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.

INTRODUCTION

Gastrointestinal stromal tumor cases of the esophagus were primarily in the stomach (40%–70%), small intestine (20%–40%), and colon and rectum (5%–15%). Esophageal GISTs are extremely uncommon, accounting for 0.7% of all GISTs. 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 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, including 52 patients and 8 case series, 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 Committee of Xijing Hospital, Fourth Military Medical University.
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. 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, no adjuvant 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 clinicopathologic 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: ≤2 cm, 2.1–5 cm, 5.1–10 cm, >10 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 χ² test or Fisher exact test. Numerical variables were expressed as the mean ± 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 other locations, accompanied with distant metastasis, with neoadjuvant imatinib therapy, not receive R0 resection, with tumor rupture during operation, without follow-up data.

| Characteristics | Number | Percentage |
|-----------------|--------|------------|
| Age (Σ = 128)   |        |            |
| ≤60             | 65     | 50.78%     |
| >60             | 63     | 49.22%     |
| Sex (Σ = 135)   |        |            |
| Male            | 81     | 60.00%     |
| Female          | 54     | 40.00%     |
| Accompanied tumor (Σ = 87) |       |            |
| GISTs with other locations | 4 | 4.60% |
| Other type of tumors | 11 | 12.64% |
| Symptoms        |        |            |
| Dysphagia (Σ = 129) |   | 38.76% |
| Chest pain (Σ = 109) | 16 | 14.68% |
| Bleeding (Σ = 109) | 9   | 8.26%     |
| Others (Σ = 109) |        |            |
| Fatigue, cough, dyspnea | 10 | 9.17% |
| Location (Σ = 114) |      |            |
| Upper           | 2      | 1.76%      |
| Middle          | 13     | 11.40%     |
| Lower           | 99     | 86.84%     |
| Tumor size (Σ = 125) |      |            |
| ≤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 (Σ = 135) |     |            |
| Complete resection | 121 | 98.63% |
| Incomplete resection | 4  | 3.26% |
| No surgery      | 10     | 7.41%      |
| Histologic type (Σ = 93) |      |            |
| Spindle         | 77     | 82.80%     |
| Epithelioid     | 8      | 8.60%      |
| Mixed           | 8      | 8.60%      |
| Lymph node metastasis (Σ = 22) | | |
| Yes             | 1      | 4.55%      |
| No              | 21     | 95.45%     |
| Mitotic index (Σ = 121) |     |            |
| ≤5              | 68     | 56.20%     |
| >5              | 53     | 43.80%     |
| Immunohistochemistry |      |            |
| CD117 (Σ = 123) | 119  | 96.75%     |
| CD34 (Σ = 117)  | 110   | 94.02%     |
| DOG-1 (Σ = 13)  | 11     | 84.62%     |
| Mutational status (Σ = 25) |   |            |
| KIT             | 15     | 60.00%     |
| PDGFRA          | 0      | 0.00%      |
| Wild type       | 10     | 40.00%     |
| NIH risk category (Σ = 120) |     |            |
| Very low risk   | 15     | 12.50%     |
| Low risk        | 18     | 15.00%     |
| Intermediate risk | 2   | 1.67%     |
| High risk       | 85     | 70.83%     |
| Adjuvant therapy (Σ = 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 (10/135, 7.41%), and 10 patients did not receive surgical resection (10/135, 7.41%).

The relationship between clinicopathologic characteristics was 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).

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.

The clinicopathologic 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.
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 inter-group 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
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. Clinico-pathologic features of 55 esophageal GISTs were analyzed in the study. In their series, 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.

In our current study, the most common location of esophageal GISTs was also lower esophagus, followed by middle 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 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.

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.
It was reported that KIT gene mutation occurred in approximately 70% to 80% of GISTs. Among them, most are exon 11 mutations, followed by exon 9, 13, and 17 mutations. Only 20% to 25% of gastric GISTs were associated with platelet-derived growth factor receptor \( \alpha \) mutations, including exon 18 and exon 12 mutations. B-type Raf kinase mutation occurred rarely according to the previous report. 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. 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 into the superior vena cava and also drain into the portal venous systems. Thus, the difference between esophageal and other

| Exclusion criteria: |  |
|---|---|
| 1. Accompanied with other malignant tumors |  |
| 2. Accompanied with GIST in other locations |  |
| 3. Accompanied with distant metastasis |  |
| 4. With neoadjuvant imatinib therapy |  |
| 5. Not receive R0 resection |  |
| 6. With tumor rupture during operation |  |
| 7. Without follow up data. |  |

Matched according to the following parameters:
1. Tumor size: 0-2cm, 2.1-5cm, 5.1-10cm, >10cm
2. Mitotic index: ≤5/50HPF, >5/50HPF
3. Adjuvant imatinib therapy: yes, no

| TABLE 6. Comparison of Predefined Variables Between Esophageal and Gastric Gastrointestinal Stromal Tumors |
|---|---|---|
| Characteristics | Esophagus | Stomach | \( P \) 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 cm ≤5 cm | 25 | 25 |  |
| >5 cm ≤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 |  |

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

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.53 In our current study, the clin-
icopathologic 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 classi-
fication were significantly different between esophageal and
gastric GISTS. The esophageal GISTs showed larger tumor size
and higher risk classification than gastric GISTs. The distribu-
tion 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 al74 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 distri-
bution 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 sig-
ificantly from gastric GISTS in respect to clinicopathologic
features. The prognosis of esophageal GISTS was worse than
that of gastric GISTS.

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