



ORIGINAL ARTICLE

The impact of hiatal hernia on survival outcomes in patients with gastroesophageal junction adenocarcinoma

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Abstract

Aim: A hiatal hernia (HH) complicates the diagnosis and surgical treatment of gastroesophageal junction (GEJ) cancer. This study aimed to investigate the effect of HH on the survival outcomes of GEJ cancer patients.

Methods: This single-center study reviewed clinical data of 78 patients with GEJ adenocarcinoma who underwent R0 resection from 2008 to 2017. The patients were divided into two groups according to whether they presented with or without HH: the HH (+) group (n = 46) and the HH (-) group (n = 32).

Results: Patients in the HH (+) group were older than those in the HH (-) group (69.0 vs 67.5 years, $P = .018$). Regarding surgical outcomes, intra-abdominal infectious complications was more common in the HH (+) group than in the HH (-) group (23.9% vs 9.4%, respectively; $P = .089$), particularly abscess formation (17.4% vs 3.1%, respectively; $P = .036$). Neither overall survival (OS) nor relapse-free survival (RFS) differed between the two groups. However, survival rates were significantly worse in a subset of patients with T3-4 disease (OS: log-rank, $P = .036$) (RFS: log-rank, $P = .040$) in the HH (+) group. In a multivariate analysis for OS in this cohort, HH was an independent prognostic factor (hazard ratio 3.60; 95% confidence interval 1.06-11.9, $P = .032$).

Conclusion: Hiatal hernia may adversely affect surgical and survival outcomes in patients with GEJ cancer. Thus, surgical strategy must be carefully considered in these patients.

KEYWORDS

gastric cancer, gastroesophageal junction cancer, hiatal hernia, surgical resection, survival outcome

1 | INTRODUCTION

The incidence of gastroesophageal junction (GEJ) cancer is increasing globally.^{1,2} Previous studies suggest that patient prognosis is less

favorable in GEJ cancer compared with gastric cancer, even after curative surgical resection.³ This may reflect the more difficult surgical approach required or the more complicated metastatic spread that occurs due to the anatomical features of the GEJ.⁴ A recent

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Japanese multicenter cohort study undertook lymph node metastasis mapping in GEJ cancer patients.⁵ This study recommended basing the extent of lymph node dissection on the estimated length of esophageal invasion.⁶ However, the optimal surgical approach for GEJ cancer resection is still controversial, especially when the esophageal invasion length is between 2 and 4 cm. The transhiatal approach has been performed in most surgical resections of GEJ cancer in Japan, but reconstruction is technically challenging. Therefore, the safest method that provides clean surgical margins and does not cause post-surgical gastroesophageal reflux is still under debate.

The prevalence of hiatal hernia (HH) is also increasing, due to our aging population and the rising global prevalence of obesity. In HH, the cardia herniates into the mediastinum via the hiatus. HH can coexist with GEJ cancer.⁷ Clinically, the presence of HH can make the preoperative diagnosis of GEJ cancer difficult, for example estimating the anatomical tumor location or the esophageal invasion length. Misidentification of the anatomical tumor location may make transhiatal surgery much more complicated and lead to a higher rate of postoperative complications. For example, unexpected high-level esophageal resection forces challenging intra-mediastinal anastomosis. Development of severe postoperative complications is known to be a critical risk factor for the long-term prognosis of all types of cancer.⁸⁻¹¹ In addition, the lymphatic drainage route may be altered due to the presence of HH. Therefore, HH may influence not only short-term but also long-term outcomes in patients with GEJ cancer.

In this context, we hypothesized that the presence of HH may adversely affect surgical and survival outcomes in patients with GEJ cancer. Few studies have examined the link between HH and survival outcomes in GEJ cancer patients. This study aimed to assess the impact of HH on the surgical and survival outcomes in patients with GEJ cancer.

2 | METHODS

2.1 | Patients

Patients who underwent R0 surgery via the transhiatal approach (total/proximal gastrectomy and lower esophageal resection with lower mediastinal lymphadenectomy) for primary GEJ adenocarcinoma (with an epicenter within 2 cm of the GEJ) at the National Cancer Center Hospital East, Japan, from January 2008 to December 2017 were included in this study. The clinical data of these patients were reviewed using an in-house database. The exclusion criteria were as follows: (1) patients who received preoperative chemotherapy; (2) conversion surgery for cStage IVB patients; (3) presence of other primary malignant disease; (4) GEJ cancer at the remnant stomach; (5) R1/R2 resection. This study was approved by the Institutional Review Board of the National Cancer Center Hospital East.

2.2 | Definition and assessment of HH

The presence of HH was diagnosed by preoperative endoscopy and barium contrast X-ray. The degree of HH was graded according to Makuuchi's classification¹² using endoscopic findings (Figure 1). This classification is as follows from the most severe: Grade A) gastric mucosa is seen more than 3 cm above the hiatus; Grade B) gastric mucosa is seen circularly less than 3 cm above the hiatus; Grade C) gastric mucosa is seen partially above the hiatus; Grade D) the mucosal junction is seen below the hiatus. Following this classification, the patients were divided into a HH (+) group and a HH (-) group. The patients diagnosed as Grade A, B, or C were categorized as HH (+). The patients diagnosed as Grade D were categorized as HH (-). The diagnosis was made by a board-certified fellow of the Japan

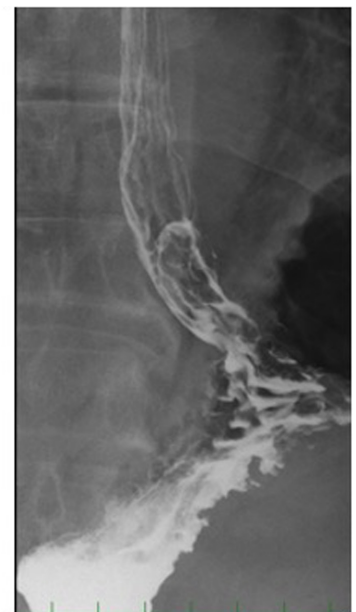
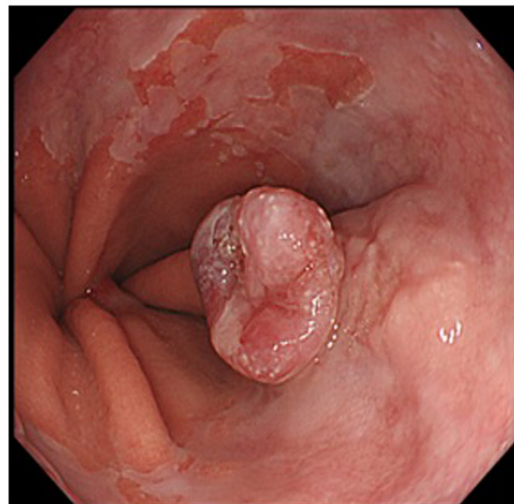


FIGURE 1 Representative images of gastroesophageal junction cancer accompanied with hiatal hernia (Grade A according to Makuuchi's classification)

Gastroenterological Endoscopy Society with abundant experiences of esophageal/gastric cancer treatment.

2.3 | Assessment of clinical parameters

The macroscopic type and tumor staging followed the Japanese classification of gastric carcinoma: 3rd English edition.¹³ Postoperative complications were graded following the Clavien-Dindo classification, and grade >II complications were recorded in this study.¹⁴ Anastomotic leakage, intra-abdominal abscess formation, and pancreatic fistula were categorized as "intra-abdominal infectious complication."

2.4 | Statistical analysis

The Student's *t*-test or Fisher's exact test were used to assess the differences in characteristics between the two groups. Survival curves were drawn using the Kaplan-Meier method, and differences were determined by the log-rank test. Univariate and multivariate analyses were performed with a Cox hazard model to detect the independent prognostic factors. All statistical analyses were performed using the JMP software program, version 15 (SAS Institute). All *P*-values were two-sided, and *P* < .05 was considered statistically significant.

3 | RESULTS

3.1 | Clinicopathological characteristics

In total, 84 patients were screened from the database. A total of six patients were excluded, therefore 78 patients were included in this study. According to the Makuuchi classification, the degree of HH in these 78 patients was as follows: seven patients had Grade A; 21 patients had Grade B; 18 patients had Grade C; and 32 patients had Grade D. Therefore, 46 patients were assigned to the HH (+) group

and 32 patients to the HH (-) group (Figure 2). The clinicopathological characteristics of patients in the HH (+) and the HH (-) group are summarized in Table 1. Patients in the HH (+) group were slightly older than those in the HH (-) group (69.0 vs 67.5 years old, *P* = .018). There was no significant difference in the body mass index, histological type, cT factor, cN factor, tumor size, or esophageal invasive length between the two groups. The median length of esophageal invasion was 10 mm (range: 0-40 mm). In terms of surgical approach, 58% (45/78) of patients underwent total gastrectomy and 42% (33/78) underwent proximal gastrectomy. Similarly, 62% (48/78) of patients underwent open surgery and 38% (30/78) underwent laparoscopic surgery.

3.2 | Surgical outcomes

Surgical outcomes of the HH (+) and the HH (-) groups are shown in Table 2. No significant difference was seen in operative time or intraoperative blood loss between the two groups. Additional intraoperative resections of the esophageal stump due to a tumor-positive margin diagnosed by frozen section was more frequent in the HH (+) group (19.6% vs 6.3%, *P* = .082), but this did not reach statistical significance. There was no patient who needed conversion to thoracic approach. In terms of postoperative complications, intra-abdominal infectious complications (leakage, intra-abdominal abscess, and pancreatic fistula) was more common in the HH (+) group than in the HH (-) group (23.9% vs 9.4%, *P* = .089), but this did not reach statistical difference. However, the incidence of intra-abdominal abscess in the HH (+) group was significantly higher than that in the HH (-) group (17.4% vs 3.1%, *P* = .036).

3.3 | Survival outcomes

The median follow-up period was 46.5 (4-113) months in the HH (+) group and 60.0 (10-107) months in the HH (-) group, respectively.

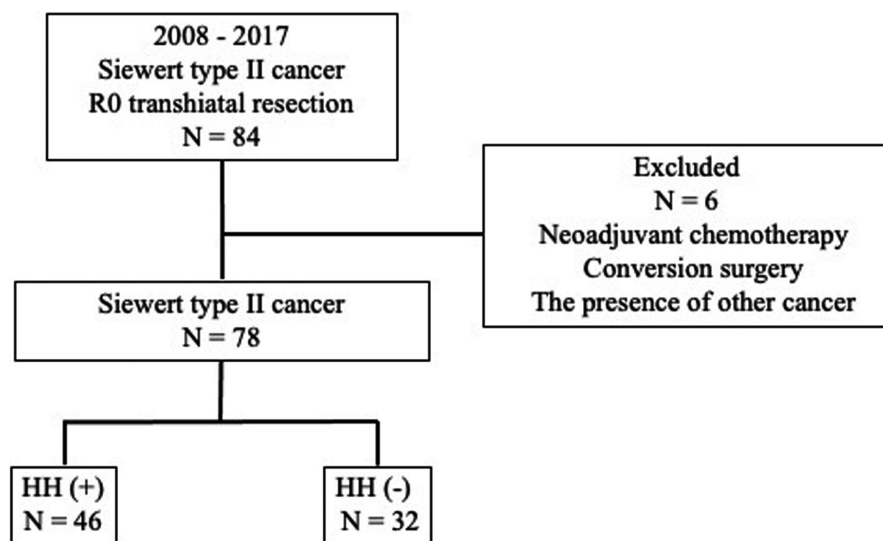


FIGURE 2 Flow chart depicting the patient selection process. Grade A, B, and C were classified into HH (+). Grade D was classified into HH (-)

TABLE 1 Baseline patient characteristics

	Hiatal Hernia (+) n = 46	Hiatal Hernia (-) n = 32	P-value
Age, years	69 (37-86) ^a	67.5 (40-83) ^a	.018
Sex (M/F)	39 (84.8%)/7 (15.2%)	26 (81.3%)/6 (18.7%)	.681
BMI, kg/m ²	22.6 (15.8-32.6) ^a	22.6 (18.9-31.3) ^a	.952
ASA-PS (1-2/3)	45 (97.8%)/1(2.2%)	30 (93.7%)/2 (6.3%)	.669
Histological type (diff./undiff.)	33 (71.7%)/13 (28.3%)	27 (84.4%)/5 (15.6%)	.342
Gross appearance Type 3/4	14 (30.4%)	11 (34.4%)	.714
Presence of esophageal invasion	37 (80.4%)	29 (90.6%)	.220
Esophageal invasive length ^b , mm	10 (0-40) ^a	10 (0-40) ^a	.545
Presence of short segment Barrett's esophagus	7 (15.2%)	1 (3.1%)	.067
Tumor size, mm	35 (10-100) ^a	40 (20-80) ^a	.343
Clinical T (1-2/3-4)	29 (63.0%)/17 (37.0%)	13 (40.6%)/19 (59.4%)	.066
Clinical N (-/+)	31 (67.4%)/15 (32.6%)	16 (50.0%)/16 (50.0%)	.123
Operation method (TG/PG)	29 (63.0%)/17 (37.0%)	16 (50.0%)/16 (50.0%)	.252
Approach (open/laparoscopic)	31 (67.4%)/15 (32.6%)	17 (53.1%)/15 (46.9%)	.203
Postoperative adjuvant chemotherapy	19 (41.3%)	19 (59.4%)	.115

Abbreviations: ASA-PS, American Society of Anesthetists–Physical Status; BMI, Body mass index; Diff., Differentiated; PG, Proximal gastrectomy; TG, Total gastrectomy; Undiff, Undifferentiated.

^aMedian (range).

^bMeasured by preoperative endoscopy.

The overall survival (OS) and relapse-free survival (RFS) was compared between the HH (+) and the HH (-) groups. Both OS and RFS were slightly lower in the HH (+) group than in the HH (-) group, but this did not reach statistical difference (Figure 3A). Selection bias was suspected, so we further analyzed the survival outcomes in stratified cohorts according to clinical T factors. In patients with T1-2, the survival curves were similar (OS: $P = .789$, RFS: $P = .503$). However, in patients with T3-4, the survival outcomes were significantly worse in the HH (+) group than in the HH (-) group, both in terms of the OS ($P = .036$, hazard ratio [HR]: 3.06, 95% confidence interval [CI]: 1.02-9.18) and the RFS ($P = .039$, HR: 2.96, 95% CI: 0.99-8.89) (Figure 3B). Next, we analyzed the patients in stratified cohorts according to pathological stage of disease. In patients with pStage I, survival curves were almost the same (OS: $P = .631$, RFS: $P = .631$). However, in pStage II/III, the survival outcomes were worse in the HH (+) group, both in terms of the OS ($P = .103$, HR: 2.34, 95% CI: 0.81-6.75) and the RFS ($P = .119$, HR: 2.25, 95% CI: 0.78-6.49) (Figure 3C).

3.4 | Multivariate analyses in patients with T3-4

Consequently, univariate and multivariate analyses were carried out to detect prognostic factors in patients with T3-4 tumors using the Cox proportional hazard model (Table 3). If the P -value of a factor in univariate analysis was lower than 0.05, that variate was further analyzed in the multivariate analysis. Histological type (undifferentiated), esophageal invasive length (>20 mm), and coexistence of HH were identified as poor prognostic factors for OS. In the subsequent

multivariate analysis, esophageal invasive length (>20 mm) (hazard ratio [HR] 4.81; 95% confidence interval [CI] 1.30-17.8, $P = .014$) and coexistence of HH (HR 3.60; 95% CI 1.06-11.9, $P = .032$) were identified as independent prognostic factors. In the same analysis for RFS, the univariate analysis showed pathological T3-4, pathological N (+), histological type (undifferentiated), esophageal invasive length (>20 mm), and coexistence of HH as prognostic factors for lower RFS. In the subsequent multivariate analysis, esophageal invasive length (>20 mm) was identified as an independent prognostic factor (HR 4.09; 95% CI 1.11-15.0, $P = .034$).

3.5 | Recurrence

The recurrence rates during the follow-up period in the HH (+) and the HH (-) groups were 29.1% and 21.9%, respectively. The distribution of recurrence sites is summarized in Table 4. Mediastinal and paraaortic lymph node metastases tended to be more common in the HH (+) group (33% vs 14%, $P = .30$), but this did not reach statistical significance. Similarly, peritoneal recurrence was more common in the HH (+) group (58% vs 14%, $P = .06$).

4 | DISCUSSION

This study showed that HH is associated with increased postoperative complications after GEJ cancer surgery. Intra-abdominal abscesses were more common in the HH (+) group. Furthermore, HH was correlated with unfavorable survival outcomes after GEJ cancer surgery,

TABLE 2 Surgical outcomes

	Hiatal Hernia (+) n = 46	Hiatal Hernia (-) n = 32	P-value
Operative time, min	274.5 (136-511) ^a	278.0 (160-370) ^a	.428
Blood loss, mL	39.0 (0-876) ^a	52.5 (4-981) ^a	.875
Additional resection of the esophageal stump	9 (19.6%)	2 (6.3%)	.082
Intra-abdominal infectious complications	11 (23.9%)	3 (9.4%)	.089
Leakage	2 (4.4%)	0	.143
Abdominal abscess	8 (17.4%)	1 (3.1%)	.036
Pancreatic fistula	4 (8.7%)	2 (6.3%)	.687
Other complications			
Ileus	3 (5.5%)	0	.052
Pneumonia	6 (11.1%)	4 (8.7%)	.687
Cholecystitis	0	1 (2.2%)	.211
Postoperative in-hospital days	10 (7-60) ^a	10 (7-57) ^a	.357
Amylase levels of drainage fluid, IU/L	168 (31-1953) ^a	122 (21-3044) ^a	.949
Esophageal invasive length ^b , mm	8.0 (0-37) ^a	8.5 (0-30) ^a	.343
Tumor size, mm	48.5 (10-137) ^a	57.5 (23-124) ^a	.904
Pathological T (1-2/3-4)	25 (54.4%)/21 (45.6%)	16 (50.0%)/16 (50.0%)	.705
Pathological N (-/+)	13 (40.6%)/19 (59.4%)	23 (50.0%)/23 (50.0%)	.413
Pathological Stage (I/II/III)	19 (41.3%)/15 (32.6%)/12 (26.0%)	11 (34.4%)/10 (31.2%)/11 (34.4%)	.710

^aMedian (range).

^bMeasured by postoperative pathology.

particularly in patients with advanced disease. These findings suggest that HH adversely affects the treatment outcomes of patients with GEJ cancer, and special consideration is required when treating such patients. Increased postoperative complications indicate that HH increases surgical difficulty. To the best of our knowledge, this is the first study to describe this issue focusing on GEJ cancer.

The GEJ is anatomically defined as a boundary between the esophageal and stomach muscular layers.¹⁵ The level of the GEJ should be almost identical with that of the esophageal hiatus, but the GEJ is displaced into the mediastinum in patients with HH. Esophageal invasion length is known to be a critical parameter when deciding the surgical approach or the extent of lymph node dissection required.^{5,16-19} In patients with HH, a discrepancy may happen; that is, the tumor may be located further away from the hiatus than the estimated esophageal invasion length. In fact, additional resection of the esophageal stump was more frequently required in the HH (+) group in this study. Such a situation makes transhiatal anastomosis much more challenging, which may have contributed to the higher incidence of postoperative complications seen in HH (+) patients in this study.

As expected, the HH (+) group also had less favorable survival outcomes than the HH (-) group. One possible explanation may be the association between increased postoperative complications and poorer survival outcomes. Several publications have suggested that postoperative complications have an adverse impact on survival outcomes in cancer surgery.²⁰⁻²² The mechanisms behind this

association are not fully known, but may include increased levels of cytokines and chemokines,^{23,24} host immunosuppression such as increased regulatory T cells,²⁵ and delayed initiation of adjuvant chemotherapy.²⁶ Another explanation may be that HH alters the lymphatic drainage route around the GEJ. Normally, lymphatic drainage from the GEJ flows in several directions, namely through perigastric, retroperitoneal, and mediastinal routes. The GEJ is normally located between the positive pressure in the abdomen and the negative pressure in the thorax. However, once the GEJ moves through a HH into the mediastinum, the lymphatic flow may be changed. Flow to the mediastinum may be enhanced due to the negative intra-thoracic pressure.²⁷ Interestingly, the HH (+) group in this study showed slightly higher recurrence levels in the mediastinal lymph nodes, which might support this hypothesis. Likewise, Maruyama et al²⁷ investigated the correlation between HH and survival outcomes in patients with proximal gastric or GEJ cancer and suggested that HH may affect the lymphatic drainage. They proposed that the distance between the tumor and the vena caval foramen may be a more accurate parameter to decide the best surgical approach and the extent of lymphadenectomy. Yet another point may be that the higher mediastinal anastomosis possibly will increase the reflux esophagitis or aspiration of pneumonia, which can be one of the causes of death. However, no difference was seen regarding the incidences of pneumonia between the two groups in this study, and pneumonia was not recorded as a cause of death even in the long-term follow-up.

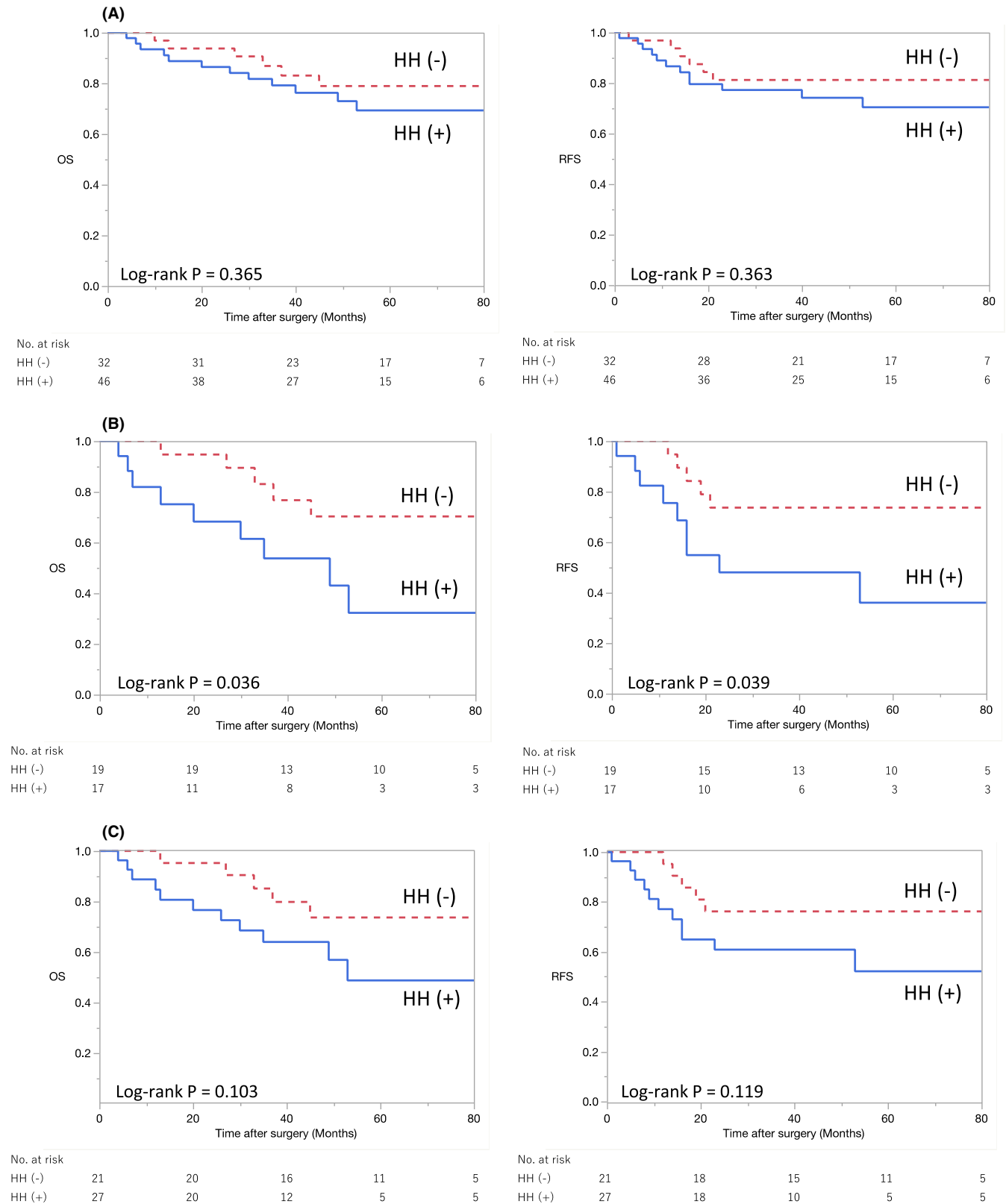


FIGURE 3 Overall survival (OS) and relapse-free survival (RFS) curves of GEJ cancer. (A) OS and RFS curves of all patients with GEJ cancer. (B) OS and RFS curves of cT3-4 GEJ cancer patients. (C) OS and RFS curves of pStage II/III GEJ cancer patients

Gastroesophageal junction cancer is likely to be treated in the same way as gastric cancer, especially in East Asia. However, GEJ cancer is well-known to possess unique oncological features due to

its anatomy. The general prognosis is reported to be worse in GEJ cancer than in gastric cancer.^{3,28} Moreover, the mechanisms of tumor development are different in these two diseases.^{4,29} Considering the

TABLE 3 Univariate and multivariable analysis for overall and recurrence-free survival in patients with T3-4 GEJ cancer

	Overall survival				Relapse-free survival				
	Number	Univariate analysis		Multivariable analysis		Univariate analysis		Multivariable analysis	
	n = 36	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years									
>75	6	1.245 (0.347-4.472)	.741			1.232 (0.343-4.427)	.753		
≤75	30								
BMI ^a , kg/m ²									
>2.7	17	1.681 (0.583-4.850)	.332			1.661 (0.575-4.791)	.344		
≤22.7	19								
Pathological T factor									
pT3-4	27	4.876 (0.636-37.378)	.056			5.400 (7.043-41.404)	.039	1.209 (0.116-12.560)	.872
pT1-2	9								
Pathological N factor									
pN +	28	4.640 (0.606-35.507)	.065			5.213 (0.680-39.692)	.044	4.704 (0.536-41.296)	.099
pN -	8								
Tumor size ^a , mm									
>60	22	2.553 (0.701-7.242)	.153			1.997 (0.624-6.392)	.224		
≤60	14								
Histology									
Undifferentiated	6	5.653 (1.757-18.191)	.003	2.155 (0.580-8.013)	.258	5.121 (1.622-16.159)	.011	2.162 (0.538-8.680)	.277
Differentiated	30								
Esophageal invasive length, mm									
>20	16	4.553 (1.412-14.688)	.011	4.813 (1.303-17.774)	.014	4.424 (1.371-14.274)	.008	4.086 (1.111-15.019)	.034
≤20	20								
Adjuvant chemotherapy									
Yes	28	1.620 (0.451-5.815)	.439			1.738 (0.484-6.238)	.373		
No	8								
Presence of hiatal hernia									
HH (+)	17	3.055 (1.017-9.176)	.040	3.596 (1.086-11.904)	.032	2.963 (0.988-8.887)	.046	3.007 (0.791-11.423)	.106
HH (-)	19								

Abbreviations: 95% CI, 95% Confidence interval; BMI, Body mass index; HR, Hazard ratio.

^aThe cut-off value was defined by the median.

TABLE 4 Site of recurrence

	Hiatal Hernia (+) n = 46	Hiatal Hernia (-) n = 32	P-value
Overall ^a	12 (100%)	7 (100%)	.67
Lymphatic			
Abdominal	1 (8%)	2 (29%)	.36
Mediastinal	4 (33%)	1 (14%)	.30
Periaortic	4 (33%)	1 (14%)	.30
Other	0	1 (14%)	.17
Hematogenous			
Liver	4 (33%)	1 (14%)	.30
Lung	4 (33%)	3 (43%)	.91
Peritoneal	7 (58%)	1 (14%)	.06
Local	0	1 (14%)	.17
Other	1 (8%)	1 (14%)	.79

^aDuplication allowed.

rising incidence of GEJ cancer worldwide, it is crucial to understand the specific prognostic factors for GEJ cancer patients. The results of this study suggest that the presence of HH is an important prognostic factor for patients with GEJ cancer. Additionally, our data suggest that the surgical approach (transhiatal or transthoracic) and extent of lymph node resection should be carefully decided taking into account the presence of HH. In order to confirm the lymphatic flow in real time, some new technologies such as indocyanine green (ICG) fluorescence may be helpful, while we have not applied that in this study.

This study had several limitations. First, this was a single-institution retrospective study. Furthermore, even in high-volume centers, the volume of GEJ cancer surgery is small, which is reflected in the sample size in this study. Second, HH diagnosis, and Makuuchi classification, was made only by endoscopic findings. Particularly in patients with a large tumor diameter or a peripheral lesion, estimating the degree of esophageal hiatal hernia was difficult or inaccurate. To reduce this ambiguity, all patients from grade A to C were included in the HH (+) group in this study. Furthermore, we examined the prognosis stratified to the degree of HH, but neither significant difference nor tendency was seen (data not shown).

In conclusion, HH may adversely affect not only surgical, but also survival outcomes in patients with GEJ. Therefore, specific considerations regarding the surgical approach or the extent of lymph node dissection may be necessary for these patients.

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DISCLOSURE

Funding: This study was not supported by any funding source.

Conflict of Interest: The authors declare no conflict of interest.

Ethical Approval: The protocol for this study was approved by the Institutional Review Board and it conforms to the provisions of the Declaration of Helsinki. Informed consent was obtained from all patients included in this study.

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