

Clinicopathologic features and outcomes of gastrointestinal stromal tumors arising from the esophagus and gastroesophageal junction

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Background: Our aim was to characterize the clinicopathological features and outcomes of gastrointestinal stromal tumors (GISTs) arising from the esophagus and gastroesophageal junction (GEJ) and describe the survival of patients treated at our institution as well as from a national hospital-based registry.

Methods: Twenty-eight cases were identified using the Mayo Clinic Cancer Registry from 1997 to 2016, and 1,010 cases from the National Cancer Database (NCDB) between 2004 and 2014, with analysis of TNM staging, histopathological features, mitotic index, immunohistochemical studies, and KIT mutational analysis.

Results: At Mayo Clinic, the tumors ranged in size from 0.3–13 cm (mean 5.40 cm). IHC results were: CD117 (*KIT*) in 100% (23/23 cases) and DOG1 in 100% (6/6), followed by CD34 (85.7%, 12/14), smooth muscle actin (27.8%, 5/18), desmin (18.2%, 2/11), and S-100 protein (13.3%, 2/15). Mutational analysis (performed in 10 cases) showed *KIT* exon 11 mutations in 8 cases; *KIT* mutation was not identified in 2 cases (presumed wild-type). Two-thirds of patients underwent surgery, of which 70% had an esophagectomy. Fourteen patients received adjuvant imatinib mesylate. Five patients had liver metastases at the time of diagnosis; none had lymph node metastases. A total of 38.9% of cases had recurrent or metastatic disease. Complete clinical follow-up was available for 10 patients (median follow-up duration 31.5 months; range, 10–145 months): one (male) had a local recurrence at the anastomotic site and one (female) suffered a liver metastasis; the others were either disease-free or had stable disease at the time of last follow-up. There was a significant association seen among metastatic disease and mitotic count >5/50 high-powered field (HPF) ($P=0.016$), with median mitotic rate 90/50 HPF (range, 7–500) for metastatic tumors versus 6/50 HPF (range, 0–100) for non-metastatic tumors. For metastatic disease, median tumor size was 7.3 cm (range, 1–66 cm) compared to 4.8 cm (range, 0.02–71 cm) for non-metastatic disease, which was also statistically significant ($P\leq 0.0001$). Two hundred and fifty-eight NCDB cases were risk stratified using the Joensuu criteria. Among 89 low risk category tumors, only 2 (2.2%) were ultimately metastatic. A total of 10.9% (15/138) of high risk category tumors were metastatic. The median overall survival (OS) from the time of diagnosis for the Mayo Clinic cohort was 129.5 months (95% CI, 55.7–not reached), with 5-year OS 85.7%. Median OS for the NCDB cohort was 135.95 months (95% CI, 104.08–not reached) with 5-year OS 68.2%. Superior OS was seen in females (HR 0.67, 95% CI, 0.49–0.89, $P=0.006$).

Conclusions: Among esophageal and GEJ GISTs, metastatic disease was associated with increased mitotic count and increased tumor size. Men were found to have inferior OS. The Joensuu risk criteria were validated for risk stratification of esophageal and GEJ GISTs.

Keywords: Gastrointestinal stromal tumor (GIST); esophagus; gastroesophageal junction (GEJ); sarcoma

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Introduction

Gastrointestinal stromal tumors (GISTs), rare sarcomas thought to derive from the interstitial cells of Cajal, can occur anywhere within the gastrointestinal tract. GISTs of esophageal and gastroesophageal junction (GEJ) origin are exceedingly rare, constituting less than 1% of all GIST cases with an estimated incidence of 0.1 to 0.3 per million people (1-3). As such, little is known about their clinicopathological features and clinical outcomes. Previous studies have attempted to analyze the unique features and prognostic outcomes of esophageal GISTs but have involved only a small number of cases (4-6). Much of the published work on GISTs instead focuses on the features of gastric and proximal small intestinal GISTs, as these are by far the most common primary locations (1-3). Often the GIST may be asymptomatic and found incidentally, especially in those patients undergoing endoscopies for esophageal or GEJ adenocarcinomas, but they can also cause significant morbidity and mortality (7). The aim of this retrospective analysis was to further characterize the clinicopathological features and outcomes of GISTs arising from the esophagus and GEJ.

The clinical behavior of GISTs varies by location, tumor size, and mitotic activity. In 2001, Fletcher *et al.* in collaboration with investigators from the NIH proposed a scheme for stratifying risk of recurrent GIST following surgical resection (8). Since its publication, this classification has been widely used and supported by several large population-based studies. Subsequent modifications have been made, most notably by the Armed Forces Institute of Pathology (AFIP) which includes anatomic location (esophageal tumors are classified under the same criteria as jejunum and ileum), and the Joensuu risk criteria which simplifies classification of GIST by tumor size, location (gastric or non-gastric), and mitotic activity [$<5/50$, $5-10/50$, and $>10/50$ high-powered field (HPF)] (8-11) (Table 1). Throughout the gastrointestinal tract, the risk of metastatic GIST has been shown to be strongly dependent on both tumor size and mitotic activity, with metastatic disease displaying a predilection for the liver and peritoneum

(4-6,12-15). Owing to their rarity, however, esophageal and GEJ GISTs are not specifically addressed by the NIH, AFIP, or Joensuu criteria (8-11).

The discovery of *KIT* mutations as genetic drivers of GISTs resolved longstanding confusion concerning the diagnosis of GIST and provided a very sensitive diagnostic biomarker (16). Eighty-five percent of GISTs are *KIT* mutant and this corresponds to overexpression of *KIT*, detectable by immunohistochemistry. Approximately 15% of GISTs have mutations in platelet-derived growth factor receptor alpha (*PDGFRA*), *BRAF*, *SDHB*, or *NF-1*, but the majority of these cases still show *KIT* overexpression by immunohistochemistry (17). The association of *KIT* and *PDGFR* mutations with prognosis is complicated and patients with identical mutations have widely varying risks of recurrence (18). Histologically, the cells of GIST can be classified as spindle shaped, epithelioid, or mixed (19-21).

The mainstay of treatment for localized esophageal or GEJ GIST is surgery, either enucleation or esophagectomy (22), however, just over half will remain recurrence-free at 5 years (23,24). Adjuvant treatment with imatinib mesylate, an inhibitor of multiple tyrosine kinases including *KIT*, can reduce the recurrence rate following surgical resection (25,26), with some evidence that longer duration of treatment improves recurrence-free and overall survivals (OS) further (27-30). Neoadjuvant imatinib mesylate can be considered in select cases, especially for patients with larger tumors or those having tumors in locations that would make complete resection challenging (31-34). For metastatic or recurrent GIST, imatinib mesylate is the mainstay of therapy, with resection being uncommon (35,36). There remains considerable uncertainty regarding the optimal management of very small GISTs (<2 cm in size) in any anatomical location (27-30,37). Serial observation may be an option for carefully selected patients with very small GISTs (38).

In this retrospective analysis, we sought to further characterize the clinicopathological features and outcomes of GISTs arising from the esophagus and GEJ, with comparisons made to GISTs arising from other sites.

Table 1 Joensuu criteria, risk stratification

Risk category	Tumor size (cm)	Mitotic index (per 50 HPFs)	Primary tumor site
Very low risk	<2.0	≤5	Any
Low risk	2.1–5.0	≤5	Any
Intermediate risk	2.1–5.0	>5	Gastric
	<5.0	6–10	Any
	5.1–10.0	≤5	Gastric
High risk	Any	Any	Tumor rupture
	>10.0	Any	Any
	Any	>10	Any
	>5.0	>5	Any
	2.1–5.0	>5	Non-gastric
	5.1–10.0	≤5	Non-gastric

Methods

Patient selection

A retrospective analysis was performed on all cases of esophageal and GEJ GIST evaluated at each of the three Mayo Clinic sites (Minnesota, Florida, and Arizona) between 1997 and 2016. Inclusion criteria included adults over age 18 with a diagnosis of GIST arising in the esophagus or GEJ, based on well-established criteria (39-42). Those with a second concurrent malignancy were excluded from survival analyses. All available slides were re-reviewed by two pathologists (RPG and ALF). In order to provide a more comprehensive descriptive overview, we also queried the National Cancer Database (NCDB) and found an additional 1,010 cases between 2004 and 2014. The NCDB is sourced from hospital registry data from more than 1,500 facilities in the United States, and captures an estimated 70% of all newly diagnosed malignancies, making it an especially useful tool in studying rare malignancies (43). Only patients with confirmed histologic diagnosis of GIST were included among the NCDB data. Patients with more than two malignancies (non-melanoma skin cancers are reported to the NCDB), patients not treated at the reporting facility, and patients without completed follow-up were excluded. Those with GIST diagnosed in 2013 and 2014 were excluded from survival analysis.

Clinical and pathological features

Available clinical records were analyzed data for patient age

and gender, the presence of symptoms (dysphagia, pain, bleeding, reflux), the time from symptom onset to diagnosis, the tumor location (upper third of esophagus, middle third of esophagus, lower third of esophagus, GEJ/cardia), the time to surgery from diagnosis, the type of surgery (enucleation or esophagectomy), the presence or absence of metastases, and any adjuvant therapies. The patients were staged according to the 7th edition of the AJCC manual. The time to recurrence or distant metastases after surgery and survival time from diagnosis were noted. Vital status for patients in this study was assessed until September 15, 2016. Two patients had a second concurrent malignancy and were excluded from survival analyses.

Evaluated pathological parameters included tumor size, tumor morphology (spindled, epithelioid, or mixed), mitotic index (<5/50, 5–10/50, >10/50 HPF), immunohistochemical findings (CD117/*KIT*, CD34, DOG-1, desmin, smooth muscle actin, S-100 protein), and molecular diagnostics (*KIT* exon 9 mutation, *KIT* exon 11 mutation, *PDGFRA* exon 12 mutation, *PDGFRA* exon 18 mutation).

Statistical methods

All statistical analyses were performed using JMP and SAS software (SAS Institute, Cary, NC, USA). The Mayo Clinic Center for Clinical and Translational Science (CCaTS) consultative services were used for biostatistics support. Continuous features were summarized with means, medians, and ranges. Categorical features were summarized with frequency and percentages. Fisher's exact test was used

Table 2 Baseline tumor characteristics, Mayo and NCDB cohorts

Tumor characteristics	Mayo	NCDB
Primary site (%)	n=28	n=972
Upper 1/3	0 (0.0)	7 (0.7)
Middle 1/3	1 (3.6)	24 (2.5)
Lower 1/3	10 (35.7)	73 (7.5)
GE junction	17 (60.7)	868 (89.3)
T stage (%)	n=18	n=391
T1	2 (11.1)	66 (16.9)
T2	7 (38.9)	172 (44.0)
T3	6 (33.3)	120 (30.7)
T4	3 (16.7)	33 (8.4)
N stage (%)	n=13	n=363
N0	13 [100]	349 (96.1)
N1	0 (0.0)	14 (3.9)
M stage (%)	n=22	n=536
M0	17 (77.3)	460 (85.8)
M1	5 (22.7)	76 (14.2)

Table 3 Tumor size and mitotic count, Mayo and NCDB cohorts

Tumor characteristics	Mayo (n=17)	NCDB (n=393)
Mean tumor size (cm)	5.73 (range, 0.3–13)	6.14 (range, 0.02–71)
Mitotic count, HPF (%)		
<5/50	7 (41.2)	282 (71.8)
6–10/50	5 (29.4)	42 (10.7)
>10/50	5 (29.4)	69 (17.6)

to examine associations between two nominal variables. OS was estimated using the Kaplan-Meier method. Univariate associations of gender and location with OS (time from diagnosis to death) were evaluated using Cox proportional hazards regression models and summarized with hazard ratios and 95% confidence intervals. A multivariable Cox proportional hazards regression model was also established considering the variables of gender, stage (I–IV), and location (cardia or non-cardia). P values <0.05 were considered significant.

Results

Clinical features

In total, 28 cases of esophageal and GEJ GISTs evaluated at Mayo Clinic were identified and included. An additional 1,010 cases from the NCDB were analyzed. GISTs were more commonly seen in men (59.2% of Mayo Clinic cases, 52.3% of NCDB cases), and median age at diagnosis was 69 years (range, 43–89 years) in the Mayo Clinic cohort and 66 years (range, 21–90 years) in the NCDB cohort. Among the patients seen at Mayo Clinic, dysphagia (23%), pain (19%), reflux (15%), and bleeding (8%) were the most common symptoms at presentation; 23% of patients were asymptomatic at the time of diagnosis.

The majority of tumors in both cohorts were found at the GE junction (60.7% at Mayo Clinic, 89.3% in NCDB). In our cohort, 11 cases (39.3%) originated in the lower third of the esophagus, with 7.5% of the NCDB cohort. Among both cohorts, only about 3% of cases arose from the more proximal esophagus.

AJCC T staging was recorded in 18 of the 28 Mayo Clinic cases (T1 11.1%, T2 38.9%, T3 33.3%, T4 16.7%). No patient had nodal involvement at diagnosis. Five of 22 (22.7%) patients presented with metastases, all to the liver. Among the NCDB cohort, 16.9% (66 of 391) were T1 stage, 44% [172] T2 stage, 30.7% [120] T3 stage, and 8.4% [33] T4 stage. Only 3.9% of NCDB cases (14/363) had nodal involvement, with 14.2% (76/536) having distant metastases (Table 2).

Pathological features

The mean tumor size in the Mayo Clinic cohort was 5.73 cm (range, 0.3–13 cm) and 6.14 cm (range, 0.02–71 cm) in the NCDB cohort. Mitotic activity was <5 per 50 HPF in 7 of 17 cases (41.2%), 6–10 per 50 HPF in 5 cases (29.4%), and >10 per 50 HPF in 5 cases (29.4%) at Mayo Clinic. Of 393 NCDB cases with available information on the mitotic count, 282 (71.8%) had <5 mitoses per 50 HPF, 42 (10.7%) had 6–10 mitoses per 50 HPF, and 69 (17.6%) had >10 mitoses per 50 HPF (Table 3).

Molecular analysis was performed on ten Mayo Clinic cases, with *KIT* exon 11 mutations found in eight (80%). Two cases were regarded as wild-type, with testing for mutations in *PDGFRA* exons 12, 14, and 18 and *c-kit* exons 8, 9, 11, 13, and 17 performed on both. One of the

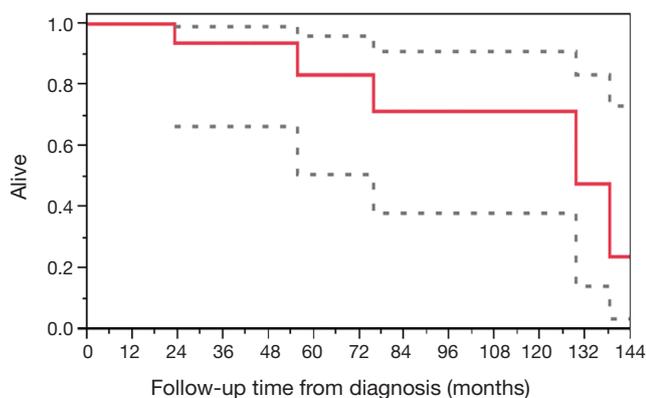


Figure 1 Overall survival, Mayo cohort. Dashed lines are 95% confidence intervals.

wild-type cases was found to be BRAF V600E positive with retained SDH expression via IHC. The majority of NCDB cases did not have mutational information available. Of those with information available, mutations were predominantly in *KIT* exon 11 (25/61, 41%), followed by *KIT* exon 17 (14/61, 23%), *KIT* exon 9 (3/61, 4.9%), and *KIT* exon 13 (2/61, 3.3%). *KIT* mutations were not identified in 17 (27.9%) of the NCDB cases.

At Mayo Clinic, tumor morphology was spindle in 12 of 15 cases (80%), epithelioid in 1 case (6.7%), and mixed in 2 cases (13.3%). By immunohistochemistry, the tumors were positive for CD117 (*KIT*) (23/23 cases, 100%), DOG1 (6/6, 100%), CD34 (12/14, 85.7%), smooth muscle actin (5/18, 27.8%), desmin (2/11, 18.2%), and S-100 protein (2/15, 13.3%).

OS and recurrences

Mayo Clinic cohort

The median time to diagnosis from symptom onset was 2 months (range, 0–29 months), whereas the median time to surgery from diagnosis was 1 month (range, 0–9 months). Surgery was performed in 17 of 26 (65.4%) patients, with the majority of those undergoing esophagectomy (12/17, 70.6%) compared to enucleation (5/17, 29.4%). In all, 14 of 22 patients (63.6%) patients received adjuvant therapy, all with imatinib mesylate.

Overall, eight patients did not receive adjuvant imatinib mesylate, while nine did not undergo surgery. Four patients received neither surgical resection nor adjuvant imatinib mesylate. One patient had a tumor 3.5 cm in size with unknown mitotic activity, and has had stable disease via

serial imaging for over 10 years. Of the other three cases, all of the tumors were 2 cm or less in size with no mitotic activity. One remained stable on serial CT imaging for 3 years before the patient died of another cause. The second case has remained stable for over 10 years. The third patient is currently undergoing serial CT imaging with stable disease over the past 18 months.

Clinical follow-up was available for 10 patients (median 31.5 months; range, 10–145 months). In all, 7 of 18 cases (38.9%) had metastatic or recurrent disease. Of these, five presented with liver metastases. Of the patients with localized disease at the time of diagnosis, one had a local recurrence and one suffered a liver metastasis. The first patient (male) underwent esophagectomy with adjuvant imatinib for T3N0M0 high-risk (9 cm, 6–10 mitoses/50 HPF) disease and developed recurrence at the anastomotic site approximately 24 months after surgery. He subsequently resumed imatinib and received 10 fractions of localized radiation with stable disease as of most recent follow-up. The second patient (female) underwent laparoscopic enucleation without adjuvant therapy for T2N0M0 high-risk disease (4.5 cm, 10 mitoses/50 HPF) and developed metastases to the liver just over 50 months after surgery. She was subsequently initiated on imatinib, with radiographic partial response prior to being lost to follow-up.

The median tumor size and mitotic rate for those esophageal and GEJ GISTs which either presented with metastases or subsequently metastasized was 7.5 cm (range, 3.2–10.5 cm) and 90/50 HPF (range, 7–500), respectively. In contrast, median tumor size and mitotic rate for those patients without evidence of metastasis was 4 cm (range, 0.3–10.5 cm) and 6/50 HPF (range, 0–100). There was a significant association seen among metastatic disease and mitotic count $>5/50$ HPF ($P=0.016$), but no association between tumor size and metastatic disease. Of the two metastasizing tumors on which mutational analysis was performed, both had *KIT* exon 11 mutations. For non-metastasizing tumors, 5 of 7 cases (71.4%) had *KIT* exon 11 mutations, with no mutation found on the remaining 2 cases (28.6%).

The median survival from time of surgery was 124.3 months (95% CI, 23.0–137.9) and the median OS from diagnosis was 129.5 months (95% CI, 55.7–not reached) (Figure 1).

NCDB cohort

Median OS in the NCDB cohort was 135.9 months (95% CI, 104.08–not reached) (Figure 2). Women had superior survival compared to men (HR 0.67, 95% CI, 0.49–0.89,

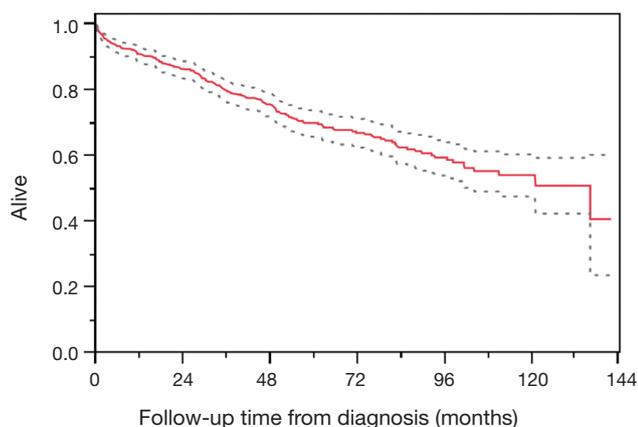


Figure 2 Overall survival, NCDB cohort. NCDB, National Cancer Database. Dashed lines are 95% confidence intervals.

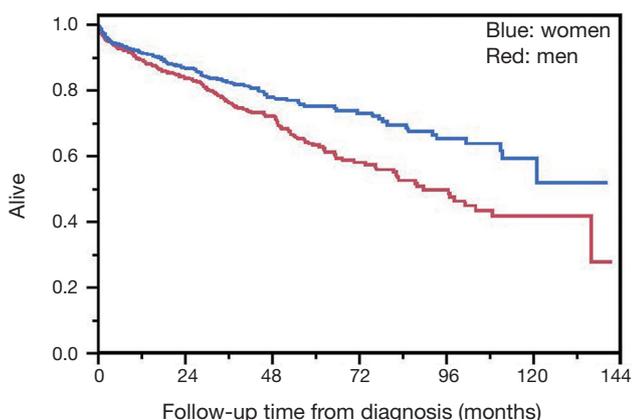


Figure 3 Survival by gender, NCDB cohort. NCDB, National Cancer Database.

$P=0.006$) (Figure 3). There was no difference in rate of metastatic disease when genders were compared. Among the entire cohort of esophageal and GEJ GISTs, there was no significant difference in OS when comparing tumor location, tumor size, mitotic count, or type of surgical resection. For metastatic disease, median tumor size was 7.3 cm (range, 1–66 cm) compared to 4.8 cm (range, 0.02–71 cm) for non-metastatic disease, which was statistically significant ($P \leq 0.0001$).

Two hundred and fifty-eight of the NCDB cases were risk stratified using the Joensuu criteria (11). Thirty-one of these were very low risk, of which none were metastatic. Among 89 low risk category tumors, only 2 (2.2%) were ultimately metastatic. A total of 10.9% (15/138) of high risk category tumors were metastatic. Tumor rupture was

not reported to the NCDB. As all tumors were non-gastric, none fell under the intermediate risk category.

Discussion

In this, the largest single institution study of esophageal and GEJ GISTs to date, we have found such tumors to most often localize to the GE junction and distal esophagus. This is consistent with previously published data and likely reflects the normal microanatomical distribution of interstitial cells of Cajal within the esophagus (4,5,44). The average tumor size of our cohort at Mayo (5.4 cm) was consistent with prior findings in esophageal GIST and those at other locations (4–6,9,10). Not surprisingly, the majority of our cases had mutated *KIT*, all in exon 11, but there were 2 presumed wild types. It has been previously reported that esophageal GIST are more likely to have wild-type status than gastric GIST (5). Rates of *KIT* mutations outside of exon 11 were higher than expected in the NCDB cohort (23% *KIT* exon 17, 4.9% *KIT* exon 9, 3.3% *KIT* exon 13), likely due to secondary mutations that developed after imatinib therapy, although it is difficult to draw firm conclusions about the prevalence of individual mutations given the small minority of cases that had mutational analysis available.

Given their rarity, esophageal GISTs are not specifically addressed by any of the prevailing GIST risk stratification schemes, including the NIH, AFIP, and Joensuu criteria (8–11,14). However, among the cases at Mayo Clinic, just under half of the tumors that would fit into the high risk category had metastases or recurrence. There were no tumors that would have fit into the intermediate risk category. Of the tumors that would be considered very low or low risk, none had recurrence or metastasis. The NCDB data showed a similar trend, with 88% of all metastatic tumors falling into the high risk category, demonstrating that these risk stratification schemes do have some utility in esophageal and GEJ GISTs.

We found a statistically significant association between metastatic disease and mitotic count $>5/50$ HPF in the Mayo Clinic cohort, and between metastatic disease and tumor size in the NCDB cohort. Of the four patients at Mayo Clinic with low-risk disease who received neither surgical resection nor adjuvant imatinib mesylate, all had good outcomes, offering some evidence that active surveillance might have more of a role in low risk disease with small primary tumor size and minimal mitotic activity in carefully selected patients.

The 39% rate of recurrence or metastases seen in the Mayo Clinic cohort is higher than has been seen in previously published studies, which showed risks of recurrent or metastatic disease in esophageal GIST ranging from 22.6% to 25.5% (4,5). This may reflect referral bias, as a significant percentage of Mayo Clinic patients had metastatic disease at presentation. In comparison, the rate of metastatic disease in GISTs at other sites ranges from 9% (rectum) to 26% (small intestine) (3). Previous studies have noted esophageal GIST to have inferior survival, larger tumor size, and higher mitotic rates when compared to gastric GIST, and it has been hypothesized that the lack of a serosal covering in the esophagus gives these tumors a greater propensity to metastasize (3-5).

We found a median OS in the Mayo Clinic cohort of 129.5 months with 5-year OS 85.7%, with median OS of 135.9 months and 5-year OS of 68.2% in the NCDB cohort. This compares to previously reported 5-year OS of 48.3–65.1% in esophageal GISTs (4,5). The relatively limited duration of follow-up likely explains the higher than expected OS we found, as we know even metastatic tumors can be imatinib responsive for years. Differences in anatomical location within the esophagus and GEJ are unlikely to explain any survival difference given the similarities in outcomes we found between the GISTs in the different locations. We cannot exclude that differences in therapy, both medical and surgical, with frequent use of adjuvant imatinib mesylate, affected the survival in these patient cohorts. We know that the patients from Mayo Clinic had a short time to diagnosis (2 months from symptom onset) and surgery (1 month from diagnosis), which could theoretically explain some survival benefit, although further research would be necessary to more fully investigate this difference.

Our results also showed that females had superior OS when compared to males, which has been previously observed in GISTs of the stomach and small intestine (14,45). The explanation behind this is not clear as there was no significant difference between risk of metastatic disease and gender.

Limitations

Although this is the largest single-institution cohort published to date, given the rarity of GISTs, especially those of the esophagus, we were only able to identify and analyze a limited number of cases, which in some cases had very limited data and follow-up. Many patients came

from outside institutions and were seen only once at Mayo for confirmation of diagnosis, and were then subsequently treated at a different institution. Our institution had a higher rate of recurrent or metastatic disease than has been previously published in the literature for esophageal GIST, and it is very possible we missed additional cases of recurrence due to inadequate follow-up (4,5). It is also plausible, however, that the rate of recurrent or metastatic disease seen at Mayo Clinic is overestimated given the low sample size, as patients with non-metastatic disease might have been less likely to return to Mayo Clinic for follow-up. The superior survival in the Mayo Clinic cohort may in part be secondary to referral and selection biases with healthier patients being more likely to be seen at a large-volume tertiary center. This phenomenon has also been observed for other malignancies where outcomes in single-center studies are superior to the outcomes seen in population-based registry studies (46). Direct comparisons between the Mayo Clinic and NCDB cohorts were unable to be made given likely crossover between the two cohorts.

It has been well demonstrated that tumor size and mitotic activity are significant prognostic factors for GISTs throughout the GI tract (4,5,22-27). Previous studies have also shown worse outcomes in esophageal GISTs compared to gastric GISTs, with larger primary tumor sizes and thus higher proportions of high-risk classifications (4,5). Unfortunately, with the limited number of cases and subsequent deaths in our institutional cohort, a more exhaustive survival analysis was not statistically possible.

The NCDB lists all tumors with mitotic count >11/50 HPF under the same code, so we were unable to further analyze the association between mitotic count and metastatic disease with this cohort. There is no centralized pathology review within the NCDB, relying instead on the individual institutions' reporting. Limited treatment data is available, as the database captures only whether the chemotherapy was single-agent or multi-agent, but does not identify the specific agent itself. Since cases are reported to the NCDB only from Commission on Cancer facilities, a proportion of cancers are missed, especially those more often managed in a physician's office.

Given that a number of tumors in the NCDB cohort presented in young patients with lymph node metastases, it is possible some of the included cases were actually advanced SDH-deficient gastric GISTs, although this information is not captured in the data submitted to the NCDB by individual institutions. Furthermore, it is difficult to draw any firm conclusions about the prevalence

of individual mutations, as only a small minority of patients in the NCDB cohort had any mutation testing available.

Conclusions

Overall, this project confirmed that GISTs of the esophagus and GEJ have similar primary tumor sizes, higher risk of recurrent or metastatic disease, and inferior survival to GISTs of other locations (3-5). Recurrences after surgical resection do occur, even with adjuvant therapy. Metastatic disease was associated with increased mitotic count and increased tumor size. Based on the higher OS seen in the Mayo Clinic cohort, early surgery and adjuvant imatinib mesylate might improve outcomes. However, this improved OS might also be secondary to selection bias of patients. Men were more likely than women to present with metastatic disease and had inferior OS. The Joensuu risk criteria were validated for risk stratification of esophageal and GEJ GISTs. Patients with low risk tumors can be observed for years with good outcomes.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical statement: The study was approved by Mayo Clinic Institutional Review Board (No. IRB00000020) and informed consent was taken from all the patients.

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