [5.0]	11 [7.2]	
Location				0.607
Upper	34 [18.4]	40 [18.4]	35 [22.9]	
Middle	108 [58.4]	120 [55.0]	77 [50.3]	
Lower	43 [23.2]	58 [26.6]	41 [26.8]	
Histological type				0.063
Differentiated	82 [44.3]	100 [45.9]	86 [56.2]	
Undifferentiated	103 [55.7]	118 [54.1]	67 [43.8]	
Primary tumor				0.437
T1	140 [75.7]	177 [81.2]	122 [79.7]	
T2	25 [13.5]	21 [9.6]	12 [7.8]	
T3	14 [7.6]	17 [7.8]	13 [8.5]	
T4	6 [3.2]	3 [1.4]	6 [3.9]	
Regional lymph nodes				0.195
N0	130 [70.3]	177 [81.2]	123 [80.4]	
N1	33 [17.8]	25 [11.5]	19 [12.4]	
N2	17 [9.2]	11 [5.0]	7 [4.6]	
N3	5 [2.7]	5 [2.3]	4 [2.6]	
Pathological stage				0.162
I	143 [77.3]	179 [82.1]	127 [83.0]	
II	31 [16.8]	35 [16.1]	19 [12.4]	
III	11 [5.9]	4 [1.8]	6 [3.9]	
IV	0	0	1 [0.7]	
Residual tumor				1.000
R0	184 [99.5]	216 [99.1]	152 [99.3]	
R1	1 [0.5]	2 [0.9]	1 [0.7]	

3.3. Long-term survival

The median follow-up of survivors was 60.9 months. Nine patients (4.9%) in the short-wait group, nine patients (4.1%) in the intermediate-wait group, and ten patients (6.5%) in the long-wait group, died of gastric cancer (Supplementary Table 1). The differences in cancer deaths were not significant. Fig. 2 shows the Kaplan–Meier OS estimates of survival in the three study groups. The 5-year OS was 90.2% in the short-wait, 93.6% in the intermediate-wait, and 88.8% in the long-wait groups. The hazard ratios (HRs) were 0.77 in the intermediate-wait ($p = 0.41$) and 1.45 in the long-wait group ($p = 0.22$) with the short-wait group as the reference. Multivariate analysis of OS found that age was independently related to OS and that wait time was not (Table 3). The adjusted HR was 0.69 ($p = 0.262$) in the intermediate-wait group and 1.03 ($p = 0.926$) in the long-wait group. RFS was 89.1% in the short-wait, 92.2% in the intermediate-wait, and 87.5% in the long-wait groups (Supplementary Fig. 1); the differences were not significant, with adjusted HRs of 0.80 in the intermediate-wait ($p = 0.476$) and 1.10 in the long-wait groups ($p = 0.740$).

4. Discussion

The present study found that a wait time of half a year or less from diagnosis to gastrectomy for clinical stage I gastric cancer was not associated with long-term survival, adjusting for covariates. The survival effect of wait time would be predicted to differ with cancer stage. Advance stage cancer may progress rapidly, with increased wait time exerting a strong negative effect on survival. However, clinical stage I gastric cancer allows to secure time before surgery. Conversely, even among stage I gastric cancers, sarcopenia has been found to be associated with poor survival among the elderly or patients with severe comorbidities [13]. Therefore, preoperative multimodal rehabilitation and nutritional intervention for such patients may contribute to reduced postoperative complications or prolonged postoperative survival.

In our center, the median wait time from diagnosis to treatment was 72 days. The results are consistent with those of Bilimoria et al.

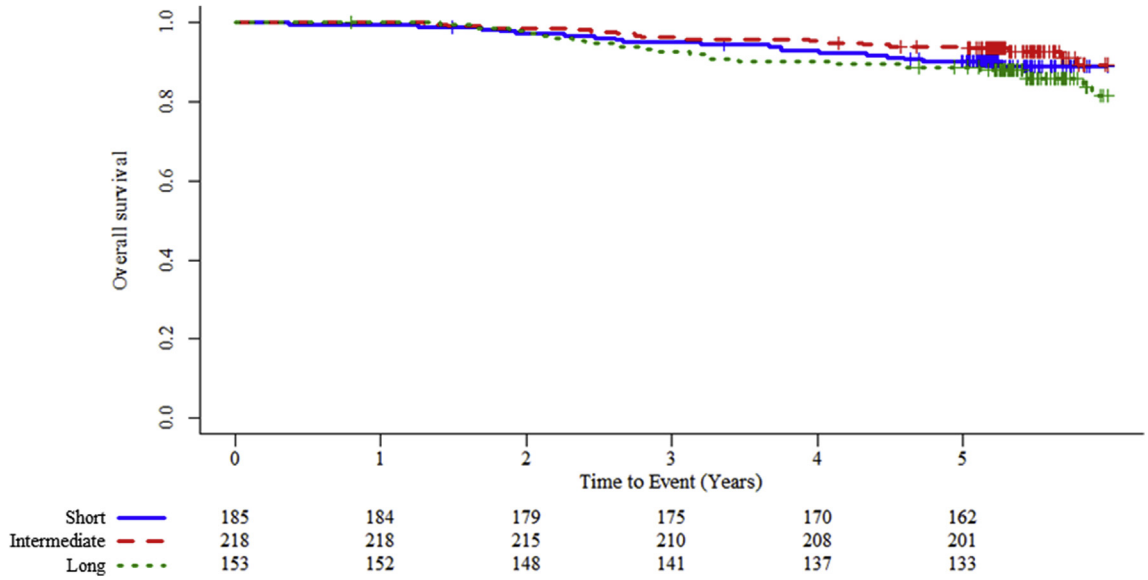

Fig. 2. Overall survival (OS) after curative gastrectomy. The hazard ratio (HR) = 0.77 (95% CI: 0.41–1.44), $p = 0.410$ in the intermediate-wait group (*dashed line*). HR = 1.45 (95% CI: 0.80–2.10), $p = 0.218$ in the long-wait group (*dotted line*) compared with OS in the short-wait group (*solid line*).

Table 3
Multivariate analysis of overall survival.

	hazard ratio	95% CI		*p*
		lower	upper	
Wait time				
Short	1			
Intermediate	0.69	0.37	1.31	0.262
Long	1.03	0.56	1.88	0.926
Age				
(1-year increment)	1.09	1.06	1.12	< 0.001
Sex				
Male	1			
Female	0.64	0.36	1.12	0.120
Comorbidities				
No	1			
Yes	0.91	0.55	1.52	0.729
Surgical procedure				
Distal gastrectomy	1			
Total/Proximal gastrectomy	1.13	0.65	1.96	0.660
Clinical stage				
cIA	1			
cIB	1.09	0.58	2.06	0.793

who reported that older patients and those with comorbidities had prolonged wait times and that patients with early stage cancer had longer wait times than those with advanced stage cancer [1]. In our study, patients in the long-wait group were older and a greater proportion had comorbidities than patients in the other groups. In the long-wait group, more time was required for screening of physiological status and evaluation of the ability to tolerate surgery.

An association of short-wait time and an advanced stage of cancer has been reported previously [6,14]. To avoid the confounding effect of cancer stage on wait time in contrast to previous studies that included stage I to IV cancers, our study population was limited to stage I cancer patients [15,16]. Our three wait-time groups did not differ in pathological stage distribution, which suggests that a wait time of up to half a year did not result in cancer progression in the clinical stage I patients. Even in subgroup analysis among patients with clinical stage IB gastric cancer, pathological stage and OS were also similar in the three groups (Supplementary Table 2). However, the analysis was performed with a small number of patients.

The evidence that treatment delay results in poor survival is weak, although a prolonged wait for treatment leads to patient anxiety and decreased social activity [17]. The concern that cancer progression occurs with prolonged wait time and decreases survival has not been supported by previous reports. A retrospective analysis of a national registry in Korea, including 147,682 patients with five different cancers, found that treatment delays of more than 1 month from gastric cancer diagnosis were not associated with decreased survival [16]. However, the analysis included variations in study populations and time frames, and no adjustment was made for cancer stage. On the other hand, shortened time to the initial treatment could not translate into improved cancer survival in a health program in the United Kingdom [15]. The problem of this program was that only 26% of the patients underwent curative treatment. Euro-American studies demonstrated no association of wait time with survival due to high prevalence of metastatic cancer [18,19]. Moreover, wait-time paradox had been reported showing that patients who waited surgery longer showed less invasive cancer and better survival [20,21]. Including a mixture of cancer stages in a study population makes it difficult to evaluate the association of wait time and survival. The strength of this study is inclusion of only patients with resectable clinical stage I gastric cancer and the analysis as adjusted for patient characteristics and pathological cancer stage. There was a trend of mortality in the long-wait group possibly because the patients in this group were older and presented with more comorbidities than those in the other groups. This trend may have been observed due to confounding factors, as evidenced by decrease in HR of survival from 1.44 in univariate to 1.10 in multivariate analyses. Our surgical quality was satisfactory, as indicated by 5-year OS rate of 88.8%–93.6%, which is comparable to the 89.0%–96.3% 5-year OS rate following gastrectomy for clinical stage I gastric cancer in previous reports [22,23].

The study limitations include its single-center retrospective design. Another limitation was the presence of differences in the patient clinical characteristics in the three study groups. A third limitation was the broad range of the wait time in the long-wait group. Only 34 patients waited more than 120 days for surgery. The survival of the 34 patients was comparable to that of the short- and intermediate-wait groups; however, further study is required to confirm that waiting more than 4 months is truly safe.

5. Conclusion

In patients with stage I gastric cancer, a wait time of up to half a year from EGD to gastrectomy may not affect long-term survival. A delay to improve general physiological status or comorbidities, or to accommodate the patient's social environment, is acceptable.

Conflict of interest

The authors declare that they have no conflicts of interest.

Ethical standards

All procedures followed the ethical guidelines of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1964 and its later versions.

Disclosures

The authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.06.006.

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