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Original Article

Gastrointestinal stromal tumors of the esophagus: evaluation of a pooled case series regarding clinicopathological features and clinical outcome

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Abstract: Background and Objectives: To elucidate diagnostic criteria, clinicopathological features and clinical outcome in patients with esophageal gastrointestinal stromal tumors (GIST), representing an extremely rare subform of GIST with an estimated incidence of about 0.1 to 0.3 per million people. Patients and methods: Esophageal GIST cases from the Ulmer GIST registry consisting of 1077 cases were pooled with case reports and case series of esophageal GIST extracted from MEDLINE. Data were compared with those from 683 cases with gastric GIST from the Ulmer GIST registry. Results: In comparison to gastric GIST, esophageal GIST (n = 55) occurred significantly more frequent in men (p = 0.035) as well as in patients younger than 60 at diagnosis (p < 0.001). Primary tumor sizes were significantly larger (p < 0.001), thereby resulting more frequently in a high-risk classification (OR = 4.53, CI 95% 2.41-8.52, p < 0.001). The 5-year rates of disease-specific survival (DSS), disease-free survival (DFS), and overall survival (OS) were 50.9%, 65.3% and 48.3%, respectively. The prognosis of esophageal GIST was less favorable compared with gastric GIST (DSS: p < 0.001, HR = 0.158, 95% CI: 0.087-0.288; DFS: p = 0.023, HR 0.466, 95% CI: 0.241-0.901; OS p = 0.003, HR = 0.481, 95% CI: 0.294-0.785; univariate Cox model) after a median follow-up time of 28 months (range 1.9 to 202). Mutational analysis for *KIT* showed more frequently wild-type status in esophageal GIST (OR = 10.13, CI 95% 3.02-33.96, p < 0.001). Conclusions: Esophageal GIST differ significantly from gastric GIST in respect to clinicopathological features and clinical outcome. To optimize treatment options further prospective data on patients with esophageal GIST are urgently warranted.

Keywords: GIST, gastrointestinal stromal tumor, esophagus, prognosis, outcome, mutation analysis

Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal neoplasms of the gastrointestinal tract with an annual incidence of 7 to 20 per million [1-6]. There is substantial evidence that GISTs differentiate parallel to the gut pacemaker cells, the interstitial cells of Cajal suggesting an origin from the Cajal cells or their progenitor cells [7-9]. Despite prognostic relevance of metastases at primary stage and tumor rupture, risk stratification in GIST is related to tumor size, mitotic rate and as recently recognized also to tumor location. The majority of GISTs are located in the stomach (60-70%) and the small intestine (25-30%), whereas GISTs of the colo-rectum (up to 5%) and extra-gastrointestinal manifestations (< 5%) are less common [10-12]. Esophageal GIST is a very rare entity of GIST and represents < 1% of all cases. Therefore data on clinicopathological characteristics and clinical outcome are limited. The aim of the present study was to elucidate comprehensively demographic and clinico-

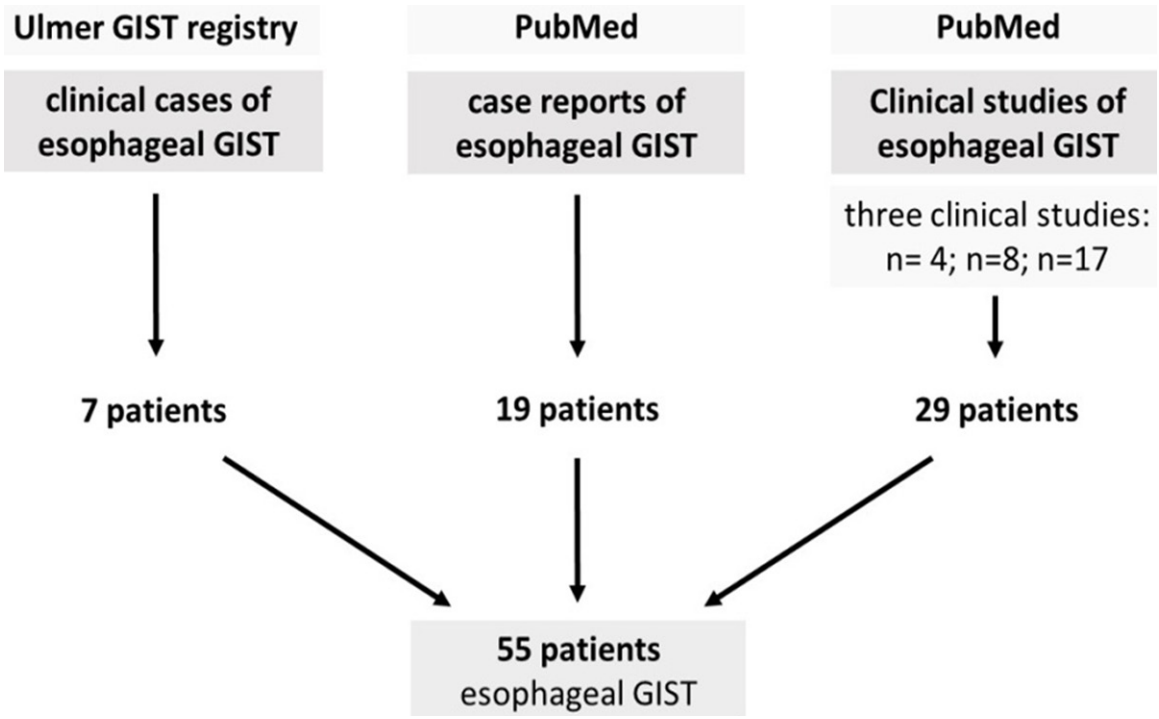

Figure 1. Schematic diagram regarding selection of esophageal GIST patients.

pathological features, diagnostic procedures and data on treatment and outcome in patients with GIST and esophageal manifestation.

Material and methods

GISTs cases of the esophagus were extracted from the Ulmer GIST registry and in addition from the literature. The multicenter Ulmer GIST registry comprises 1077 patients retrospectively collected from 18 collaborative oncological centres in Southern-Germany between 2004 and 2012. As previously outlined [13], data registration of the Ulmer GIST registry is strictly based on clearly defined methodological criteria, such as Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) Statement and the User's Guide to Registries Evaluating Patient Outcomes [14-17]. Literature search of MEDLINE was performed for all articles published from 1993 through 2013, using the following MeSH (Medical Subject Heading) terms: esophagus, gastrointestinal stromal tumor, esophageal GIST, outcome, clinicopathological features, clinical manifestation and related articles respectively.

To this end a total of 55 GIST patients with esophageal localization were identified (**Figure 1**). From the Ulmer registry seven patients with GIST of the esophagus were extracted (0.65%). Clinical manifestations, diagnostic, localization, pathological findings including mutational analysis and treatments were evaluated retrospectively, the outcome was recorded prospectively. Clinical data were collected from medical history given by the patients, from hospital records and pathology reports or as outlined in published reports. Due to data acquisition, completeness of data is limited (see **Table 1**). The diagnosis of GIST was based on well-established international criteria [18, 19] using histomorphological findings (i.e. cellular spindle/epithelioid/mixed cell tumors), immunohistochemical staining (expression of KIT/CD117, or PDGFRA) and facultatively mutational analysis. MEDLINE search resulted in 19 case reports [20-36] and 3 case series including 29 patients [37-39]. All selected esophageal GIST cases were compared with 683 GIST patients of the stomach, extracted from the multi-centric Ulmer GIST registry. Regarding clinical outcome, analyses were performed for disease-specific-survival (DSS), disease-free-survival (DFS) and overall-survival (OS). Immunohistomical features if available comprised CD117/KIT, CD34, actin, desmin, vimentin, and S100.

Table 1. Demographic and clinicopathological data of 55 patients with esophageal GIST

Parameter		Study cohort of esophageal GIST	
Age (∑ = 55)			
	Mean (yr, ± SD)	60.3 (11.9)	
	Median (yr, range)	61.0 (21.0; 87.9)	
Sex (∑ = 55)		**n**	**%**
	Female	19	34.5
	Male	36	65.5
Localization (∑ = 55)			
	Middle 1/3	2	4.0
	Middle/lower 1/3	2	4.0
	Lower 1/3	46	92.0
	Not definable	5	-
Tumor size (∑ = 52)			
	Mean (cm, ± SD)	8.0 (4.8)	
	Median (cm, range)	7.35 (0.2; 25.0)	
Mitotic rate (∑ = 41)			
	Mean (per 50HPF, ± SD)	13.4 (18.2)	
	Median (per 50HPF, range)	5.5 (0; 79)	
Risk after Fletcher et al. (∑ = 46)		**n**	**%**
	High	25	56.8
	Intermediate	10	22.7
	Low	6	13.6
	Very Low	3	6.8
Operative therapy (∑ = 33)			
	Enucleation	14	42.4
	Esophagectomy	19	57.6
TKI/Imatinib (∑ = 55)			
	Yes/No	6/49	10.9/89.1
Histological subtype (∑ = 43)			
	Spindle cell/Epithelioid or mixed	35/8	81.4/18.6
Immunohistochemistry		**pos**	**neg**
(∑ = 53)	c-kit	53	0
(∑ = 46)	CD34	45	1
(∑ = 22)	Aktin	7	15
(∑ = 10)	Desmin	4	6
(∑ = 4)	Vimentin	4	0
(∑ = 34)	S100	0	34
Mutational status (∑ = 14)		**n**	**%**
	c-kit	8	57.1
	PDGFRα	0	0.0
	wild type	6	42.9
Symptoms			
(∑ = 50)	Symptoms at diagnosis	38	76.0
	Incidental	12	24.0
(∑ = 49)	Dysphagia	26	53
	Weight loss	10	20
	Bleeding	6	12
	Abdominal pain	4	8
	Nausea	3	6
	Cough	3	6
	Vomiting/Reflux/Night sweat	1/1/1	2/2/2
Follow up time			
	Mean (m, ± SD)/median (m, range)	48.2 (46.6)/28.0 (1.9; 202.0)	

Survival rates			%
	1-/3-/5-year DSS	97.5/76.3/50.9	
	1-/3-/5-year DFS	86.6/65.3/65.3	
	1-/3-/5-year OS	95.2/72.4/48.3	
Survival data		**n**	**%**
(∑ = 55)	Recurrence or metastases	14	25.5
(∑ = 55)	Exitus letalis overall	18	32.7
(∑ = 54)	Exitus letalis GIST depend.	15	27.3

HPF, high power field; m, month; SD, standard deviation; yr, year; DSS, disease specific survival; DSF, disease free survival; OS, overall survival.

Two-sided χ^2-test or Fisher's exact test were applied, as appropriate, to check for differences of qualitative demographic, clinical and clinicopathological parameters between the independent study-cohorts. Alternatively, two-sided t-test or Wilcoxon test were applied in case of quantitative parameters. Estimates for disease-free-survival (DFS), disease-specific-survival (DSS) and overall-survival (OS) were obtained by the Kaplan-Meier method and differences between Kaplan-Meier curves were investigated by the log-rank test. For analysis of DSS non GIST-related deaths were censored. If applicable, the Hazard Ratio (HR) and 95% confidence interval (95% CI) were calculated regarding tumor-related death and tumor recurrence and/or metastasis by applying univariate Cox proportional hazards regression models. To prove the most relevant findings of those univariate and Kaplan-Meier analyses, an additional multivariate Cox proportional hazards regression model has been established considering the variables age, gender, size of primary tumor and mitotic rate. Statistical analysis was performed using SPSS V19.0 (SPSS Inc., USA). A p-value ≤ 0.05 was considered as significant. The study was approved by the independent institutional ethics committee of the university of Ulm (Study-No: 90 & 91/2006). All patients gave written formed consent.

Results

Descriptive and clinical data of extracted esophageal GIST cases are given in **Table 1** and Supplemental Table 1. Mean follow-up-time for all 55 patients was 48.2 months (SD ± 46.6). The male to female ratio was 1.9:1 (male n = 36, female n = 19). The median age was 61.0 years (range 21.0 to 87.9 years). Nearly half of the patients (49.1%) were younger than 60 years, 16.4% were younger than 50 years. Regarding risk classification for GIST 57% (CI 95% 0.44, 0.70; n = 25) of the patients were classified as high risk according to Fletcher et al. [40] whereas similar figures were found for intermediate (23%, n = 10) and low/very low risk (21%, n = 9) patients. Immunohistochemical analyses were performed and available most frequently for CD117/KIT (n = 53) and CD34 (n = 46) while staining for actin (n = 22), desmin (n = 10) and S100 (n = 34) was done only for selected cases. CD117/Kit and CD34 staining was positive for all cases in 100% and 98%, respectively. In contrast immunohistochemistry for actin and desmin was positive in 32% and 40%, respectively and negative for S100 in all cases investigated. Data on mutational analysis for gain of function variants were available only in 14 GIST cases resulting in seven patients carrying a mutation in exon 11 of *KIT*, and one patient in exon 13. The remaining six patients were *KIT* wild type. PDGFRα variants were not detected in these 14 cases.

With regard to clinical features, 46 of 50 esophageal GIST were localized in the distal esophagus, 38 of 50 patients (76%, CI 95% 0.64; 0.88) presented with clinical symptoms. Interestingly, 12 of 50 patients (24%, CI 95% 0.1; 0.36) were detected incidentally. The most common symptom was dysphagia (26/49 = 53%, CI 95% 0.39; 0.67) whereas 10/49 patients reported weight loss. Other symptoms occurred in descending order: 6/49 gastrointestinal bleeding, hemoptysis or melena, 4/49 abdominal pain, 3/49 nausea, 3/49 cough, 1/49 vomiting, 1/49 gastro-esophageal reflux and 1/49 night sweat. Data on operative procedures were limited and only available for n = 33/55 patients (66%). 14 patients of them (42%, CI 95% 0.28-0.56) received local excision/enucleation of the tumor (range of tumor size: 1.8 cm; 12.5 cm), whereas partial esophagectomy/oesophagogastrostomy was performed in 19 patients (58%, CI 95% 0.41; 0.75). Patients with local

Table 2. Comparison of selected clinicopathological parameters between esophageal and gastric GIST

Basic parameters	Esophagus n = 55	Stomach n = 683	*p*-value
Age at diagnosis			
Mean (yr, ± SD)	60.3 (11.9)	66.8 (12.6)	< 0.001 (t-test)
Median (yr, range)	61.0 [21.0; 87.9]	68.7 [12.8; 94.8]	
Size of primarius			
Mean (cm, ± SD)	8.0 (4.8)	5.1 (4.6)	< 0.001 (t-test)
Median (cm, range)	7.35 [0.2;25.0]	4.0 [0.1; 32.0]	
Mitotic rate per 50 HPF			
Mean (per 50HPF, ± SD)	13.4 (18.2)	8.0 (28.1)	0.005 (Wilcoxon test)
Median (per 50HPF, range)	5.5 [0.0; 79.0]	2.0 [0.0; 500.0]	
Follow-up-time (months)			
Mean (m, ± SD)	48.2 (46.6)	59.3 (46.4)	-
Median (m, range)	28.0 [1.9; 202.0]	49.2 [0.0; 271.4]	

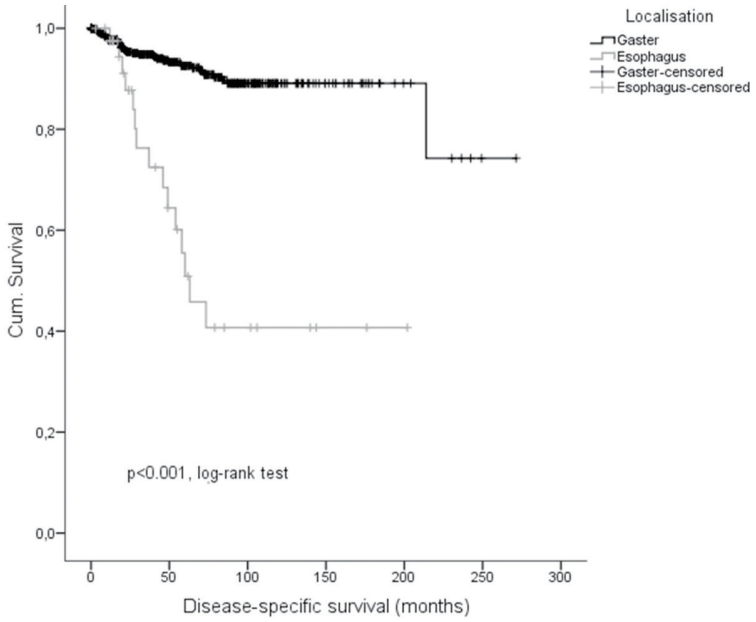

Figure 2. Disease-specific-survival of esophageal and gastric GIST.

excisions showed a significantly better outcome (DSS: p = 0.035, log-rank-test; OS: p = 0.035, log-rank-test; DFS: p = 0.049, log-rank-test; p = 0.07, Cox model; HR = 0.232, 95% CI: 0.05-1.13) in comparison to patients with more radical surgery. Regarding OS and DSS, calculation of the corresponding OR or HR failed since only censored events were observed in the enucleation group. Imatinib application was reported in 6/55 patients. The median follow-up time was 28.0 months (range 1.9 to 202). Of the 55 GIST patients 14 (25%, CI 95% 0.14; 0.36) and 18 (33%, CI 95% 0.21; 45) cases showed disease progression (recurrence or metastasis) or died, respectively. GIST-related deaths occurred in 15 cases (27%, CI 95% 0.15; 0.39).

For comparative evaluation, registry data of 683 patients with GIST of the stomach were used. Main results are given in **Tables 1** and **2** and Supplemental Table 1. The male to female ratio was 1:1 (male n = 346, female n = 337). The median age was 68.7 years (range 12.8 to 94.8). 25% (n=165) of patients were younger than 60 years, 10% (n = 64) younger than 50 years. Immunohistochemical staining was positive in 97% (n = 597/613) and 96% (n = 471/496) of cases for CD117/KIT and CD34, respectively. Actin staining was positive in 32% (n = 112/347), desmin staining in 16% (n = 53/325) and S100 immunohistochemistry in 13% (n = 48/363). The median follow-up time was 49.2 months (range 0.0 to 271.4). Disease progression (recurrence or metastasis) and GIST-related deaths were found in 13% (n = 91/683) and 6% (41/683) of patients, respectively.

When we compared data regarding GIST of the stomach vs. esophageal GIST, some significant differences were found. GIST of the esophagus was significantly associated with male gender (OR = 1.8, CI 95% 1.03; 3.28, p = 0.034, χ^2-test) and overall the mean age at diagnosis was significantly lower (p < 0.001, t-test). In more detail

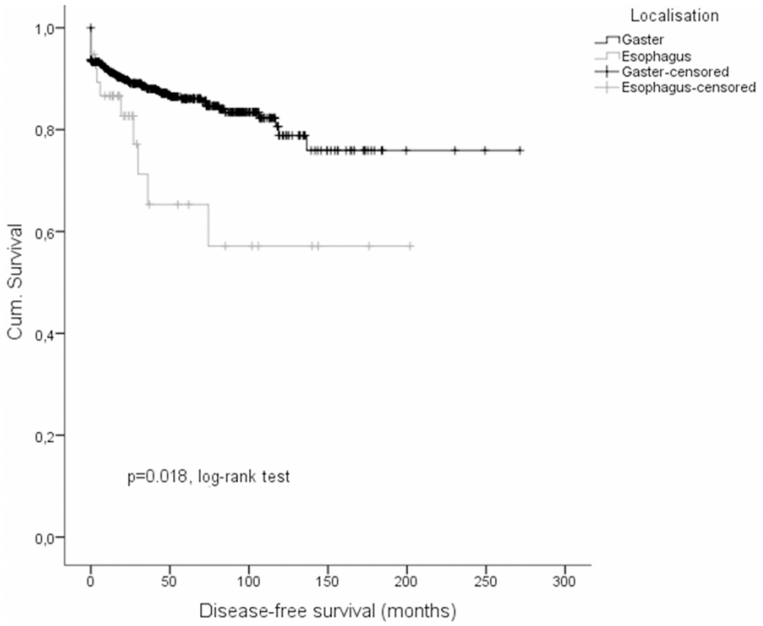

Figure 3. Disease-free-survival of esophageal and gastric GIST.

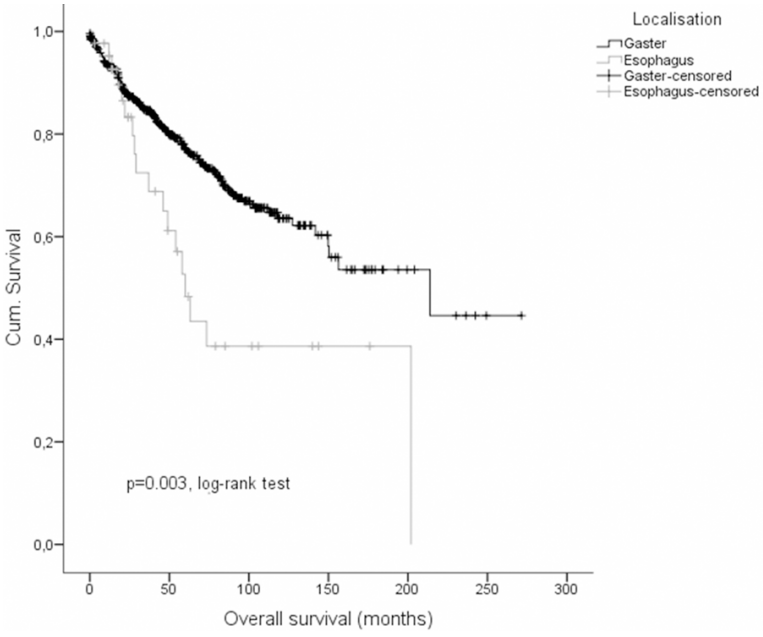

Figure 4. Overall-survival of esophageal and gastric GIST.

patients were more often younger than 60 years at date of diagnosis (OR = 2.85, CI 95% 1.62; 5.03, $p < 0.001$, χ^2-test). Generally, the primary tumor size was significantly larger ($p < 0.001$, t-test). Tumor sizes in esophageal GIST were increased (> 5 cm, OR = 4.03, CI 95% 2.14; 7.58, $p < 0.001$, χ^2-test; > 10 cm, OR = 3.51, CI 95% 1.88; 6.56, $p < 0.001$, χ^2-test), thereby resulting more frequently in a high-risk classification according to Fletcher et al. (OR = 4.53, CI 95% 2.41; 8.52, $p < 0.001$, χ^2-test). Mutational analysis for *KIT* showed more frequently wild-type status for esophageal vs. gastric GIST (OR = 10.13, CI 95% 3.02; 33.96, $p < 0.001$, χ^2-test). No significant differences were found regarding histological subtypes, and immunohistochemical staining for CD117/KIT, CD34, aktin, and desmin.

Regarding clinical outcome, we performed Kaplan-Meier survival analyses (**Figures 2**-**4**) to elucidate differences between esophageal and gastric GIST. Consistently data for disease-specific- (DSS), disease-free- (DFS) as well as overall-survival (OS) were significantly less favor in patients with esophageal GIST in comparison to gastric GIST. 1-, 3-, and 5-years DSS rates were 97.5% (95% CI: 92.6; 100), 76.3% (95% CI: 60.6; 92.0) and 50.9% (95% CI: 31.1; 71.0) in patients with esophageal GIST compared to 97.7% (95% CI: 96.3; 99.1), 94.9% (95% CI: 92.9; 96.9) and 92.6% (95% CI: 90.1; 95.1) in patients with gastric GIST ($p < 0.001$, log-rank-test; $p < 0.001$, cox model; HR = 0.158 95% CI: 0.087; 0.288), respectively. 1-, 3-, and 5-years DFS rates were 86.6% (95% CI: 75.6; 97.6), 65.3% (95% CI: 45.1; 85.5) and 65.3% (95% CI: 45.1; 85.5) in patients with esophageal GIST compared to 91.4% (95% CI: 89.0; 93.8), 88.0% (95% CI: 85.3; 90.7) and 86.1% (95% CI: 83.0; 89.2) in patients with gastric GIST ($p = 0.018$, log-rank-test; $p = 0.023$, cox model; HR = 0.466, 95% CI: 0.241; 0.901). 1-, 3-, and 5-years OS rates were 95.2% (95% CI: 88.7; 100), 72.4% (95% CI: 56.7; 88.1) and 48.3% (95% CI: 29.3; 67.3) in patients with

Table 3. Comparative survival analyses of esophageal and gastric GIST using univariate & multivariate cox regression models

(n_{total} = 55/683)	Esophagus	Stomach	Univariate Cox model	Multivariate Cox model
	% (n)	% (n)	p-, HR (95% CI)	p-, HR (95% CI)
Disease-specific-survival				
1-yr-DSS	97.5 (40)	97.7 (490)	p < 0.001, HR 0.158	p < 0.001, HR 0.132
3-yr-DSS	76.3 (20)	94.9 (355)	(0.087; 0.288)	(0.062; 0.282)
5-yr-DSS	50.9 (12)	92.6 (236)		
10-yr-DSS	40.7 (4)	89.1 (49)		
Disease-free-survival				
1-yr-DFS	86.6 (31)	91.4 (466)	p = 0.023, HR 0.466	p = 0.140, HR 0.566
3-yr-DFS	65.3 (12)	88.0 (328)	(0.241; 0.901)	(0.266; 1.204)
5-yr-DFS	65.3 (9)	86.1 (214)		
10-yr-DFS	57.1 (4)	78.8 (42)		
Overall-survival				
1-yr-OS	95.2 (40)	93.1 (513)	p = 0.003, HR 0.481	p < 0.001, HR 0.284
3-yr-OS	72.4 (20)	84.6 (372)	(0.294; 0.785)	(0.158; 0.510)
5-yr-OS	48.3 (12)	77.1 (246)		
10-yr-OS	38.6 (4)	63.6 (52)		

yr, year; DSS, disease specific survival; DSF, disease free survival; OS, overall survival; p, *p*-value; HR, hazard ratio. Multivariate Cox proportional hazards regression model has been adjusted considering the variables age, gender, size of primary tumor & mitotic rate.

esophageal GIST compared to 93.1% (95% CI: 90.9; 95.3), 84.6% (95% CI: 81.5; 87.7) and 77.1% (95% CI: 73.2; 81.0) in patients with gastric GIST (p = 0.003, log-rank-test; p = 0.003, cox model; HR 0.481, 95% CI: 0.294; 0.785). Results of the multivariate Cox models are given in **Table 3**.

Discussion

Gastrointestinal stromal tumors located in the esophagus constitute a very rare subform of GISTs with limited data on their demographic and clinic-pathological features. Therefore, we evaluated data of 55 pooled esophageal GISTs (**Figure 1**) from our Ulmer GIST registry and the literature with regard to clinical symptoms, diagnostic features, risk factors, treatment and outcome. The current study represents the largest analysis of esophageal GIST estimating an annual incidence of about 0.1 to 0.3 per million (approximately 8-12 per year in Germany). The present study indicates some characteristics significantly associated with esophageal GIST.

In comparison to the most common GIST of the stomach, esophageal GIST occurred significantly more frequent in men (p = 0.035) as well as in patients younger than 60 at diagnosis (p < 0.001). The significant predominance of men within the 5th decade in esophageal GIST is in accordance with previous published data [38, 39, 41]. However, despite 25% of incidental, asymptomatic tumors at diagnosis, 75% of patients with esophageal GIST present most commonly with dysphagia (51%), weight loss (20%) and bleeding (10%) [20-39, 42]. With regard to cell morphology the majority (81%, CI 95% 0.71; 0.91) of esophageal GISTs show spindle cell morphology which is comparable to data from the literature [42]. With a 100% positivity of KIT expression and 98% of CD34 expression, GIST of the esophagus seem to have an immune-profile similar to their gastric counterparts.

With a mean tumor size of 8.0 cm and a mean mitotic rate of 13/50 HPF, esophageal GISTs are significantly larger and show a higher mitotic rate than GIST of the stomach [20-39]. Hence, esophageal GIST are generally classified more frequently as high risk GIST according to Fletcher et al. (56.8% versus 22.5%, p < 0.001, χ^2-test). Regarding mutational status, data are limited and therefore conclusion should be drawn with caution. Only in 14/55 GIST patients the mutation status of *KIT* was available. Eight had *KIT* gain of function variants and none *PDGFRα* mutations. A wild type frequency of 42.9% is remarkably higher compared to GISTs from other sites.

With a 5 year DSS, DFS, and OS of 50.9%, 65.3% and 48.3% esophageal GIST present a significantly worse prognosis in comparison to GIST of the stomach (HR = 0.158, 95% CI: 0.087; 0.288, p < 0.001; HR = 0.466, 95% CI: 0.241; 0.901, p = 0.023; HR = 0.481, 95% CI: 0.294; 0.785, p = 0.003; - univariate Cox models). In contrast, Tran et. al. report a 5 year survival rate of 14%, but they do not differentiate DSS, DFS and OS and the acquisition of patients was performed in the *pre* imatinib-era [4]. Nevertheless, the majority reports from the literature support a higher malignant potential of esophageal GIST with a high risk for metastases and/or tumor recurrence and unfavorable outcome with a high mortality rate [38]. Most likely poor outcome in esophageal GIST is related to the above described significant higher rate of large tumor size and higher mitotic rate. Definite cellular mechanisms need to be addressed in future work.

Regarding the management of esophageal GIST three pillars need to be considered and linked together: i) appropriate pre-therapeutic histological diagnostics including biopsies, ii) alternative surgical procedures (i.e. radical resection vs. local tumor excision/enucleation), and iii) administration of tyrosine kinase inhibitors (e.g. imatinib) in different settings (i.e. neo-adjuvant, adjuvant, additive). Since controlled trials for esophageal GIST are missing due to the low incidence, neither the best surgical procedure, nor the impact of adjuvant or neo-adjuvant tyrosine kinase inhibitor therapy is well established. Currently, complete surgical elimination of the tumor appears to be the only curative therapeutic option in the management of non-metastatic, resectable esophageal GIST [43]. The outcome after local tumor enucleation compared to post-esophagectomy seems to be more favorable as mentioned above, however the mean tumor size in the enucleation group 5.8 cm [1.8-12.5] was significantly smaller with subsequent lower risk classification. Nevertheless, the decision which surgical procedure should be performed in esophageal GIST is still discussed controversially [41, 44-47]. Driven by the goal to achieve R_0 resection by highest radicality, local tumor enucleation might be limited and primary radical surgical resection may be the treatment of choice, as appropriate, combined with tryosine kinase inhibitor therapy [46, 47]. With regard to post-surgical morbidity and mortality, the local tumor enucleation seems a probate and less traumatic option, particularly in patients with significant comorbidities [37, 38, 41, 44]. As long as the tumor is entirely eliminated with intact pseudo tumor capsule and without tumor spread (R_0), tumor up to a size of 12.5 cm are reported to be safely enucleated [37]. Generally, enucleation of esophageal GIST are recommended for smaller tumors (2 to 5 cm) [37, 41], whereas esophagectomy should be performed for GIST above 9 cm in size [38]. In all cases between, the surgical procedure should be chosen based on the patient's individual surgical risk under consideration of underlying comorbidities [37, 38, 41, 44].

About 25% of mesenchymal esophageal tumors are GIST [39]. The role of pre-therapeutic histological and genetic diagnosis is judged individually, as it is essential for neo-adjuvant or dose adjusted TKI treatment. Ultrasound guided fine needle aspiration or core biopsy is reported to be a secure procedure and enables differentiation of mesenchymal tumors including GIST [37, 48, 49]. Whether biopsy induced scars may complicate subsequent tumor enucleation is under debate [41]. Indicators for preoperative biopsies are tumors above 2 cm in size with observed enlargement and/or intended neo-adjuvant TKI treatment [37, 41, 42, 48, 49]. In the presented study only in six of 55 patients, the application of imatinib was reported. Currently the ESMO-guidelines recommend adjuvant imatinib treatment at least for high-risk GIST based on the mutational status [43]. However, it has been reported that in large tumors neo-adjuvant application of imatinib may be beneficial too with regard to surgical and oncological outcome of these patients [37, 41].

The presented study lacks systematic prospective data acquisition and therefore in part completeness of data is limited. The heterogeneity of data selection based on registry data, case reports and small case series does not exclude some selection bias. Nevertheless, our work provides important information of the largest cohort of esophageal GIST so far. Esophageal GIST differ significantly from gastric GIST in respect to clinicopathological features and clinical outcome. To optimize treatment options further prospective data on patients with esophageal GIST are urgently warranted.

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Disclosure of conflict of interest

The authors have no conflict of interest or financial disclosure to declare.

Abbreviations

yr, years; mo, month; DFS, disease-free-survival; DSS, disease-specific-survival; HPF, high power field; SD, standard deviation; GIST, gastrointestinal stromal tumor; TKI, tyrosine kinase inhibitor.

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Supplemental Table 1. Overview of patient's characteristics in detail

	clinical symptoms				diagnostic					pathology				treatment & outcome			
Sex/age (L)	Inc	DP	WL	BL	EGD	FNA	ES	EUS	CT	Loc	Size	MR	CM	Surg	TKI	FU	Outcome
f/67 (1)	+	-	-	-	-	-	+	-	+	L	3.0	< 5/50	ND	EN	-	ND	ND
m/53 (2)	-	+	+	-	-	-	-	-	+	L	13.0	5-10/50	ND	-	+	ND	ND
f/74 (3)	-	+	-	-	+	+	-	-	+	M-L	12.0	ND	Sp	TEE	-	24	NoRec
f/54 (4)	+	-	-	-	-	-	-	-	+	L	11.0	2-3/10	Sp	TEE	+	79	Rec
m/74 (5)	+	-	-	-	+	-	-	-	+	ND	0.2	4/50	ND	TEE	-	ND	ND
m/62 (6)	+	-	-	-	+	-	-	-	+	L	6.8	6/50	ND	TEE	-	12	NoRec
f/58 (7)	-	-	-	-	-	-	-	-	+	L	> 10.0	5/50	ND	TEE	ND	ND	ND
m/21 (8)	-	+	-	-	+	-	-	-	+	M-L	4.8	0/50	Sp	EN	-	18	NoRec
m/36 (8)	-	+	-	-	-	-	-	+	+	L	6.5	0/50	Sp	EN	-	24	NoRec
m/69 (8)	-	+	+	-	+	+	-	-	+	L	6.0	> 50/50	Sp	TEE	+	12	Rec
f/66 (9)	-	-	-	+	-	-	-	+	+	L	3.0	< 1/10	ND	EN	-	ND	ND
m/57 (10)	-	ND	ND	ND	-	-	-	-	+	M + L	2.8 + 3.8	ND	ND	-	+	19	NoRec , SD
m/61 (11)	-	+	-	-	-	+	+	-	-	L	7.7	3/50	Sp	-	+	2	NoRec, SD
m/34 (12)	-	-	+	-	+	-	-	+	+	L	5.2	ND	ND	TEE	-	12	DOD
m/57 (13)	-	+	+	-	+	-	-	-	+	L	12.7	ND	Mix	TEE	-	3	Rec
m/75 (14)	-	-	-	+	+	-	-	+	+	L	14.0	1/10	ND	TEE	-	ND	ND
m/59 (15)	+	-	-	-	+	-	-	+	+	L	13.5	2/50	ND	TEE	-	12	NoRec
m/46 (16)	-	+	+	-	-	-	-	-	-	M	8.5	0/50	Sp	EN	-	14	NoRec
m/71 (17)	-	+	-	-	-	+	-	+	-	M	5.3	ND	ND	TEE	-	9	NoRec
m/57 (18)	-	+	-	+	+	-	-	-	-	L	16.0	30/50	Sp	TEE	-	60	Rec, DOD (i1)
m/57 (18)	-	-	-	+	+	-	-	-	-	L	11.0	25/50	Sp	TEE	-	58	Rec, DOD
m/49 (18)	+	-	-	-	+	-	-	-	-	L	3.0	0/50	Sp	EN	-	202	DDD
f/58 (18)	-	+	-	-	-	-	-	-	-	L	12.0	16/50	Ep	TEE	-	28	Rec, DOD (i2)
f/71 (18)	-	+	-	-	+	-	-	-	-	L	9.0	< 5/50	Sp	TEE	-	102	NED
m/56 (18)	-	+	-	-	+	-	-	-	-	L	15.0	22/50	Sp	TEE	-	63	Rec, DOD
m/52 (18)	+	-	-	-	+	-	-	-	-	L	4.5	< 5/50	Sp	EN	-	14	NED
f/64 (18)	-	+	-	-	+	-	-	-	-	L	7.5	0/50	Sp	EN	-	14	NED
f/74 (19)	-	-	-	-	+	+	-	+	-	L	12.5	30/50	Sp	EN	+	49	Rec, AWD (i3)
m/60 (19)	+	-	-	-	+	+	-	+	-	L	5.5	8/50	Ep	EN	-	41	Rec, NED (i4)
m/60 (19)	-	+	-	+	+	+	-	+	-	L	8.2	8/50	Mix	EN	-	26	NED
f/75 (19)	+	-	-	-	+	+	-	+	-	L	7.2	5/50	Sp	EN	-	17	NED
m/61 (20)	ND	ND	ND	ND	ND	ND	ND	ND	ND	L	2.6	10/50	Sp	ND	-	14	DDD (i5)
m/54 (20)	+	-	-	-	ND	ND	ND	ND	ND	L	3.5	2/50	Sp	ND	-	55	NED
m/50 (20)	+	-	-	-	ND	ND	ND	ND	ND	L	4.0	6/50	Sp	ND	-	106	NED
m/49 (20)	-	+	+	-	ND	ND	ND	ND	ND	L	4.5	0/50	Sp	ND	-	176	NED
m/56 (20)	-	+	-	-	ND	ND	ND	ND	ND	L	5.0	14/50	Sp	ND	-	20	DOD (i6)

f/66 (20)	-	+	-	-	ND	ND	ND	ND	ND	L	6.0	15/50	Sp	ND	-	62	NED
m/65 (20)	-	-	-	+	ND	ND	ND	ND	ND	L	7.0	1/50	Ep	ND	-	2	DUC
m/55 (20)	-	+	-	-	ND	ND	ND	ND	ND	L	8.0	26/50	Sp	ND	-	140	NED
f/58 (20)	-	+	+	-	ND	ND	ND	ND	ND	L	8.5	59/50	Sp	ND	-	ND	ND
m/69 (20)	-	+	-	-	ND	ND	ND	ND	ND	L	9.0	20/50	Sp	ND	-	27	DOD
m/63 (20)	-	+	-	-	ND	ND	ND	ND	ND	L	10.0	79/50	Sp	ND	-	29	DOD
m/52 (20)	-	+	+	-	ND	ND	ND	ND	ND	L	11.0	21/50	Sp	ND	-	54	DOD (i7)
f/66 (20)	-	-	-	-	ND	ND	ND	ND	ND	L	15.0	16/50	Ep	ND	-	46	DOD (i8)
f/68 (20)	-	-	-	-	ND	ND	ND	ND	ND	L	17.0	28/50	Ep	ND	-	49	DOD
f/70 (20)	-	-	-	-	ND	ND	ND	ND	ND	L	25.0	5/50	Sp	ND	-	18	DOD
m/68 (20)	ND	ND	ND	ND	ND	ND	ND	ND	ND	L	ND	15/50	Ep	ND	-	22	DOD
m/75 (20)	ND	ND	ND	ND	ND	ND	ND	ND	ND	L	ND	64/50	Sp	ND	-	37	DOD
f/77	-	+	+	-	-	-	+	+	-	ND	9.0	ND	Sp	TEE	-	73	Rec/DOD
f/47	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	1.5	ND	ND	ND	ND	ND	ND
m/68	-	+	+	-	-	-	+	-	+	L	6.0	ND	Sp	TEE	-	ND	ND
f/37	-	-	-	-	ND	ND	ND	ND	ND	ND	1.8	1/50	Sp	EN	-	119	NoRec
f/63	-	+	-	-	ND	ND	ND	ND	ND	L	5.0	1/50	Sp	EN	-	55	NoRec
m/88	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	3/50	Sp	ND	ND	ND	ND
m/62	+	-	-	-	-	-	-	-	-	L	0.6	0/50	Sp	TEE	-	8	NoRec

+/-: yes/no; AWD-alive with disease; BL-bleeding (gastrointestinal bleeding, hemoptysis, melena); CM-cell morphology; CT-(PET)CT; DDD-died of different disease; DOD-died of disease; DP-dysphagia; DUC-died of unknown cause; EGD-esophagogastroduodenoscopy; EN-thoracotomy, enucleation with excision of surrounding muscle (no mucosal excision); Ep-epitheloid; ES-endoscopy; EUS-endoscopic ultrasound; FNA-fine needle aspiration; FU-follow up (months); Inc-incidental; (L)-Literature; Loc-localisation-upper/middle/lower third of esophagus; Mix-mixed; MR-mitotic rate (x/x HPF); NED-no evidence of disease; ND-no data; NoRec-norecurrence; Rec-recurrence/metastasis; SD-stable disease; Size-size (cm); Sp-spindle; Surg-surgery; TEE-thoracotomy, esophagectomy, esophagogastrostomy; TKI-tyrosine kinase inhibitor; WL-weight loss. Additional information: i1-liver metastases after 30 months; i2-liver metastases after 4 months; i3-recurrence after 36 months; i4-recurrence after 19 months, therefore TEE, now NED; i5-cerebrovascular incident; i6-liver metastases at surgery; i7-lung metastases; i8-lung metastases. Literature: (1)-Yamada/2011 [1]; (2)-Ozan/2010 [2]; (3)-Kaida/2010 [3]; (4)-Hamada/2010 [4]; (5)-Spinelli/2008 [5]; (6)-Sakai/2008 [6]; (7)-Papaspyros/2008 [7]; (8)-Fang/2007 [8]; (9)-Portale/2007 [9]; (10)-Graham/2007 [10]; (11)-Al-Salam/2006 [11]; (12)-Axel/2005 [12]; (13)-Padula/2005 [13]; (14)-Manu/2005 [14]; (15)-Gouveia/2005 [15]; (16)-Ertem/2004 [16]; (17)-Iijima/2002 [17]; (18)-Jiang/2010 [18]; (19)-Blum/2007 [19]; (20)-Miettinen/2000 [20]. Esophageal GIST patients: Green: case reports from the literature; Blue: case series from the literature; Yellow: patients extracted from Ulmer GIST registry.