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Clinicopathological features and treatment outcome of oesophageal gastrointestinal stromal tumour (GIST): A large, retrospective multicenter European study

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ABSTRACT

Background: Oesophageal gastrointestinal stromal tumours (GISTs) account for ≤1% of all GISTs. Consequently, evidence to guide clinical decision-making is limited.
Methods: Clinicopathological features and outcomes in patients with primary oesophageal GIST from seven European countries were collected retrospectively.
Results: Eighty-three patients were identified, and median follow up was 55.0 months. At diagnosis, 59.0% had localized disease, 25.3% locally advanced and 13.3% synchronous metastasis. A biopsy (Fine Needle aspiration n = 29, histological biopsy n = 31) was performed in 60 (72.3%) patients. The mitotic count was low (<5 mitoses/50 High Power Fields (HPF)) in 24 patients and high (≥5 mitoses/50 HPF) in 27 patients. Fifty-one (61.4%) patients underwent surgical or endoscopic resection. The most common reasons to not perform an immediate resection (n = 31) were; unresectable or metastasized GIST, performance status/comorbidity, patient refusal or ongoing neo-adjuvant therapy. The type of resections were enucleation (n = 11), segmental resection (n = 6) and oesophagectomy with gastric conduit reconstruction (n = 33), with median tumour size of 3.3 cm, 4.5 cm and 7.7 cm, respectively. In patients treated with enucleation 18.2% developed recurrent disease. The recurrence rate in patients treated with segmental resection was 16.7% and in patients undergoing oesophagectomy with gastric conduit reconstruction 36.4%. Larger tumours (≥4.0 cm) and high (>5/5hpf) mitotic count were associated with worse disease free survival.

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Conclusion: Based on the current study, enucleation can be recommended for oesophageal GIST smaller than 4 cm, while oesophagectomy should be preserved for larger tumours. Patients with larger tumours (>4 cm) and/or high mitotic count should be treated with adjuvant therapy.

Introduction

Gastrointestinal stromal tumours (GISTs) are rare mesenchymal malignancy often occurring in the stomach and small intestine, affecting 17 patients per million per year [1]. Oesophageal GIST accounts for ≤1% of all GISTs [2]. Consequently, there is limited evidence to guide decisions regarding the diagnosis and management of oesophageal GIST.

In oesophageal GISTs it is unclear how the ideal diagnostic work-up should be conducted. Various imaging methods, such as computed tomography (CT), endoscopic ultrasound (EUS), and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) are used. On any diagnostic modality it is difficult to distinguish oesophageal GIST from leiomyoma, which is the most frequent connective tissue tumour of the oesophagus and resembles GIST [3–6]. Fine-needle aspiration (FNA) could provide definitive diagnosis. Nevertheless, the value of FNA compared to traditional histologic biopsy is debated, because of its inability to show a reliable mitotic count.

In gastric and small bowel GISTs, segmental and wedge resections are performed. In oesophageal GIST, these surgical approaches are not suitable, due to anatomical features of the oesophagus. Options for resection of oesophageal GIST are limited to surgical removal by oesophagectomy or endoscopic intervention by enucleation. While oesophagectomy is an effective treatment, it is a high risk surgical procedure with a complication rate of 17% in oesophagectomy for carcinoma (Clavien Dindo >3b) [7] potentially leading to functional morbidity [8,9]. By performing enucleation the tumour is removed, while the integrity of the oesophagus is preserved [10]. Until now, it is not clear which range of tumour size is suitable for enucleation and how to choose the optimal type of therapy in oesophageal GIST.

Several GIST risk-stratification criteria are used to assess risk of relapse, based on tumour size, mitotic count, location of the primary tumour, and peri-operative tumour rupture [2,11–13]. Risk classification models are mainly based on pathological features of gastric and small bowel GIST. Their use in oesophageal GIST is uncertain. We performed a multicenter, international study involving patients with oesophageal GIST to investigate the clinicopathological features and outcome of (neo) adjuvant, endoscopic and surgical treatments.

Methods

Patients and study design

A retrospective, multicenter study was performed including patients from seven European countries, with histologically proven primary oesophageal GIST, diagnosed between January 2000 and September 2019. Data were collected from the Netherlands (Dutch GIST consortium involving UMC Groningen, Antoni van Leeuwenhoek - Netherlands Cancer Institute, Leiden University Medical Center, Erasmus MC, and Radboud MC), Poland (Maria Sklodowska-Curie National Research Institute of Oncology), Germany (Mannheim University Medical Center), Belgium (Leuven Cancer Institute University Hospitals), England (the Royal Marsden Hospital), Italy (Fondazione IRCSS Istituto Nazionale dei Tumori Milano) and Spain (Virgen del Rocio University Hospital, Seville). The local Medical Ethics Review Committee of LUMC confirmed that the Medical Research Involving Human Subjects Act does not apply for this study (G19.069).

Variables of interest

Data on patient characteristics, clinical presentation, and tumour features (size, location in the oesophagus, mutational status and mitotic count) were collected. Mitotic count was collected as number of mitotic figures per 50 High Power Fields (HPF), semi-equivalent to 5 mm^2. In patients treated with neoadjuvant therapy, the pre-treatment mitotic count was included in the analyses. In other patients, if the mitotic count of biopsy was not available, then the mitotic count of resection specimen was included. Location of the tumour in the oesophagus was categorised into upper oesophagus (20 to <25 cm from incisors), middle oesophagus (25 to <30 cm from incisors) and lower oesophagus (30 to <40 cm from incisors).

Outcomes

Recurrence-free survival (RFS) and disease-free survival (DFS) were primary outcomes. Secondary outcomes were pathological features (and their prognostic impact), surgical complications and the use of systemic treatment.

Statistical analysis

The duration of follow-up was calculated from date of diagnosis to date of last follow up or death. The Kaplan Meier method was performed to estimate survival and groups were compared by log-rank test. RFS was calculated from date of surgery to date of recurrence or last follow-up. DFS was calculated from date of diagnosis to date of recurrence, progression or death. By using multiple imputation, the missing data of variables with possible prognostic value were completed: 50 iterations were generated, with a model including the following variables; gender, age at diagnosis, presentation of oesophageal GIST, location in the oesophagus, tumour size, mitotic count, mutational status, systemic treatment, local recurrence, distant recurrence, progression of GIST and death.

Potential prognostic variables were analysed with Cox proportional hazards regression. First, potential prognostic factors were analysed using univariate cox regression. Next, factors with a p-value less than 0.2 were included in a multivariable model. Statistical tests were two-sided and a p-value of <0.05 was labelled as significant. IBM SPSS Statistics 25 was used to perform the statistical analysis.

Results

Demographic and clinicopathological characteristics

Eighty-three patients from seven European countries (Germany:

24, Poland: 13, The Netherlands: 13, England: 11, Spain: 10, Italy: 8 and Belgium: 4) were included. The demographic and clinicopathological features are listed in Table 1. The mitotic count was classified in 24 patients as low (<5 mitoses per 50 HPF), and 27 patients had high mitotic count (≥5 mitoses per 50 HPF). In 32 patients, mitotic count was not available. Mutational analysis was available in 43 patients (53.0%), with *KIT* exon 11 in 81.8%, *KIT* exon 13 in 1.2%, *KIT* exon 9 in 1.2%, and non-*KIT*/*PDGFRA* in 7.2%.

Table 1
Clinicopathological characteristics.

Original data set			Multiple imputations
Characteristics	No.	%	%
Number of patients	83		
Gender			***
Male	59	71.1	
Female	24	28.9	
Age at diagnosis mean (SD)	61.8 (11.1)		***
Stage at diagnosis			
localized	49	59.0	60.0
locally advanced	21	25.3	25.8
metastasized	11	13.3	14.2
unknown	2	2.4	
Tumour Size in mm median (range)	60 (8−320)		***
Presentation			
incidentally*	20	24.1	27.3
symptoms	56	67.5	72.7
unknown	7	8.4	
Most prominent symptom			***
dysphagia	32	38.6	
chest pain	7	8.4	
abdominal pain	1	1.2	
cough	7	8.4	
bleeding	2	2.4	
weight loss	4	4.8	
other**	4	4.8	
no symptoms	10	12.0	
not specified	14	16.9	
Localization GIST in oesophagus			
upper oesophagus	3	3.6	14.0
middle oesophagus	28	33.7	38.9
lower oesophagus	33	39.8	47.1
not specified	19	22.9	
Mitotic count			
low (<5/50 HPF)	24	28,9	46.1
high (≥5/50 HPF)	27	32,5	53.9
unknown/unspecified	32	38.6	
Biopsy prior to diagnosis			
yes	60	72.3	78.0
no	14	16.9	22.0
unknown	9	10.8	
Mutation status			
KIT exon 11	36	43.4	50.9
KIT exon 13	1	1.2	17.2
KIT exon 9	1	1.2	15.5
wildtype (*KIT*/*PDGFR*)	6	7.2	16.4
unknown/not performed	39	47.0	
Resection			***
yes	51	37.3	
no	31	61.4	
unknown	1	1.2	
Surgical technique			***
open	38	74.5	
minimal invasive	12	23.5	
unknown	1	2.0	
Systemic therapy			***
yes	58	69.9	
no	23	27.7	
unknown	2	2.4	
Purpose systemic therapy			***
(neo)adjuvant	34	51.5	
palliative	32	48.5	

* Incidentally: oesophageal GIST was found when diagnostic imaging with other indications (e.g. CT scan in setting of chronic pulmonary disease or endoscopy in setting of gastro-oesophageal reflux) was performed. ** Other: vomit, gastro oesophageal reflux, fever, unspecified *** multiple imputation not performed.

Diagnostic workup

A biopsy (FNA or histological biopsy), leading to diagnosis of oesophageal GIST, was performed in 60 (72.3%) patients, using FNA in 29 patients, and histological biopsy (e.g. core biopsy) in the remaining 31 patients. By comparing the results of FNA and resection specimen, using FNA led to detection of 86.2% of oesophageal GISTs and the rate of false negative result was 13.8%. Using histological biopsy, no false negative result was observed. In the remaining 23 patients the diagnosis of oesophageal GIST was established by pathological examination of the resection specimen. An EUS was performed in 42 patients, which was interpreted as possible, probable or definite GIST in 32 patients (76.2%) whereas in 10 patients (23.8%), the result of EUS was false negative.

Resection

In this cohort, resection was performed in 51 patients (61.4%), whereas 31 patients (37.3%) did not undergo resection (Fig. 1). The main reason for declining surgery was metastatic disease or unresectable oesophageal GIST. In all but one patient the type of intervention was documented (Fig. 1). Two main types of intervention were distinguished; endoscopic resection, which consisted of enucleation (n = 11, 20%) and surgical resection (n = 40, 80%). Surgical treatment was subdivided in oesophagectomy with gastric conduit reconstruction (n = 33, 82.5%) and segmental resection without reconstruction (n = 6, 15.0%). In this procedure, a segmental resection is performed with primary closure of oesophageal wall to restore its continuity. Patients treated with enucleation had a median tumour size of 3.3 cm (range 2.2–6.0 cm) and patients undergoing surgical treatment had a median tumour size of 7.0 cm (range 3.9 cm–20.0 cm) (Table 2). An R1 resection margin was observed in 5 (45.5%) patients in the enucleation group, while oesophagectomy had resulted in 3 (7.7%) patients with a R1 or a R2 resection margin. Tumour rupture was observed in 1 patient, who had undergo enucleation, having a tumour size of 6.0 cm, with no signs of recurrence during follow up time of nearly 10 months. Post-surgical complications (Clavien-Dindo grade ≥3b) occurred in four patients (abdominal wound dehiscence, anastomotic leakage and dehiscence of anastomosis, damage of vena azygos) who underwent oesophagectomy.

Outcomes

Total cohort

Median follow-up time was 55.0 months (range 1–198 months). Median overall survival was 148 months (95% CI 92.0–204.0). In total, death occurred in 22 patients (26.5%), with progressive oesophageal GIST as cause of death in 15 patients, non-GIST related causes in 5 patients (gastric cancer, breast cancer and non-malignancy diseases) and unspecified causality of death in 2 patients. Number of patients with any event (local recurrence, distant recurrence, progression of oesophageal GIST or death) observed in our study was 34.

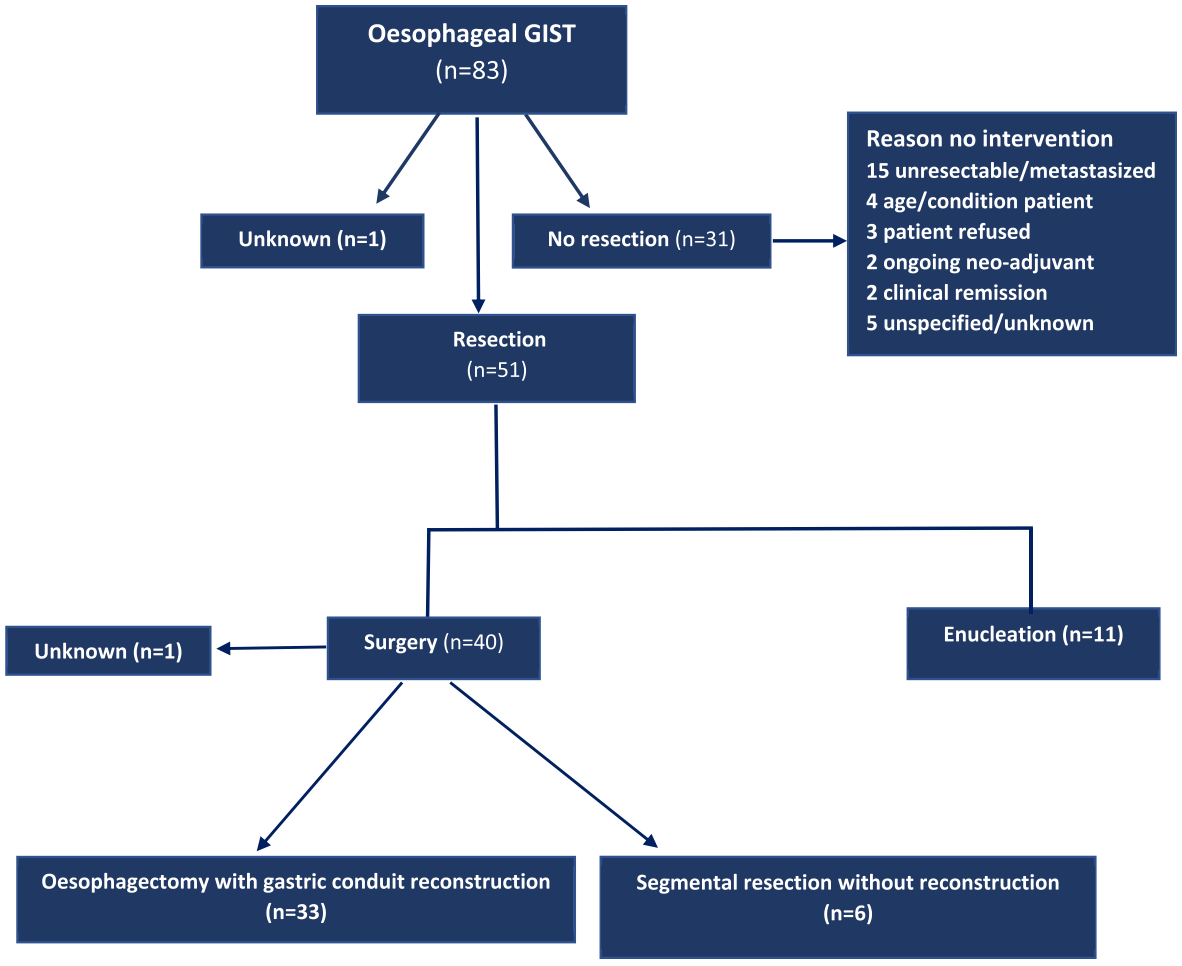

Fig. 1. Flowchart patients with oesophageal GIST.

Table 2
Characteristic patients with endoscopic and surgical resection.

	Endoscopic	Surgical	
	Enucleation (%)	Segmental resection without reconstruction (%)	Oesophagectomy + reconstruction (%)
Number of patients	11	6	33
Age mean (SE)	59.6 (8.6)	64.3 (9.0)	56.6 (9.6)
Tumour Size in mm, Median (range)	33.0 (22–60)	45.0 (8–67)	77.0 (15–200)
Location oesophagus			
upper oesophagus	1 (9.1)	0 (0.0)	1 (3.0)
middle oesophagus	4 (36.4)	5 (8.3)	6 (18.2)
lower oesophagus	2 (18.2)	1 (16.7)	22 (66.7)
not specified	4 (36.4)	0 (0.0)	4 (12.1)
Mitotic count			
low (<5/50 HPF)	4 (36.4)	3 (50.0)	7 (21.2)
high (≥5/50 HPF)	4 (36.4)	2 (33.3)	14 (42.4)
unknown/not specified	3 (27.3)	1 (16.7)	12 (36.4)
Mutation status			
KIT exon 11	6 (54.5)	2 (33.3)	16 (48.5)
KIT exon 9	1 (9.1)	0 (0)	0 (0)
wildtype (non-*KIT/PDGFR*)	0 (0)	0 (0,0)	5 (15.2)
unknown	4 (36.4)	4 (66.7)	12 (36.4)
Resection margin			
R0	5 (45.5)	5 (83.3)	28 (84.8)
R1	5 (45.5)	0 (0.0)	1 (3.0)
R2	0 (0)	1 (16.7)	1 (3.0)
unknown	1 (9.1)		3 (9.1)
Perioperative tumour rupture			
no	7 (63.6)	3 (50.0)	24 (72.7)
yes	1 (9.1)	0 (0.0)	0 (0)
Unknown	3 (27.3)	3 (50.0)	9 (27.3)
Complications (Clavien-Dindo ≥ 3b)			
no	10 (90.9)	4 (66.7)	21 (63.6)
yes	0 (0)	1 (16.7)	3 (9.1)
unknown	1 (9.1)	1 (16.7)	9 (27.3)
Systemic therapy			
no	8 (72.7)	4 (66.7)	7 (21.2)
yes	3 (27.3)	2 (33.3)	26 (78.8)
Purpose systemic therapy			
(neo)adjuvant	3 (100)	2 (66.7)	23 (69.7)
palliative	0 (0)	1 (33.3)	10 (30.3)

No local treatment

Patients who did not undergo resection (n = 31) had a median overall survival of 59.0 months (95% CI 16.6–101.4). Progression of oesophagus GIST was detected in non-surgical treated group in 12 (38.7%) patients.

Patients with local treatment

For patients treated with an endoscopic or surgical resection the median overall survival was not reached, the mean survival time was 143.8 months (95% CI 118.0–169.6). Local and distant recurrence after resection by enucleation was observed in 2 patients (18.2%). Patients who underwent surgery showed a median DFS of 93.0 months (95% CI 30.7–155.3), and in patients treated with enucleation, the median was not reached. The local and distant recurrence rate in patients undergoing oesophagectomy with gastric conduit reconstruction was 6.1% (n = 2) and 30.3% (n = 10), respectively. The metastases were located in the liver (n = 2), peritoneum (n = 4), mediastinum (n = 1), and liver and peritoneum simultaneously (n = 3). In patients treated with segmental resection without reconstruction (n = 6) no local recurrence was observed while 1 (16.7%) patient had distant recurrence in the liver. The overall median disease-free survival (DFS) after endoscopic or surgical intervention was 170 months (95% CI 58.4–284.5).

Systemic therapy

Overall, 58 of 83 patients (69.9%) were treated with systemic therapy (Table 1). The majority (96.4%) received imatinib. Detailed data whether patients received both neoadjuvant and adjuvant therapy was not consistently available. The purpose of systemic treatment was in 51.5% (neo)adjuvant and in 48.5% palliative. The duration of treatment with neoadjuvant imatinib was available in 15 patients, having a median duration of 11.0 months. A recurrence rate of 20.6% was observed among patients treated with (neo) adjuvant imatinib. In patients who received adjuvant imatinib therapy only (n = 9), 44.4% developed a recurrence during follow-up. Seven of these patients had a high mitotic count with a median tumour size of 7.0 cm (range 3.3–32.0 cm) and a median duration of 28.1 months of adjuvant therapy.

Prognostic factors for disease-free survival

When exploring the relationship between tumour size and DFS with the Kaplan Meier, different cut-off points were evaluated. It was demonstrated that tumours from 4 cm and larger had a significant shorter DFS (84 months (95% CI 37.2–130. 8)) compared to tumours with a size below 4 cm (not reached (p = 0.03)) (Fig. 2A). As illustrated in Fig. 2B, patients with a high mitotic count had a median DFS of 31.0 months (95% CI 0.0–85.3), while the median DFS in patients with low mitotic count was not reached (p = 0.01). Studying patients with large tumours (≥4 cm) (Table 3 and Fig. 2C)

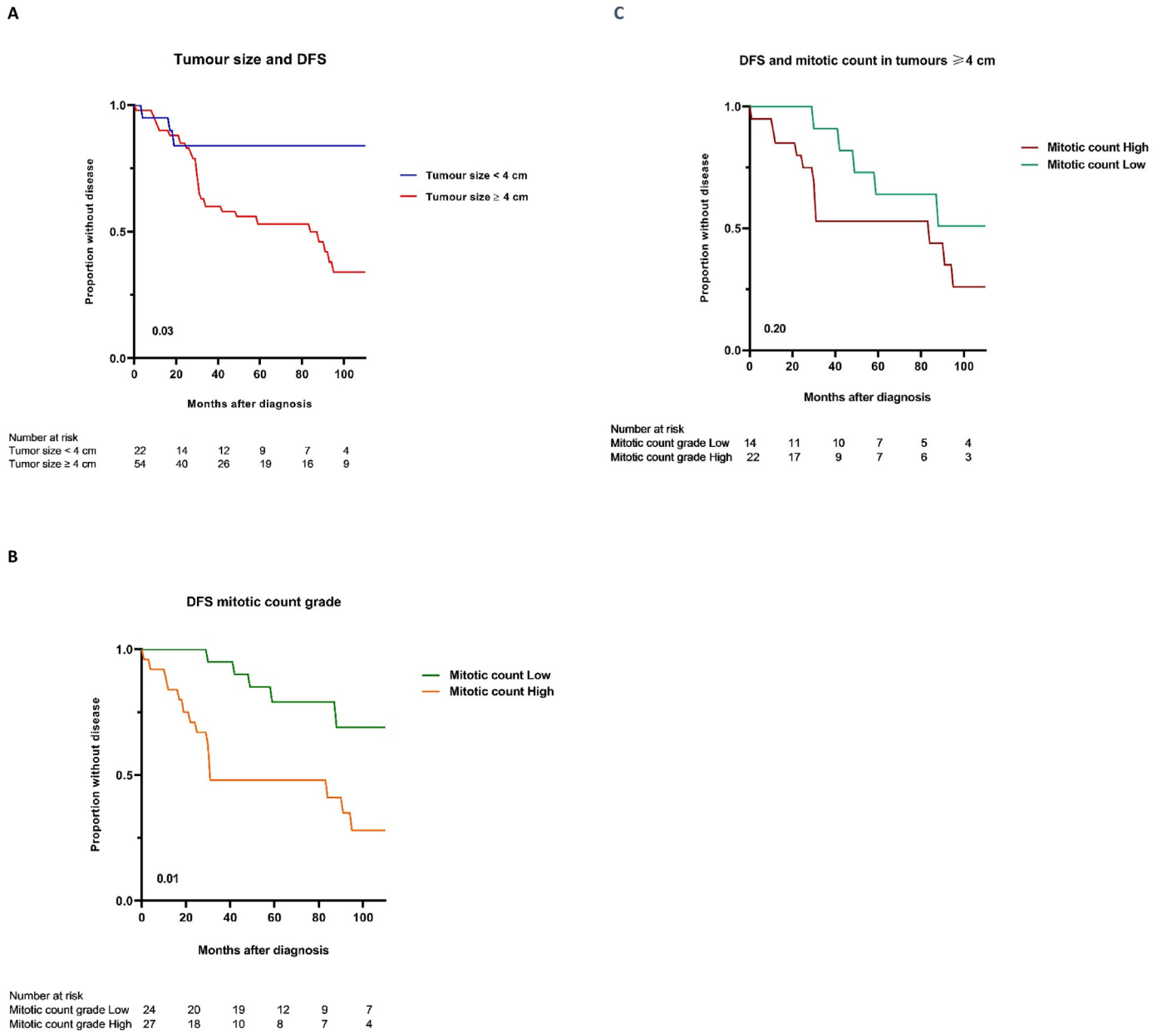

Fig. 2. A: DFS for tumour size < 4 cm vs ≥ 4 cm.B: DFS for low mitotic count vs high mitotic count C: DFS for low mitotic count vs high mitotic count in patients with large tumours (≥4 cm).

revealed no significant difference in DFS between low mitotic count and high mitotic count. DFS of 84 months (95% CI 30.8−137.2) was found in patients with high mitotic count, while median DFS was not reached in group with low mitotic count ($p = 0.20$). But, given the small sample size, it is necessary to be cautious in drawing conclusions. Regarding the radicality of the resection margin, there were no differences in DFS between subgroups.

After multiple imputation of missing data (Table 1), we evaluated prognostic factors for DFS. An association with shorter DFS was observed in older patients, GIST in upper and middle part of the oesophagus, increasing tumour size, higher mitotic count and systemic treatment. When these variables were entered in multivariate cox regression analysis, using p-value below 0.05, no significant prognostic factors were found (Table 4). Despite just not significant, a trend of shorter DFS in GIST located in upper (and middle) oesophagus was observed.

Discussion

The current study explores the clinicopathological features, outcome of resection and potential prognostic factors of oesophageal GIST. Compared to patients with gastric or small bowel GIST [1], patients with oesophageal GIST are younger (average age of 61.8 years at diagnosis), and predominance of males is more evident (male: 71.1%). Regarding the diagnostic approach of oesophageal GIST, imaging methods appear to struggle to distinguish oesophageal GIST from leiomyoma. In this study, EUS showed false negative results in 23.8%. In addition, FNA can provide definitive diagnosis, however an accurate assessment of mitotic count is not possible and a false negative rate of 13.8% was observed. Therefore the use of histologic biopsy is advised, at least when (neo) adjuvant treatment is warranted. Smaller tumours with a median of 3.3 cm (range 2.2−6.0 cm) were removed by enucleation with a recurrence rate of

Table 3
Characteristics patients with small tumours (<40 mm) and large tumours (≥40 mm).

Characteristics	Tumour size < 40 mm	Tumor size ≥ 40 mm
	No (%)	No (%)
Number of patients*	21	55
Gender		
Male	17 (81.0)	37 (67.3)
Female	4 (19.0)	18 (32.7)
Age at diagnosis mean (SD)	62.9 (11.8)	61.4 (11.3)
Stage at diagnosis		
localized	14 (66.7)	31 (56.4)
locally advanced	5 (23.8)	15 (27.3)
metastasized	1 (4.8)	9 (16.4)
unknown/unspecified	1 (4.8)	0 (0)
Mitotic count		
low (<5/50 hpf)	10 (47.6)	14 (25.5)
high (≥5/50 hpf)	4 (19.1)	22 (40.0)
unknown/unspecified	7 (33.3)	19 (34.5)
Resection		
Yes	10 (47.6)	16 (29.1)
No	11 (52.4)	39 (70.9)

* unknown/not reported n = 7.

18.2%. Patients who underwent oesophagectomy had larger tumours with a median of 7.0 cm (range 3.9–20.0 cm). The recurrence rate (local and distant) in these patients was 30.8%. Patients with a tumour size larger than 4 cm have a significantly worse disease-free survival (DFS) compared with tumours smaller than 4 cm. This suggests that the use of enucleation is a safe method with favourable oncological outcomes in oesophageal GIST with a size of up to 4 cm. Accordingly, previous studies reported a tumour size of 2–5 cm to be suitable for enucleation [5,8,14]. Regarding the surgical margins, nearly all patients (83.3%) with a R1 resection were treated with enucleation. More frequent occurrence of R1 resection after enucleation is not surprising, due to the nature of the procedure. However, despite the failure of achieving clear surgical margins, a lower recurrence rate was observed after enucleation than after oesophagectomy. A possible explanation is the smaller tumours size encompassing a relatively low risk of progression. While type of resection (endoscopic versus surgical) and surgical technique (open versus minimally invasive) were almost invariably known, the surgical approach (transhiatal versus transthoracic)

Table 4
Cox Regression analysis of DFS in patients with resection, after multiple imputation of missing data.

	Univariate analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Gender				
male	1 (ref)			
female	0.72 (0.32–1.61)	0.425		
Age *	1.02 (1.02–1.03)	0.000	1.02 (0.98–1.06)	0.333
Presentation *				
incidentally	1 (ref)			
due to symptoms	0.49 (0.22–1.11)	0.087	0.61 (0.20–1.83)	0.379
Stage at diagnosis*	1.02 (0.99–1.06)	0.184		
local	1 (ref)			
locally advanced	1.48 (0.69–3.24)	0.324	0.61 (0.22–2.46)	0.609
metastasized	1.84 (0.72–4.69)	0.199	0.931 (0.24–3.70)	0.952
Specific location in oesophagus*				
lower oesophagus	1 (ref)			
upper oesophagus	2.97 (0.877–10.01)	0.081	4.78 (0.87–25.67)	0.069
middle oesophagus	1.44 (0.61–3.39)	0.405	2.95 (0.98–8.82)	0.054
Tumour size *	1.01 (1.0–1.02)	0.000	1.01 (1.00–1.02)	0.064
Tumour size categorical *				
< 40 mm	1 (ref)			
≥ 40 mm	3.58 (1.08–11.82)	0.037	1.81 (0.23–14.24)	0.572
Tumour size categorical *				
< 50 mm	1 (ref)			
≥ 50 mm	3.28 (1.25–8.61)	0.016	0.73 (0.07–7.43)	0.793
Type of resection				
Enucleation	1 (ref)			
Oesophagectomy with reconstruction	2.12 (0.48–9.39)	0.324		
Segmental resection without reconstruction	1.44 (0.20–10.25)	0.715		
Tumour rupture				
no	1 (ref)			
yes	1.13 (0.94–1.35)	0.197	1.05 (0.87–1.23)	0.586
Surgical margin				
R0	1 (ref)			
R1	0.414 (0.05–3.2)	0.395		
Mitotic count Grade *				
low	1 (ref)			
high	2.94 (1.06–8.20)	0.039	3.31 (0.86–12.81)	0.083
Mutational status				
exon 11	1 (ref)			
exon 13	0.81 (0.15–4.50)	0.808		
exon 9	1.78 (0.32–10.0)	0.511		
non-PDGFRA/KIT	2.05 (0.37–11.20)	0.406		
Systemic treatment *				
no	1 (ref)			
yes	3.26 (1.14–9.29)	0.027	2.76 (0.49–15.67)	0.248

*only variables with P < 0.2 in univariate cox regression analysis, included in multivariable model.

was not consequently reported. The precise location of GIST in the oesophagus partly determines the type of resection and reconstruction. For the anatomical classification of adenocarcinomas of the oesophagogastric junction, the Siewert-Stein classification is used [15,16]. Development of a similar classification for GIST might be useful, as location of GIST in the oesophagus is an important factor.

In our study, a tumour rupture was reported in one patient, who underwent enucleation, with no signs of recurrence yet. However, with a follow up of nearly 10 months it is too early to draw conclusion about recurrence. Furthermore, we hypothesize that no recurrence has yet developed, because a tumour rupture inside the gastrointestinal tract might be less risky to develop recurrence, than a tumour rupture occurring in the intraperitoneal cavity.

In the current study, the proportion of patients without resection (37.3%) seems larger than expected. The most frequent reason to refrain from surgery was metastatic or unresectable tumour (n = 15). However, a significant number of patients (n = 7) did not undergo resection due to age, patient's condition or patients refusal. It is very plausible that in oesophageal GISTs, risks of a major surgical procedure as oesophagectomy, leads more often to declining of surgery (either by surgeon or by patient) than in gastric GISTs where the surgical treatments have relatively minor risks. Stringent patient selection could also explain low complication rate in the oesophagectomy cohort (4 out of 33 with Clavien Dindo $\geq$3b).

For various reasons, mutational analysis is highly important in GIST and is strongly recommended by clinical practice guidelines [17]. In CD117/DOG1 negative GIST, mutational testing is necessary to confirm the diagnosis. Furthermore, type of mutation has prognostic value and predicts sensitivity to systemic treatment [18,19]. In our cohort, mutational analysis was performed in only 53% of patients. This could be explained by insufficient recognition of importance of mutational analysis and the less experienced technical ability to perform mutation testing in early 2000s. However, the spectrum of mutation is similar to more common GISTs.

Similar to other GISTs, tumour size had a significant negative effect on the DFS in oesophageal GIST, with the difference that the cut-off in oesophageal GIST is 4 cm instead of 5 cm in gastric/small bowel GIST. The same relation was observed in higher mitotic count. Interestingly, an obvious trend was observed when the specific location of GIST in oesophagus was studied. Patients with GIST located in upper and middle oesophagus had a shorter DFS than GIST located in the lower part of oesophagus. In the multivariable analysis this statistical significance was just lost, which might indicates the absence of an overt independent prognostic factor. However, the small sample size and the missing data are important factors that should be considered as possible alternative explanation.

The main limitation of this study is the incomplete data for some of the variables which was managed by multiple imputation of missing data. Furthermore, the retrospective nature of this study makes it difficult to determine the selection criteria for type of resection. Nevertheless, this research is the largest European study of oesophageal GIST including description of detailed data on relevant topics.

In conclusion, this study comprises the largest cohort of oesophageal GIST patients with a detailed description of clinicopathological features, diagnostic modalities and outcomes after treatment. Histologic biopsy is preferred over FNA when (neo) adjuvant treatment is warranted. Enucleation is feasible for tumours smaller than 4.0 cm while oesophagectomy should preserved for larger tumours. Neo-adjuvant and adjuvant treatment is recommended for in patients with tumours $\geq$ 4 cm and/or high mitotic count.

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CRediT authorship contribution statement

Mahmoud Mohammadi: Methodology, Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing, Project administration. **Nikki S. IJzerman:** Formal analysis, Investigation, Writing – original draft. **Peter Hohenberger:** Investigation, Writing – review & editing. **Piotr Rutkowski:** Investigation, Writing – review & editing. **Robin L. Jones:** Investigation, Writing – review & editing. **Javier Martin-Broto:** Investigation, Writing – review & editing. **Alessandro Gronchi:** Investigation, Writing – review & editing. **Patrick Schöffski:** Investigation, Writing – review & editing. **Nikolaos Vassos:** Investigation. **Sheima Farag:** Investigation, Writing – review & editing. **Marco Baia:** Investigation. **Astrid W. Oosten:** Investigation, Writing – review & editing. **Neeltje Steeghs:** Writing – review & editing. **Ingrid M.E. Desar:** Writing – review & editing. **An K.L. Reyners:** Investigation, Writing – review & editing. **J.W. van Sandick:** Conceptualization, Writing – original draft, Writing – review & editing. **Esther Bastiaannet:** Investigation, Formal analysis. **Hans Gelderblom:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Project administration. **Yvonne Schrage:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Verschoor AJ, et al. The incidence, mutational status, risk classification and referral pattern of gastro-intestinal stromal tumours in The Netherlands: a nationwide pathology registry (PALGA) study. Virchows Arch 2018;472(2):221–9.
[2] Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23(2):70–83.
[3] Miettinen M, et al. Esophageal stromal tumors: a clinicopathologic, immunohistochemical, and molecular genetic study of 17 cases and comparison with esophageal leiomyomas and leiomyosarcomas. Am J Surg Pathol 2000;24(2):211–22.
[4] Park JW, et al. Role of F-fluoro-2-deoxyglucose positron emission tomography in gastric GIST: predicting malignant potential pre-operatively. J. Gastric Canc. 2011;11(3):173–9.
[5] Blum MG, et al. Surgical considerations for the management and resection of esophageal gastrointestinal stromal tumors. Ann Thorac Surg 2007;84(5):1717–23.
[6] Stelow EB, et al. Endoscopic ultrasound-guided fine-needle aspiration findings of gastrointestinal leiomyomas and gastrointestinal stromal tumors. Am J Clin Pathol 2003;119(5):703–8.
[7] Low DE, et al. Benchmarking complications associated with esophagectomy. Ann Surg 2019;269(2):291–8.
[8] Lee HJ, et al. Surgical resection of esophageal gastrointestinal stromal tumors. Ann Thorac Surg 2009;87(5):1569–71.
[9] Lott S, et al. Gastrointestinal stromal tumors of the esophagus: evaluation of a pooled case series regarding clinicopathological features and clinical outcome. Am. J. Canc. Res. 2015;5(1):333–43.
[10] Coccolini F, et al. Esophagogastric junction gastrointestinal stromal tumor: resection vs enucleation. World J Gastroenterol 2010;16(35):4374–6.
[11] Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med 2006;130(10):1466–78.
[12] Joensuu H. Risk stratification of patients diagnosed with gastrointestinal

stromal tumor. Hum Pathol 2008;39(10):1411–9.
[13] Joensuu H, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol 2012;13(3):265–74.
[14] Jiang P, et al. Clinical characteristics and surgical treatment of oesophageal gastrointestinal stromal tumours. Eur J Cardio Thorac Surg 2010;38(2):223–7.
[15] Siewert JR, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. Br J Surg 1998;85(11):1457–9.
[16] Siewert JR, Stein HJ, Feith M. Adenocarcinoma of the esophago-gastric junction. Scand J Surg 2006;95(4):260–9.
[17] Casali PG, et al. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:68–78.
[18] Joensuu H, et al. Effect of KIT and PDGFRA mutations on survival in patients with gastrointestinal stromal tumors treated with adjuvant imatinib: an exploratory analysis of a randomized clinical trial. JAMA Oncol. 2017;3(5):602–9.
[19] Corless CL, et al. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. J Clin Oncol 2014;32(15):1563–70.