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ORIGINAL ARTICLE

Prognostic factors affecting mortality in patients with esophageal GISTs

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Summary

Purpose: *Esophageal gastrointestinal stromal tumors (GISTs) compose a very rare clinical entity, representing 0.7% of all GISTs. Therefore, the clinicopathological factors that affect mortality are currently not adequately examined. We reviewed individual cases of esophageal GISTs found in the literature in order to identify the prognostic factors affecting mortality.*

Methods: *MEDLINE, EMBASE, and the Cochrane Library were systematically searched to identify clinical studies and case reports referring to esophageal GISTs. The clinicopathological features were recorded and evaluated.*

Results: *A total number of 105 patients were found. The median age of patients was 58 years (mean 52.4%). The majority of patients (71.6%) presented with tumor-associated symptoms. Tumors were mostly located at the lower esophagus (72.9%), and the median tumor size was 7 cm. Esophagectomy was the most common surgical approach (54.3%), followed by tumor enucleation (45.7%). The median follow-up period was 34 months; tumor recurrence occurred in 18 cases (18.9%) and 19 died of disease (19.2%). The overall survival rate was 75.8%. We found out that tumor size and high mitotic rate (>10 mitosis per hpf) were significant prognostic factors for survival. Presence of symptoms, ulceration, and tumor necrosis as well as tumor recurrence were also significant prognostic factors (p<0.01).*

Conclusions: *Esophageal GISTs' tumor size and mitotic rate are the most significant factors for survival. For dubious cases, a pre-operative biopsy can auspiciously establish the diagnosis of an esophageal GIST. Regarding surgical treatment, tumor enucleation can be safely and feasibly performed for relatively small, intact tumors, whereas large, aggressive tumors are resected with radical esophagectomy.*

Key words: *GIST, esophagus, prognostic factors, enucleation, esophagectomy*

Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. GIST's annual incidence is estimated at 7 to 20 cases per 1,000,000 [1,2], accounting for 1-3% of all gastrointestinal tumors [3,4] and 5.7% of sarcomas [5]. The most common sites are stomach (60-70%) and small intestine (20-30%), followed by colon-rectum (up to 5%) [6,7]. Esophageal GISTs though, are extremely uncommon, as they represent 0.7% of all GISTs [1,8].

The term 'GIST' was firstly coined by Mazur and Clark in 1983 [9]; until then, esophageal GISTs were falsely diagnosed as leiomyomas, which are the most frequent mesenchymal tumors of the esophagus [10], but their clinical course is totally different. The advents in immunohistochemistry

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allowed the differentiation of GISTs from leiomyomas, leiomyoblastomas and leiomyosarcomas. The distinction between GISTs and leiomyomas is pivotal, as esophageal GISTs tend to pursue an aggressive clinical course, whereas leiomyomas are considered to be benign [11]. Preoperative biopsy or fine-needle aspiration cytology are used routinely today to discern GISTs from leiomyomas with high sensitivity and specificity [12].

Although gastric or intestinal GISTs are quite studied during the past decades, esophageal GISTs have been seldom reported in the literature. Mostly, they have been described in case reports, while only a few case series about esophageal GISTs have been published; thus, there is no standard treatment strategy for esophageal GISTs. In the past, esophageal GISTs were treated according to their size; small lesions were removed with tumor enucleation, whereas esophagectomy was preserved for large-size tumors. However, management of esophageal GISTs should be more individualized, taking into account other factors which evince their malignant potential. In this study, we systematically reviewed individual data from patients operated for esophageal GISTs, aiming to highlight the prognostic factors which affect mortality and should be taken into consideration before choosing the optimal treatment approach.

Methods

A systematic literature review was performed using MEDLINE, EMBASE and the Cochrane Library databases (Search date: 08 April 2018). Phrase searches, adjacent free text terms and medical subject headings were used. The search strategy was: gastrointestinal stromal tumors OR GIST OR GISTs AND esophagus. Inclusion criteria were: patient's age > 18 years old, individual data regarding tumor characteristics, surgical procedure and survival. Cases of esophageal GISTs treated without surgery were excluded from our analysis, as they cannot provide reliable information regarding tumor characteristics. The search resulted in 37 case reports [13-49] reporting 40 patients and 8 case series [50-57] including 65 patients. A total number of 105 esophageal GIST patients were identified.

Data extraction was performed using a standard pro forma. Data were extracted by two reviewers (GB and DS) and checked by a third (EM). Any discrepancy was resolved by a fourth reviewer (TL). Clinicopathologic data, including age, sex, symptoms, location, tumor size, metastasis at presentation, surgical intervention, histologic type, macroscopic tumor features, mitotic index, immunohistochemical staining features, mutational status, neoadjuvant and adjuvant therapy, tumor recurrence or metastasis, and survival data were extracted. Tumors were categorized into very low, low, intermediate, and high-risk groups according to the modified NCNN risk classification [11].

Table 1. Clinicopathological characteristics

Characteristics	*n*	*%*
Age (years)	105	58 median (18-82)
Gender	105	
Male	55	52.4
Female	50	47.6
Size (cm)	103	7 median (0.6-30)
Metastases at presentation	105	
Yes	2	1.9
No	103	98.1
Symptomatic	102	
Yes	73	71.6
No	29	28.4
Location	85	
Upper	1	1.2
Middle	22	25.9
Lower	62	72.9
Cellular pattern	79	
Spindle	64	81.0
Epitheliod	9	11.4
Mixed	6	7.6
Ulceration	59	
Yes	19	32.2
No	40	67.8
NCNN risk stratification	101	
Very low	5	4.9
Low	21	20.8
Intermediate	20	19.8
High	55	54.5
Mitotic count	98	
≤5 per 50 hpf	49	50.0
5 – 10 per hpf	11	11.2
>10 per hpf	38	38.8
Necrosis	54	
Yes	18	33.3
No	40	66.7
Neoadjuvant therapy	105	
Yes	8	7.6
No	97	92.4
Operation	105	
Enucleation	48	45.7
Esophagectomy	57	54.3
Adjuvant	105	
Chemotherapy	23	21.9
Radio-chemotherapy	1	0.9
No	81	77.6
Follow-up (months)	85	34 median (1-202)
Reccurence	95	
Yes	18	18.9
No	77	81.1
Disease-free survival (months)	75	29 median (1-202)
GIST-specific deaths	99	19 patients, 19.2
Overall survival rate	99	75 patients, 75.8

Table 2. Comparison of pre- and post-operative immunohistochemistry results

Authors	*CD 34*		*CD117*		*SMA*		*S100*	
	pre-OP	*post-OP*	*pre-OP*	*post-OP*	*pre-OP*	*post-OP*	*pre-OP*	*post-OP*
Blum et al 2007 #1	NR	+	+	+	NR	NR	NR	NR
Blum et al 2007 #2	NR	+	+	+	NR	NR	NR	NR
Blum et al 2007 #3	NR	+	+	+	NR	NR	NR	NR
Blum et al 2007 #4	NR	+	+	+	NR	NR	NR	NR
Takeno et al 2014	+	+	+	+	-	-	-	-
Nakano et al 2015	-	+	-	+	-	-	NR	-
Yanagawa et al 2014	+	-	+	+	NR	NR	NR	NR
Krishnamurthy et al 2013	+	+	+	+	NR	NR	NR	NR
Neofytou et al 2015	+	+	+	+	NR	NR	NR	NR
Feakins et al 2005	+	+	+	+	-	-	-	-
Wang et al 2011	+	+	+	+	NR	NR	+	-
Koyanagi et al 2010 #1	-	NR	-	+	NR	-	+	-
Padula et al 2005	+	+	+	+	-	-	-	-
Papaspyros et al 2008	+	+	NR	+	NR	+	NR	-
Axel et al 2005	+	+	+	+	+	+	-	-
Koide et al 2004	-	+	-	+	-	-	-	-

Statistics

Statistical analyses were performed using the R environment for Statistical Computing. Study variables were assessed for normality using the Shapiro-Wilks test. On normally distributed variables, Student's t-test and x^2 or Fischer's exact test were applied to quantitative and qualitative data, respectively. Non-parametric tests used were Wilcoxon rank-sum test and Kruskal-Wallis test. Survival analysis was performed for disease-specific-survival (DSS), disease-free-survival (DFS) and overall-survival (OS) using Kaplan-Meier curves and their differences were evaluated using the log-rank test. Hazard ratios (HR) were calculated for tumor-related death using the Cox proportional hazards models. The level of statistical significance was set at 0.05.

Table 3. Immunohistochemistry results

Results	*n*	*%*
CD34 (n=95)		
Positive	90	94.7
Negative	5	5.3
CD117 (n=97)		
Positive	97	100,0
Negative	0	0
SMA (n=81)		
Positive	15	18.5
Negative	66	81.5
s100 (n=80)		
Positive	7	8.8
Negative	73	91.2

Results

The clinicopathologic features are summarized in Table 1. There were 55 men (52.4%) and 50 women (47.6%). The median age of patients was 58 years (18-82). The most common tumor site was the lower esophagus (including gastroesophageal junction) (72.9 %), followed by the tumors of the middle esophagus (25.9 %); only 1 patient had tumor in upper esophagus. The tumor size ranged from 0.6 cm to 30 cm (median 7 cm). The majority of patients (71.6%) presented with tumor-associated symptoms, with dysphagia being the most common, followed by chest pain and cough; yet, only 2 patients had metastatic liver lesions already at presentation (1.9%). Tumor size was statistical significantly correlated with symptomatic course; the larger the tumor was, the more likely the presence of symptoms was ($p<0.01$). Results of pre-operative biopsies were reported in 16 cases; although the number of reported cases was remarkably low, a strong concordance between pre-operative and definite immunohistochemistry results was observed (Table 2). This concordance reflected the calculated positive predictive value of CD 34 and CD 117, which was 0.89 (0.52-1.00) and 0.99 (0.72-1.00), respectively.

The primary treatment approach was surgery; only 8 patients (7.6%) received neoadjuvant therapy with imatinib. Esophagectomy was the most common surgical approach, performed in 57 patients (54.3%), while tumor enucleation was performed in 48 patients (45.7%). Postoperatively, adjuvant therapy with imatinib was administered in 23 patients

(21.6%) and in one patient with hepatic, osseous and peritoneal metastases a radio-chemotherapy was implemented. In 18 patients the disease recurred later on (18.9%), and the median disease-free survival was 108 months (1-202). From a total of 99 patients, 75 were reported alive in a median follow up time of 34 months (1-202), whereas 19 patients (19.2%) died of disease.

Macroscopically, tumors were usually intact; ulceration was found in 19 cases and necrotic isles were found in 18 cases. Histopathologically, the most common cellular pattern was spindle, found in 64 cases (81.0%), followed by epithelioid (11.4%), and mixed (7.6%). The mitotic rate in resected tumors was relatively low, as in 49 cases (50.0%) the mitoses found per 50 high-power fields were less than 5. However, in 38 cases (38.8%) more than 10 mitoses per 50 high-power fields were found. Immunohistochemically, the tumors were positive for CD34 and CD117 (94.7% and 100%, respectively) and mostly negative for smooth muscle actin and S100 (18.8% and 8.8% positivity, respectively) (Table 3). Combining the above findings we were able to calculate the risk for each patient according to NCCN risk stratification criteria. From a total of 101 patients, 55 (54.5%) had high risk tumors, 20 (19.8%) had intermediate risk tumors, 21 (20.8%) had low risk tumors and 5 (4.9%) had very low risk tumors.

Regarding the choice of surgical approach, we correlated the clinicopathological features to surgical approach (Table 4). Patient age and tumor

Table 4. Correlation between clinicopathologic characteristics and surgical intervention

Operation	*Enucleation*	*Esophagectomy*	*p value*
Location			0.50
Upper	1	0	
Median	9	13	
Lower	29	33	
Size (in cm, median)	4.5 (3.625 IQR)	9.2 (6.75 IQR)	<0.01
Ulceration			<0.01
Yes	4 (13%)	15 (52%)	
No	26 (87%)	14 (48%)	
Age (in years, mean)	56.5	58.0	0.55
NCCN risk category			<0.01
Very low	4	1	
Low	18	3	
Intermediate	11	9	
High	14	41	

Table 5. Prognostic factors for overall survival, univariate analysis

Factors	*n*	*Hazard ratio (95% CI)*	*p value*
Age	99	1.04 (1.00-1.09)	0.13
Gender (Male vs Female)	99	1.51 (0.58-3.90)	0.40
Size	99	1.13 (1.04-1.23)	<0.01
Symptomatic vs no symptomatic	96	11.0 (1.46-83.6)	<0.01
Location (lower esophagus vs upper + middle esophagus)	104	3.48 (0.29-26.6)	0.20
Cellular pattern (spindle vs epithelioid)	79	0.53 (0.15-1.90)	0.59
Ulceration vs no ulceration	56	10.9 (1.22-97.2)	<0.01
NCNN risk stratification (high risk vs intermediate + low + very low)	96	15.7 (2.07-119.3)	<0.01
Mitotic rate (>10/hpf vs 5-10/hpf	93	8.42 (1.91-37.2)	<0.01
Mitotic rate (5-10/hpf vs <5/hpf)	93	2.19 (0.20-24.4)	0.25
Necrosis vs no necrosis	57	11.7 (1.43-96.2)	<0.01
Neoadjuvant vs no neoadjuvant	99	NA	0,99
Operation (enucleation vs esophagectomy)	99	0.12 (0.03-0.53)	<0.01
Adjuvant vs no adjuvant	99	0.91 (0.26-3.20)	0.42
Recurrence no recurrence	95	3.70 (1.42-9.61)	<0.01

site didn't affect the choice of surgical approach (p=0.50); nevertheless, the tumor size appeared to have a strong correlation with the surgical approach, as larger tumors were more likely to be treated with esophagectomy (p<0.01). Subsequently, tumors categorized as high risk according to NCCN criteria (which are defined by tumor size and mitotic rate) were mostly treated with radical esophagectomy. Another factor that influenced the choice of surgical approach was tumor ulceration; ulcerative tumors were more likely to be removed with an esophagectomy (p<0.01).

In order to define the prognostic factors for overall mortality we performed a univariate Cox regression analysis (Table 5). Tumor size and the presence of symptoms were found to be prognostic factors for overall mortality (p<0.01), while tumor site did not seem to affect mortality. Ad-

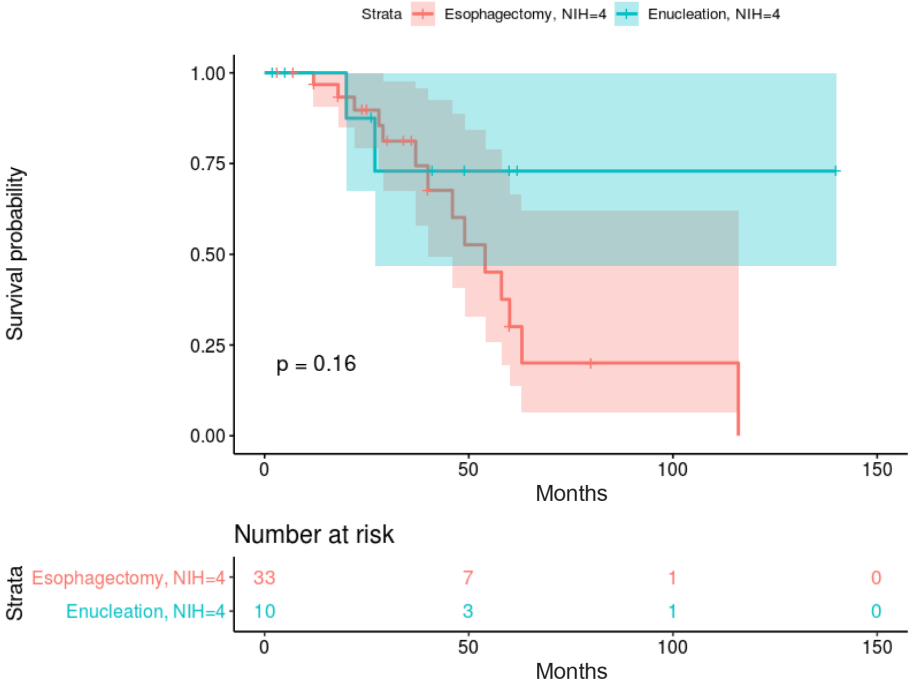

Figure 1. Overall survival of high-risk esophageal GIST patients.

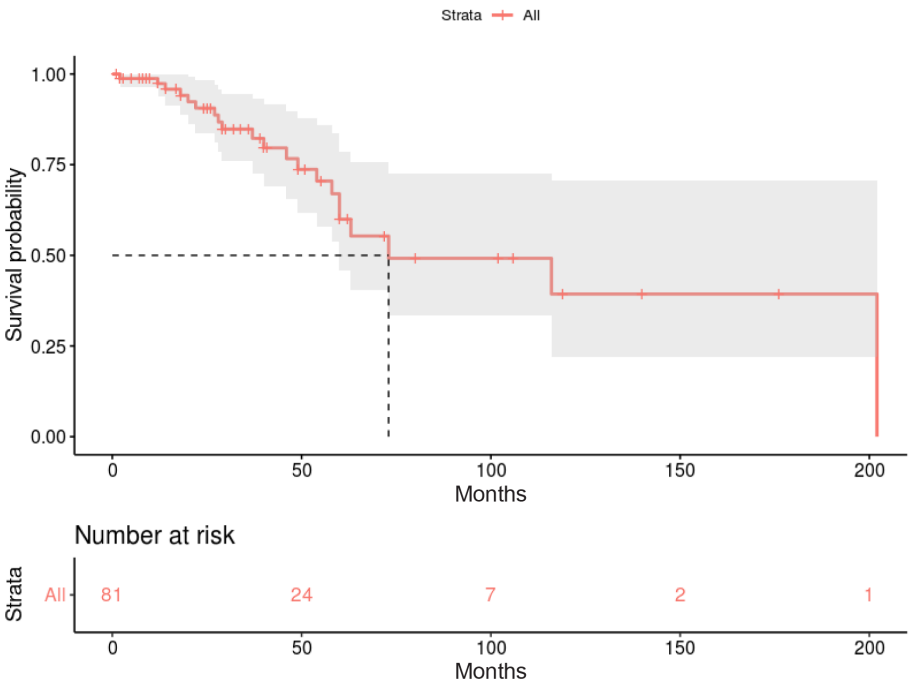

Figure 2. Overall survival of esophageal GIST patients after resection.

ditionally, macroscopic features of the tumor like ulceration and necrosis were significantly correlated with mortality (p<0.01). Higher mitotic rate (>10 mitoses/hpf) was also a prognostic factor and subsequently, patients with high risk tumors according to NCNN risk classification for esophageal GISTs had also worse prognosis (p<0.01). Administration of neoadjuvant or adjuvant therapy did not affect mortality (hazard ratio of neoadjuvant therapy could not be calculated as none of the patients who received neoadjuvant therapy died). However, in the univariate analysis, surgical approach seemed to be statistically correlated with mortality; patients treated with esophagectomy had increased mortality rate compared to patients who underwent tumor enucleation (p<0.01). We assumed however that there would be a selection bias (patients with larger, more aggressive tumors are more likely to be treated with esophagectomy), thus, we ran a Kaplan-Meier survival analysis for the subgroup of patients with high risk tumors (NCCN risk category 'very high'). We observed that there was no significant difference in survival between those who underwent esophagectomy and those who underwent tumor enucleation (Figure 1). Finally, as expected, tumor recurrence was a significant prognostic factor for overall mortality (p<0.01). The Kaplan-Meier survival curve is presented in Figure 2. The 1-, 2-, and 5- year survival rate were 97%, 91% and 60% respectively.

Discussion

GISTs of the esophagus are an extremely rare entity; therefore, the available data from the literature are limited. Many case series are focusing on imaging and pathologic analysis of esophageal GISTs, reporting no treatment strategy or outcome. In this study we evaluated the data from 105 patients operated for esophageal GISTs, focusing on the clinicopathologic factors that might impact prognosis.

Male gender didn't seem to affect survival in patients with esophageal GISTs, unlike esophageal cancer, where male gender is assumed to be a prognostic factor for mortality [58]. Patient's age wasn't a prognostic factor for mortality (HR 1.04, p=0.13). It needs to be mentioned though, that the median age of patients with esophageal GISTs is slightly younger contrary to GISTs in other sites [58,59]; due to the nature of the esophagus, symptoms such as dysphagia and chest pain appear early on the disease course, as even a relatively small GIST of the esophagus can cause symptoms; thus the diagnosis is established earlier. In our study, the presence of symptoms was significantly correlated with larger tumor size (p<0.01), contrary to GISTs in other sites, where even large tumors may not cause any symptoms [60]. As symptomatic course is correlated with larger tumor size, the correlation between presence of symptoms and mortality is easily explainable; larger tumors which are also more aggressive cause symptoms early on the disease course. In fact, the majority of patients in our study (69.8%) presented with symptoms and the most common symptom was dysphagia, followed by chest pain and cough. Interestingly, in a study by Winant et al [54], the symptomatic clinical course was correlated with tumors of the left esophageal wall, without providing an adequate explanation for this finding. As we mentioned above, tumor size in our study was also correlated with higher mortality rate; GISTs' size is undoubtedly a prognostic factor for survival, irrespective of their location [61]. Feng et al also found that tumor size was the only independent risk factor for the prognosis of esophageal GISTs [62].

Tumor site didn't have an impact on survival, nevertheless, we observed that the majority (71.7%) of our cases were tumors of the lower esophagus. The frequency of GISTs of lower esophagus can be partially explained through their pathophysiology. GISTs are considered to arise from the interstitial cells of Cajal. Radenkovic et al showed that Cajal cells were abundant in the lower esophagus, less numerous in the middle esophagus, and rare in the upper esophagus [63].

The first suspicion for an esophageal GIST arises from imaging studies and endoscopy. However, considering their submucosal location and their rarity, these diagnostic tools alone without histological analysis cannot often establish a definite diagnosis. Esophageal GISTs express all the histologic features found in gastric or intestinal GISTs; these are atypical, spindle shaped neoplastic cells which express CD117 (c-kit) and CD34 [11,64,65], whereas smooth muscle Actin (SMA) and Desmin are usually not expressed [66]. These features are notably significant for differential diagnosis between esophageal GISTs and the much more frequent esophageal leiomyomas, as in leiomyomas, desmin and SMA are usually positive, and CD34 and CD117 are negative [50]. An early differential diagnosis between esophageal GISTs and leiomyomas is of high significance; leiomyomas are usually managed conservatively; an operative resection is discussed only when a leiomyoma is too big that causes symptoms affecting patient's quality of life. Therefore, preoperative biopsy should be performed when doubts about the diagnosis are raised. Our analysis showed that preoperative immunohistochemistry analysis of biopsy specimens had

similar results to definite immunohistology, while positive predictive value of CD34 and CD117 was high (0.89 and 0.99, respectively). We need to mention though, that preoperitve immunohistochemistry results were reported only in 16 cases, a sample too small to extract reliable conclusions about its efficiency. Still, conduct of preoperative biopsy of esophageal stromal lesions is a matter of debate. The NCCN guidelines do not suggest preoperative biopsy of a resectable mass [11] due to higher risk of a tumor rupture, which may affect the surgical outcome and induce tumor dissemination, which subsequently may lead to tumor recurrence [67]. In our analysis though, conduct of preoperative biopsy was neither affecting mortality, nor tumor recurrence (p=0.48 and p=0.24, respectively). Generally, a preoperative biopsy is rarely performed if a well-circumscribed, submucosal mass has been detected during endoscopic procedures, as such a lesion mostly represents GISTs. These lesions are usually soft and fragile, and biopsy may cause haemorrhage. When a haemorrhagic or necrotic tissue is acquired, the pathological and immunohistochemical analysis usually provides confusing results [68]. Furthermore, a preoperative biopsy is supposed to lead in intraoperative difficulties, such as adhesions to the mucosa or the muscolaris prorpia. Blum et al (2007) found adhesions in all lesions that were previously biopsied [51]. It is also proposed that the acquired mucosal injury from a biopsy may increase the risk for a postoperative esophageal leak [52]. However, with the advances in immunohistochemistry and more frequent use of the endoscopic ultrasonography (EUS) in diagnostic procedures, the sensitivity and specificity have increased and tumors can be safely and feasibly biopsied. In a recent study by Robb et al in 2015, no intraoperative difficulties or tumor recurrence were reported in patients who were preoperatively biopsied [56]. To conclude, with the use of EUS, preoperative biopsy can be safely performed; it should be reserved though only for cases where a discrimination between GISTs and other esophageal stromal tumors is difficult.

The mitotic index was another prognostic factor for mortality in our study; GISTs with high mitotic rate, regardless of their location, are more likely to be malignant and to lead in distant metastases [61]. Literally, tumor size and mitotic count are considered the more significant prognostic factors for GISTs, hence, the NCCN criteria for risk stratification for esophageal GISTS were based on these two important factors. As a result, it comes with no surprise that the NCCN score is also well correlated with prognosis in our study. To the best of our knowledge, this NCCN risk stratification was previously evaluated in gastric and intestinal GISTs [61], but not in esophageal GISTs so far. Macroscopic endoscopic findings, such as tumor ulceration and necrosis, were also significantly correlated with worse prognosis. Nevertheless, these two tumor features are not included in the NCCN criteria, while their correlation to prognosis is rarely examined. Generally though, GISTs, regardless their site, with ulceration and necrosis are considered malignant and lead in earlier tumor recurrence and worse disease-specific survival [69].

Due to their rarity, there is still a debate about the surgical treatment of esophageal GISTs. In our study, patients treated with esophagectomy had increased mortality rate compared to patients who underwent tumor enucleation (p<0.01). However, this correlation could be falsely positive due to a selection bias; patients with larger, more aggressive tumors are more likely to be treated with esophagectomy, whereas tumor enucleation is mostly preserved for small tumors, without ulceration and necrosis. In the subgroup analysis of patients with high risk tumors (NCCN risk category 'high') this difference did not reach the level of statistical significance (Figure 2), but there was clearly a trend towards increased mortality. An explanation to this phenomenon could be the esophagectomy-associated large morbidity and mortality rate, compared to tumor enucleation, which is a less invasive operation [65]. We could not retrieve much information about the postoperative morbidity, as only a few studies reported about the postoperative course; hence, we could not compare postoperative morbidity.

As surgical treatment appears to have an impact in overall survival, the question about which surgical approach to follow and when is even more crucial. Traditionally, it was recommended that GISTs with size less than 2 cm should not be initially resected, as they are of low risk [11]. Considering GISTs' malignant risk in total, however, Robb et al [56] have proposed that even tumors less than 2cm size, whose preoperative biopsy is positive for GIST, should be evaluated for tumor enucleation. Given the scarce experience with esophageal GISTs, the optimal surgical treatment is still a matter of debate. In order to avoid tumor rupture, Blum et al [51] suggested that a tumor enucleation should be preserved only for small lesions (< 2cm), since, due to poor tumor coherence and a lack of a true capsule, a rupture is more likely to happen in bigger tumors. On the contrary, Lee et al [70] concluded that tumor enucleation is safe and feasible when performed in tumors whose size doesn't exceed 5 cm; literally all of their patients who underwent tumor enucleation had no signs of tumor recurrence. As the experience in man-

agement of esophageal GISTs grows, even bigger tumors are enucleated. The most recent study by Robb et al [56] suggested that all tumors with size under 6.5 cm and no evidence of mucosal ulceration should be treated with tumor enucleation. They stated also that tumor enucleation is safe and feasible, even after preoperative diagnostic biopsy. Although tumors with large size have been reported to be enucleated, we propose that tumors with size over 90 mm and/or high mitotic index should be radically resected with esophagectomy as they are more likely to be malignant and therefore larger surgical margins are needed. The optimal surgical procedure for tumors sized between 65 and 90 mm needs further clarification, and the presence of ulceration should also be taken into account; an ulcerative tumor should be removed with esophagectomy in order to eliminate the risk for tumor dissemination.

The management of metastatic esophageal GISTs is even more dubious, as the acquired experience is extremely low; in our study, only 2 patients had metastatic disease at presentation. However, considering all GISTs independently of its primary location, metastatic GISTs are not rare, occurring in 21-23% of patients [71,72]. Due to the lack of experience in metastatic esophageal GISTs the treatment strategy is not standardized. Huang et al [30] reported a case of esophageal GIST of the lower esophagus with hepatic metastasis in the liver segments VII-VIII. The patient received neoadjuvant chemotherapy with imatinib, with good response, and 3 months later a tumor enucleation with segmental hepatectomy was carried out. Postoperatively, the patient received adjuvant chemotherapy and after 36 months of follow-up, the patient was alive and disease-free. On the other hand, Axel et al [47] reported also a case with esophageal GIST and hepatic metastasis in the segment VIII. This patient did not receive neoadjuvant chemotherapy, but he was primarily operated; an esophagectomy with resection of the liver metastasis was performed. Postoperatively, the patient received adjuvant radio-chemotherapy, yet he died after 1 year because of significant tumor progression. The different strategy followed in these two cases underlines the problem of lack of standardized treatment for esophageal GISTs. Generally, for metastatic GISTs (including gastric and intestinal GISTs), the standard approach is the cytoreductive resection, followed by adjuvant treatment [73]. Treatment outcomes are considered decent, implying that surgical treatment of metastatic GISTs is a potent alternative [73]. Hence, radical surgical treatment of metastatic esophageal GISTs with subsequent adjuvant treatment is clearly proposed.

Apart from surgical treatment, the management of GISTs has been revolutionized with the introduction of imatinib therapy. Imatinib, which can be used as neoadjuvant or adjuvant therapy, has led to a significant increase in the median survival of patients with advanced GIST, from approximately 20 to 60 months [74,75]. In our series the application of neoadjuvant or adjuvant imatinib therapy was not correlated with longer survival ($p>0.1$ and $p>0.5$, respectively) though; yet, patients undergoing neoadjuvant chemotherapy showed satisfying response rates. Shinagare et al [53] reported that both the primary and metastatic GISTs responded to imatinib treatment in the form of reduced tumor size. Choi et al [76] suggested that even a decrease in tumor size of more than 10% or a decrease in tumor density of more than 15% on CT is a good predictor of favorable treatment response. Nevertheless, the use of adjuvant and neoadjuvant chemotherapy in our series was relatively sparse (21.9 and 7.6%, respectively), hence limited conclusions about the use and significance of chemotherapy could be extracted.

Our study presents some limitations. As a retrospective analysis, it lacks systematically collected prospective data. Moreover, the sample size of esophageal GISTs was not large enough, as it is an extremely rare clinical entity with only few studies published and even fewer reporting surgical outcomes. As we mentioned above, reliable conclusions about the efficiency of preoperative biopsy could not be extracted, as the number of studies reporting preoperative immunohistological outcomes was low.

Conclusions

In this study we tried to identify the prognostic factors affecting mortality in patients with esophageal GISTs. We found that tumor size and high mitotic rate are significant prognostic factors for mortality, whereas the presence of ulceration and necrosis also affect mortality. The radical surgical treatment with esophagectomy appeared to have an influence on survival, however, when we analyzed the subgroup of patients with high risk tumors, this correlation did not reach the level of statistical significance. All clinicians should not only be aware of this rare entity but are also encouraged to consistently report such cases in order to enhance available literature towards more solid conclusions.

Conflict of interests

The authors declare no conflict of interests.

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