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Clinicopathologic Features and Clinical Outcomes of Esophageal Gastrointestinal Stromal Tumor

Evaluation of a Pooled Case Series

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Abstract: Clinicopathologic features and clinical outcomes of gastrointestinal stromal tumors (GISTs) in esophagus are limited, because of the relatively rare incidence of esophageal GISTs. Therefore, the aim of the current study was to investigate the clinicopathologic features and clinical outcomes of esophageal GISTs, and to investigate the potential factors that may predict prognosis.

Esophageal GIST cases were obtained from our center and from case reports and clinical studies extracted from MEDLINE. Clinicopathologic features and survivals were analyzed and compared with gastric GISTs from our center.

The most common location was lower esophagus (86.84%), followed by middle and upper esophagus (11.40% and 1.76%). The majority of esophageal GISTs were classified as high-risk category (70.83%). Mitotic index was correlated with histologic type, mutational status, and tumor size. The 5-year disease-free survival and disease-specific survival were 65.1% and 65.9%, respectively. Tumor size, mitotic index, and National Institutes of Health risk classification were associated with prognosis of esophageal GISTs. Only tumor size, however, was the independent risk factor for the prognosis of esophageal GISTs. In comparison to gastric GISTs, the distribution of tumor size, histologic type, and National Institutes of Health risk classification were significantly different between esophageal GISTs and gastric GISTs. The disease-free survival and disease-specific survival of esophageal GISTs were significantly lower than that of gastric GISTs.

The most common location for esophageal GISTs was lower esophagus, and most of the esophageal GISTs are high-risk category. Tumor size was the independent risk factor for the prognosis of esophageal GISTs. Esophageal GISTs differ significantly from gastric GISTs in respect to clinicopathologic features. The prognosis of esophageal GISTs was worse than that of gastric GISTs.

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Abbreviations: DFS = disease-free survival, DSS = disease-specific survival, GIST = gastrointestinal stromal tumor, HPF = high power field, ICC = interstitial cells of Cajal, NIH = National Institutes of Health, PDGFRA = platelet-derived growth factor receptor α.

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the alimentary tract. It represents approximately 1% to 2% of all the alimentary malignancies.[1] Based on their phenotypic similarities, GISTs are considered to arise from muscularis propria of gastrointestinal tract, and derived from the interstitial cells of Cajal (ICC).[2] Histologically, the majority of GISTs display spindle cell morphology (70%), followed by epithelioid morphology (20%), and mixed morphology (10%).[3] Most of the GISTs were positive for CD117 and CD34.[4] In 1998, gain-of-function mutations in the c-kit proto-oncogene protein (KIT) protooncogene in GISTs were demonstrated by Hirota et al.[5]

Gastrointestinal stromal tumors can occur anywhere throughout the gastrointestinal tract and are seen most commonly in the stomach (40%–70%), small intestine (20%–40%), and colon and rectum (5%–15%).[6] Esophageal GISTs are extremely uncommon, accounting for 0.7% of all GISTs.[7] The reporting of esophageal GISTs has been limited to individual case reports and case series of small numbers. Studies involving large numbers of esophageal GISTs are lacking, many questions remain unanswered regarding the clinicopathologic profiles and clinical outcomes. Therefore, the aim of the current study was to explore the clinicopathologic characteristics and clinical outcome of esophageal GISTs, and to investigate the potential factors that may predict postoperative outcomes.

PATIENTS AND METHODS

Gastrointestinal stromal tumor cases of the esophagus were from our center and in addition from the literature. From May 2010 to March 2015, 7 patients of esophageal GISTs were diagnosed and received treatment in our center. Literature search of MEDLINE was performed for all articles in English published from 2000 through 2015. MEDLINE search resulted in 46 case reports,[8–53] including 52 patients and 8 case series,[54–61] including 76 cases. To this end, a total of 135 esophageal GISTs patients were identified (Figure 1). In addition, the clinicopathologic characteristics and prognosis of 297 patients of gastric GISTs were analyzed and compared with esophageal GISTs. This study was approved by the Ethics

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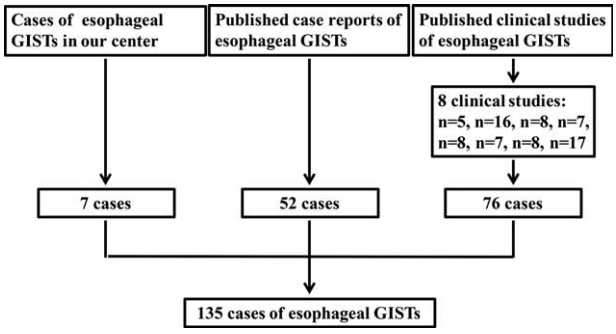

FIGURE 1. Schematic diagram regarding selection of esophageal gastrointestinal stromal tumors.

Committee of Xijing Hospital, and written informed consent was obtained from the seven patients in our center.

Clinicopathologic data, including age, sex, accompanied tumor, symptoms, location, tumor size, surgical intervention, histologic type, lymph node metastasis, mitotic index, immunohistochemical features, mutational status, National Institutes of Health (NIH) risk classification, adjuvant imatinib therapy, tumor recurrence or metastasis, and survival data were recorded from hospital medical records in our center or extracted from published reports and studies. The tumors were categorized into very low, low, intermediate, and high-risk groups according to the modified NIH risk classification criteria reported by Joensuu et al.[62] For survival analysis, the exclusion criteria were listed as follows: accompanied with other malignant tumors, accompanied with GISTs in other locations, accompanied with distant metastasis, with neoadjuvant imatinib therapy, not receive R0 resection, with tumor rupture during operation, without follow-up data. Owing to data acquisition, completeness of data is limited.

The clinicophathologic characteristics, including age, sex, tumor size, histologic type, mitotic index, and NIH risk classification were compared with gastric GISTs in our center. For survival analysis between the 2 groups, patients with gastric GISTs in our center were matched with esophageal GISTs based on the following parameters: tumor size: $\leq$2.0, 2.1 to 5.0, 5.1 to 10.0, or $>$10.0 cm; mitotic index: 5 or less, or more than 5/50 high power fields (HPFs); and adjuvant imatinib therapy: yes or no.

Data were processed using SPSS 16.0 for Windows (SPSS Inc, Chicago, IL). Discrete variables were analyzed using the χ^2 test or Fisher exact test. Numerical variables were expressed as the mean $\pm$ SD unless otherwise stated. Significant predictors for survival identified by univariate analysis were further assessed by multivariate analysis using the logistic regression analysis. Evaluation for disease-free survival (DFS) and disease-specific survival (DSS) were obtained by the Kaplan–Meier method and differences between curves were compared using log-rank test. Non-GIST-related deaths were censored for analysis of DSS. The *P* values were considered to be statistically significant at the 5% level.

RESULTS

The clinicopathologic features were summarized in Table 1. There were 81 men (60%) and 54 women (40%). The patient age ranged from 12 to 87 years (median, 60 years; mean, 58.6 years). Four patients accompanied with GISTs in

TABLE 1. Clinicopathologic Characteristics of 135 Patients of Esophageal Gastrointestinal Stromal Tumors

Characteristics	Number	Percentage
Age ($\Sigma = 128$)		
$\leq$60	65	50.78%
$>$60	63	49.22%
Sex ($\Sigma = 135$)		
Male	81	60.00%
Female	54	40.00%
Accompanied tumor ($\Sigma = 87$)		
GISTs with other locations	4	4.60%
Other type of tumors	11	12.64%
Symptoms		
Dysphagia ($\Sigma = 129$)	50	38.76%
Chest pain ($\Sigma = 109$)	16	14.68%
Bleeding ($\Sigma = 109$)	9	8.26%
Others ($\Sigma = 109$)		
Fatigue, cough, dyspnea	10	9.17%
Location ($\Sigma = 114$)		
Upper	2	1.76%
Middle	13	11.40%
Lower	99	86.84%
Tumor size ($\Sigma = 125$)		
$\leq$2 cm	20	16.00%
2.1–5 cm	34	27.20%
5.1–10 cm	41	32.80%
$>$10 cm	30	24.00%
Surgical resection ($\Sigma = 135$)		
Complete resection	121	89.63%
Incomplete resection	4	2.96%
No surgery	10	7.41%
Histologic type ($\Sigma = 93$)		
Spindle	77	82.80%
Epithelioid	8	8.60%
Mixed	8	8.60%
Lymph node metastasis ($\Sigma = 22$)		
Yes	1	4.55%
No	21	95.45%
Mitotic index ($\Sigma = 121$)		
$\leq$5	68	56.20%
$>$5	53	43.80%
Immunohistochemisty		
CD117 ($\Sigma = 123$)	119	96.75%
CD34 ($\Sigma = 117$)	110	94.02%
DOG-1 ($\Sigma = 13$)	11	84.62%
Mutational status ($\Sigma = 25$)		
KIT	15	60.00%
PDGFRA	0	0.00%
Wild type	10	40.00%
NIH risk category ($\Sigma = 120$)		
Very low risk	15	12.50%
Low risk	18	15.00%
Intermediate risk	2	1.67%
High risk	85	70.83%
Adjuvant therapy ($\Sigma = 134$)		
Yes	38	28.36%
No	96	71.64%

DOG-1 = discovered on GIST 1, GIST = gastrointestinal stromal tumor, NIH = National Institutes of Health, PDGFRA = platelet-derived growth factor receptor α.

other locations (4.6%), including 2 patients of liver metastasis, 1 patient of liver and pleural metastasis, and 1 patient of bone and lung metastasis. Eleven patients accompanied with other malignant tumors (12.64%), including 7 patients of esophageal squamous cell carcinoma, 2 patients of Barrett carcinoma, 1 case of cardia adenocarcinoma, and 1 case of bladder carcinoma. The most common symptom was dysphagia (50/129, 38.76%), followed by chest pain (16/109, 14.68%), bleeding (9/109, 8.26%), and other symptoms including fatigue, cough, and dyspnea (10/109, 9.17%). The most common location was lower esophagus (99/114, 86.84%), followed by middle esophagus (13/114, 11.4%), and upper esophagus (2/114, 1.76%). A total of 121 patients underwent complete surgical resection (121/135, 89.63%), 4 patients underwent palliative surgical resection (4/135, 2.96%), and 10 patients did not receive surgical resection (10/135, 7.41%).

The tumors ranged from 0.2 to 30 cm in maximum diameter (median, 6 cm; mean, 7.3 cm). The mitotic index of 53 patients exceeded 5/50 HPF (53/121, 43.8%). Seventy-seven patients display spindle cell morphology (77/93, 82.8%), 8 patients display epithelioid morphology (8/93, 8.6%), and 8 patients display mixed morphology (8/93, 8.6%). Among the 22 patients with lymph node dissection, only 1 patient had lymph node metastasis (1/22, 4.55%). CD117 positivity was detected in 119 patients (119/123, 96.75%), CD34 positivity was detected in 110 patients (110/117, 94.02%), and discovered on GIST 1 positivity was detected in 11 patients (11/13, 84.62%). Twenty-five patients were analyzed for gene mutation status. Fifteen patients carried a mutation in exon 11 of KIT (15/25, 60%). The remaining 10 patients were wild type. Platelet-derived growth factor receptor α variants were not detected in these 25 patients. According to NIH risk classification, 15 patients were classified as very low risk (15/120, 12.5%), 18 patients were classified as low risk (18/120, 15%), 2 patients were classified as intermediate risk (2/120, 1.67%), and 85 patients were classified as high risk (85/120, 70.83%). Information of adjuvant imatinib therapy was recorded in 134 patients, and 38 patients (28.36%) received imatinib therapy. Among them, 6 patients received imatinib therapy before and after surgery, 2 patients only received imatinib therapy before surgery, 22 patients received imatinib therapy after surgery, and the remaining 8 patients received imatinib therapy only.

The relationship between clinicopathologic characteristics were analyzed and summarized in Table 2. The mitotic index was correlated with histologic type, mutational status, and tumor size. The mitotic index of all the mixed histologic type exceeded 5/50 HPF ($P = 0.027$). The mitotic index exceeded 5/50 HPF for the majority of KIT exon 11 mutation but only for the minority of wild-type GISTs ($P = 0.013$). The mitotic index was positively correlated with tumor size ($P = 0.025$).

TABLE 2. The Relationship Between Clinicopathologic Characteristics

Characteristics	Mitotic Index (≤5)	Mitotic Index (>5)	*P* Value
Histologic type			
Spindle	34 (91.9%)	26 (72.2%)	0.027
Epithelioid	3 (8.1%)	4 (11.1%)	
Mixed	0 (0%)	6 (16.7%)	
Mutational status			
KIT exon 11	4 (33.3%)	10 (83.3%)	0.013
Wild type	8 (66.7%)	2 (16.7%)	
Tumor size			
≤2 cm	15 (24.2%)	2 (4.1%)	0.025
2.1–5 cm	17 (27.4%)	13 (26.5%)	
5.1–10 cm	18 (29.0%)	21 (42.9%)	
>10 cm	12 (19.4%)	13 (26.5%)	

TABLE 3. Survival Data of 97 Cases of Esophageal Gastrointestinal Stromal Tumors

Survival Characteristics	Parameter
Follow-up time	
Mean (m ± SD)	40.70 ± 36.32
Median (m, range)	28 (1, 202)
Survival data	
Recurrence or metastasis	22
GISTs-related deaths	17
Survival rates (%)	
1-/3-/5-year DSS	100/88.1/65.9
1-/3-/5-year DFS	93.3/78.3/65.1

DFS = disease-free survival, DSS = disease-specific survival, GIST = gastrointestinal stromal tumor, SD = standard deviation.

Survival data of esophageal GISTs were analyzed and summarized in Table 3. Survival data of 97 patients were eventually selected for analysis using exclusion criteria described in the materials and methods. The follow-up time ranged from 1 to 202 months (mean, 40.70 months; median, 28 months). Twenty-two patients showed recurrence or metastasis, 17 patients suffered from GISTs-related deaths. The 1-, 3-, and 5-year survival rate of DSS was 100%, 88.1%, and 65.9%, respectively. The 1-, 3- and 5-year survival rate of DFS was 93.3%, 78.3%, and 65.1%, respectively. The DFS and DSS of esophageal GISTs were analyzed using Kaplan–Meier survival analyses and shown in Figure 2.

Prognostic factors for DFS and DSS in patients with esophageal GISTs according to univariate and multivariate analysis were summarized in Table 4. The results showed that tumor size, mitotic index, and NIH risk classification were associated with prognosis of esophageal GISTs. Only tumor size, however, was the independent risk factor for the prognosis of esophageal GISTs. The DFS and DSS of esophageal GISTs according to tumor size, mitotic index, and NIH risk classification were shown in Figures 3 to 5. National Institutes of Health risk classification could not be included in the logistic regression analysis, although it showed significant correlation with prognosis, because no patients suffered from recurrence, metastasis, or death in NIH risk category 1 and 2. When calculating the log of the odds, this null frequency caused a computational error because of the presence of logarithm of zero.

The clinicophathologic features of 135 esophageal GISTs, including age, sex, tumor size, histologic type, mitotic index, and NIH risk category were compared with 297 gastric GISTs in our center (Table 5). The results showed that the distribution of tumor size, histologic type, and NIH risk classification were significantly different between esophageal GISTs and gastric GISTs (both $P = 0.000$).

To compare the prognosis of esophageal GISTs with gastric GISTs, patients were selected using the exclusion criteria described above. Then the 2 groups were matched

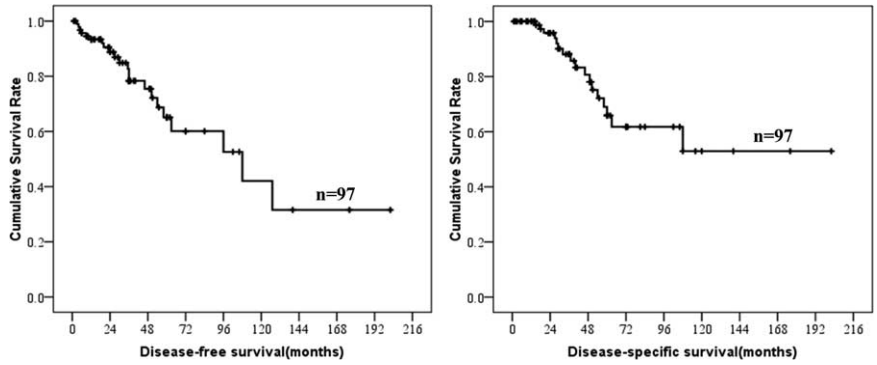

FIGURE 2. Disease-free-survival and disease-specific survival of esophageal gastrointestinal stromal tumors.

TABLE 4. Prognostic Factors for Disease-specific Survival and Disease-free Survival in Patients With Esophageal Gastrointestinal Stromal Tumors According to Univariate and Multivariate Analysis (n = 97)

	Univariate Analysis			Multivariate analysis		
Prognostic Factors	β	**Hazard Ratio (95% CI)**	***P* Value**	β	**Hazard ratio (95% CI)**	***P* value**
DSS						
Tumor size (2/5/10)	0.87	2.39 (1.23–4.63)	0.010	0.94	2.56 (1.20–5.46)	0.015
Mitotic index (≤5/>5)	1.70	5.46 (1.25–23.86)	0.024			
NIH risk category (1, 2/3, and 4)	3.49	32.63 (0.24–4377.07)	0.021			
Adjuvant therapy	−3.47	0.031 (0.00–3.751)	0.156			
DFS						
Tumor size (2/5/10)	1.11	3.03 (1.58–5.82)	0.001	0.98	2.66 (1.33–5.29)	0.005
Mitotic index (≤5/>5)	2.08	1.97 (1.85–34.40)	0.005			
NIH risk category (1, 2/3, and 4)	3.58	35.74 (0.65–1969.65)	0.003			
Adjuvant therapy	1.25	3.5 (1.41–8.70)	0.007			

CI = confidence interval, DFS = disease-free survival, DSS = disease-specific survival, NIH = National Institutes of Health.

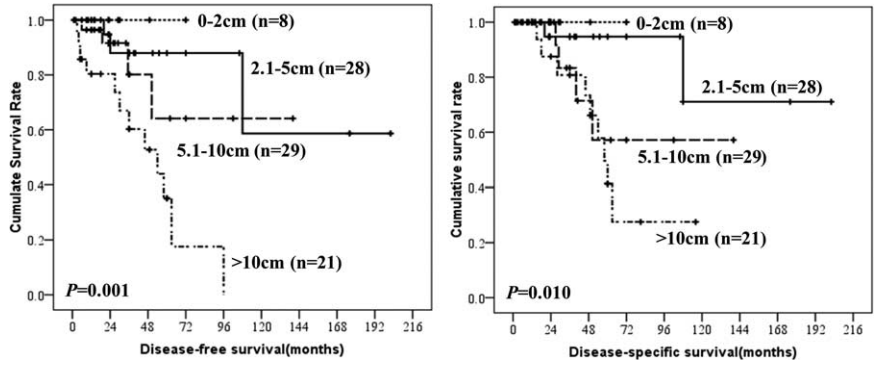

FIGURE 3. Disease-free-survival and disease-specific survival of esophageal gastrointestinal stromal tumors by tumor size.

according to tumor size, mitotic index, and adjuvant imatinib therapy described above. The entire process was shown in Figure 6. Finally, 73 patients of esophageal GISTs and 73 patients of gastric GISTs were selected. There were no intergroup differences in age, sex, tumor size, mitotic index, and adjuvant imatinib therapy (Table 6). The survival analysis showed in Figure 7 indicated that the DFS ($P = 0.026$) and DSS ($P = 0.041$) in patients with esophageal GISTs were significantly lower than that of gastric GISTs (58.3% versus 94.7%, 71.8% versus 95.2%).

DISCUSSION

Gastrointestinal stromal tumors located in the esophagus constitute a very rare subset of GISTs with limited data on the clinicopathologic features and clinical outcomes. Therefore, we

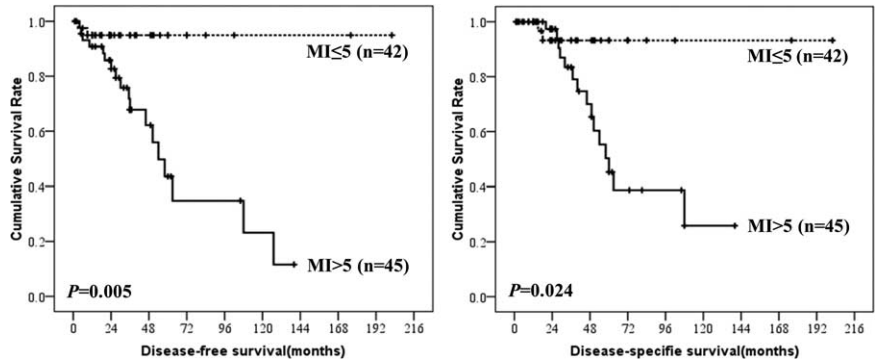

FIGURE 4. Disease-free-survival and disease-specific survival of esophageal gastrointestinal stromal tumors by mitotic index.

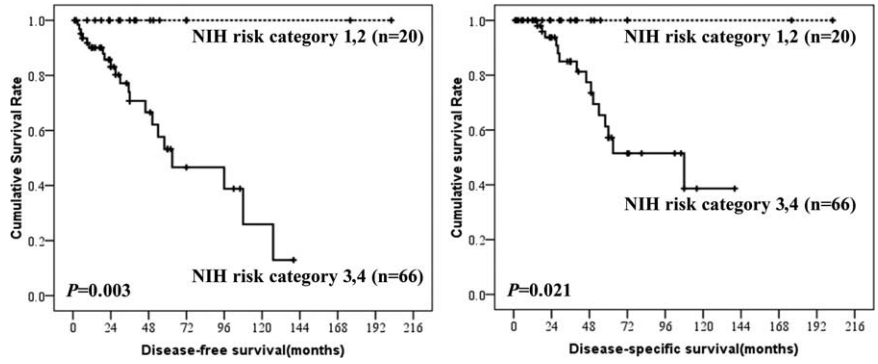

FIGURE 5. Disease-free-survival and disease-specific survival of esophageal gastrointestinal stromal tumors by National Institutes of Health risk category.

TABLE 5. Comparison of Selected Clinicopathologic Parameters Between Esophageal and Gastric Gastrointestinal Stromal Tumors

Characteristics	Esophagus (n = 135)	Stomach (n = 297)	*P* Value
Age			
≤60	65	168	0.289
>60	63	129	
Sex			
Male	81	155	0.145
Female	54	142	
Tumor size			
≤2 cm	20	96	0.000
2.1–5 cm	34	107	
5.1–10 cm	41	72	
>10 cm	30	22	
Histologic type			
Spindle	77	275	0.000
Epithelioid	8	3	
Mixed	8	19	
Mitotic index			
≤5	68	163	0.806
>5	53	134	
NIH risk category			
Very low	15	83	0.000
Low	18	58	
Intermediate	2	87	
High	85	69	

NIH = National Institutes of Health.

evaluated data of 135 cases of esophageal GISTs from our center and from literatures in MEDLINE. The current study represents the largest analysis of esophageal GISTs and indicates some features significantly associated with esophageal GISTs. We found that the most common location for esophageal GISTs was lower esophagus, and most of the esophageal GISTs are high-risk category. Tumor size was the independent risk factor for the prognosis of esophageal GISTs. Esophageal GISTs differ significantly from gastric GISTs in respect to clinicopathologic features. The prognosis of esophageal GISTs was worse than that of gastric GISTs.

There is only 1 clinical study containing a relatively larger number of esophageal GISTs reported by Lott et al.[63] Clinicopathologic features of 55 esophageal GISTs were analyzed in the study. In their series, the most common location of esophageal GISTs was lower esophagus, followed by middle esophagus. No esophageal GISTs were found in the upper esophagus. In our current study, the most common location of esophageal GISTs was also lower esophagus, followed by middle esophagus, and upper esophagus. This was consistent with the above study. It is well known that GISTs are considered to arise from the ICCs. Thus, the distribution of esophageal GISTs may be attributed to the distribution of ICCs in the esophagus. Radenkovic et al[64] investigated the distribution of ICC populations in human embryonal and fetal esophagus. They found that ICC were abundant in the lower portion, less numerous in the middle region, and rare in the upper part. The reported distribution of ICC was completely in accordance with the distribution of esophageal GISTs in our study. This partially interpreted the distribution of esophageal GISTs.

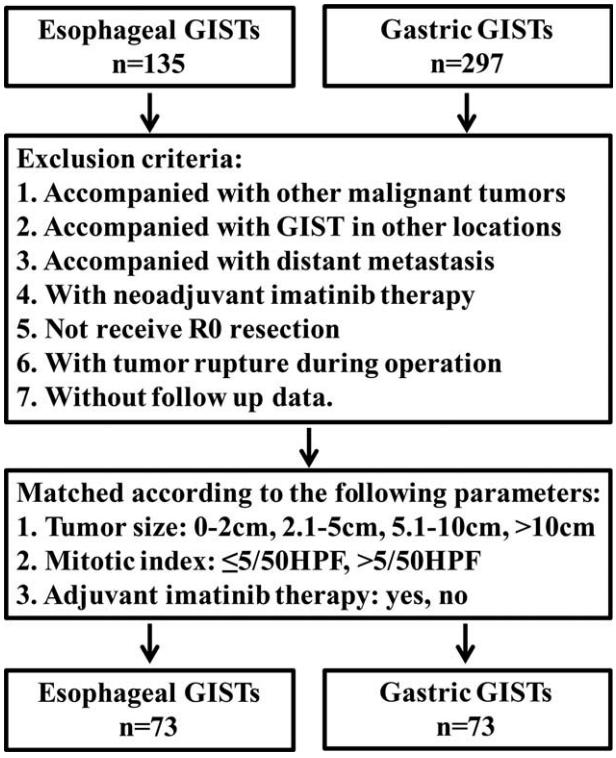

FIGURE 6. Flow chart of match strategy between esophageal and gastric gastrointestinal stromal tumors.

TABLE 6. Comparison of Predefined Variables Between Esophageal and Gastric Gastrointestinal Stromal Tumors

Characteristics	Esophagus (n = 73)	Stomach (n = 73)	*P* Value
Age			
≤60	42	38	0.618
>60	31	35	
Sex			
Male	40	32	0.247
Female	33	41	
Tumor size			
≤2 cm	7	7	1.000
2.1–5 cm	25	25	
5.1–10 cm	29	29	
>10 cm	12	12	
Mitotic index			
≤5	34	34	1.000
>5	39	39	
Adjuvant therapy			
Yes	21	21	1.000
No	52	52	

It was reported that KIT gene mutation occurred in approximately 70% to 80% of GISTs.[65] Among them, most are exon 11 mutations,[66] followed by exon 9, 13, and 17 mutations.[67] Only 20% to 25% of gastric GISTs were associated with platelet-derived growth factor receptor α mutations, including exon 18 and exon 12 mutations.[68] B-type Raf kinase kinase mutation occurred rarely according to the previous report.[69] In our current study, 25 esophageal GISTs received mutational analysis. Among them, 15 patients (60%) harbor KIT mutations in exon 11, the remaining 10 patients (40%) were KIT wild type. Interestingly, exon 11 mutation was associated with mitotic index in our current study. We found that the mitotic index exceeded 5/50 HPF in the majority of esophageal GISTs with exon 11 mutation, but only in the minority of esophageal GISTs with KIT wild type. The association between mitotic index and KIT mutation needed further investigation in future.

Even with early and R0 resection, there is a high risk of recurrence and metastasis. Distant metastases are the more frequent treatment failure for GISTs and are associated with poor prognosis. No mention of esophageal GISTs-specific recurrence, however, was made. Metastases have a predilection to the liver, omentum, peritoneum, and other intra-abdominal sites, whereas metastases outside the abdomen are uncommon.[70] In our current study, the most common site of distant metastasis in esophageal GISTs is liver, followed by lung, thoracic cavity, pleura, peritoneal, and subcutaneous. It is reported that the venous plexus of esophagus in the thorax drain through the hemiazygos and azygos veins in to the superior vena cava and also drain into the portal venous systems.[71] Thus, the difference between esophageal and other

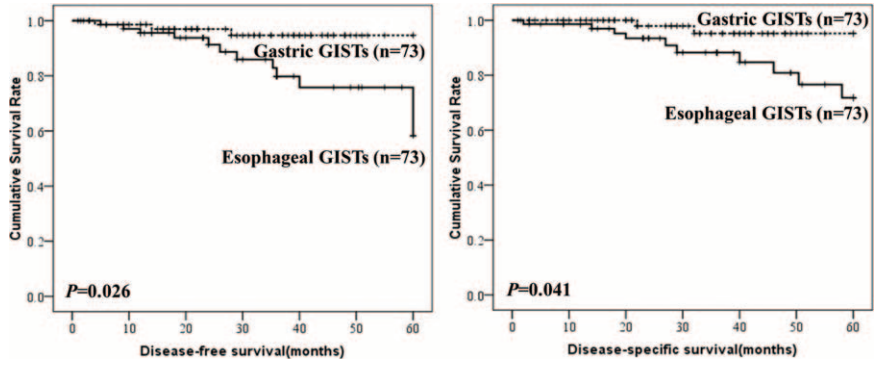

FIGURE 7. Comparison of disease-free-survival and disease-specific survival between esophageal and gastric gastrointestinal stromal tumors.

GISTs in respect to the site of metastasis may attribute to the different venous drainage and specific anatomic site of esophagus.

Approximately 10% to 30% of GISTs are regarded as clinically malignant.[72] The majority reports from the literature support a higher malignant potential of esophageal GISTs with an unfavorable outcome,[58] and it was considered that the poor outcome is related to the significant higher rate of large tumor size and higher mitotic rate.[63] In our current study, the clinicopathologic features of esophageal GISTs were compared with gastric GISTs in our center. The results showed that the distribution of tumor size, histologic type, and NIH risk classification were significantly different between esophageal and gastric GISTs. The esophageal GISTs showed larger tumor size and higher risk classification than gastric GISTs. The distribution of mitotic index between esophageal and gastric GISTs, however, was comparable in our current study.

It is reported that tumor size and mitotic index are the best prognostic indicators for determining the malignant potential of GISTs.[73] In our current study, larger tumor size, mitotic index more than 5/50 HPF, and high-risk category were associated with poorer prognosis. Tumor size, however, was the only independent risk factor for prognosis of esophageal GISTs. Rutkowski et al[74] reported that primary tumor location was an independent prognostic factor for the prognosis of GISTs. The prognostic features of esophageal GISTs, however, still remain unknown. Considering the significantly different distribution of tumor size and NIH risk category between esophageal and gastric GISTs, patients in the 2 groups were matched by tumor size, mitotic index, and adjuvant imatinib therapy to compare the prognosis between esophageal and gastric GISTs. The survival analysis showed that the DFS and DSS of esophageal GISTs were significantly lower than that of gastric GISTs.

There are some limitations of the current study. First, it is retrospective analysis and lacks systematic prospective data. Therefore, completeness of the data is limited. Second, the sample size of esophageal GISTs was not large enough, which will result in sampling error. Third, because of the limited sample size of duodenal, small intestinal and rectal GISTs in our center, we could not compare the clinicopathologic features and prognosis of esophageal GISTs with nongastric GISTs.

CONCLUSIONS

The most common location for esophageal GISTs was lower esophagus, and most of the esophageal GISTs are high-risk category. Tumor size was the independent risk factor for the prognosis of esophageal GISTs. Esophageal GISTs differ significantly from gastric GISTs in respect to clinicopathologic features. The prognosis of esophageal GISTs was worse than that of gastric GISTs.

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