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Gastrointestinal stromal tumours of the oesophagus: a clinicopathological and molecular analysis of 27 cases

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Gastrointestinal stromal tumours of the oesophagus: a clinicopathological and molecular analysis of 27 cases

Aims: Gastrointestinal stromal tumours (GISTs) may arise anywhere in the gastrointestinal tract, but are rare in the oesophagus. We describe the clinical, pathological and molecular characteristics of 27 primary oesophageal GISTs, the largest series to date.

Methods and results: DNA was extracted and exons 9, 11, 13 and 17 of *KIT*, exons 12, 14 and 18 of *PDGFRA* and exon 15 of *BRAF* were amplified and sequenced. Oesophageal GISTs occurred in 14 men and 13 women aged between 22 and 80 years (mean: 56 years). All 27 cases were immunohistochemically positive for KIT, and 92 and 47% co-expressed CD34 or smooth muscle actin, respectively. Fifteen (71% of analysed cases) harboured *KIT* exon 11 mutations and one case each had a mutation in *KIT* exon 13 (K642E) or *BRAF* exon 15 (V600E). Long-term follow-up data (median, 96.5 months) were obtained for 20 cases; two patients had metastases at presentation and seven had developed local recurrence and/or metastasis after surgery. A large tumour size (≥ 10 cm), high mitotic rate (> 5/5 mm^2), presence of a deletion mutation in *KIT* exon 11 involving codons 557–558 and a positive microscopic margin were associated with recurrence and metastasis. The *KIT* mutations identified in oesophageal GISTs are similar to those observed in gastric GISTs.

Conclusions: Complete surgical resection with clear margins is recommended, if technically feasible, and genotyping can help to improve diagnosis and further patient management in oesophageal GIST.

Keywords: gastrointestinal stromal tumour, *KIT*, mutation, oesophagus, prognosis

Introduction

Gastrointestinal stromal tumours (GISTs) in the oesophagus are very rare (< 1% of all GISTs).[1,2] Most are detected as intraluminal distal oesophageal masses that cause dysphagia, but externally extending GISTs can manifest as mediastinal tumours. Additional rare examples have been found incidentally during radiological screening or surveillance studies.[2–6]

With the growing availability of targeted therapies for GISTs, precise diagnosis and appropriate risk assessment are imperative for optimal postoperative

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management. All mesenchymal tumours with spindle or epithelioid cells in the oesophagus (i.e. leiomyoma, schwannoma) are considered in the differential diagnosis of GISTs, and an immunohistochemical panel [including KIT (CD117), DOG1, CD34, smooth muscle actin (SMA), desmin and S100 protein] is useful for distinguishing GISTs from other tumours.[7,8] Local recurrence of GISTs can occur several years after the initial resection, and most are regarded as having at least some potential for distant metastasis.[1,9] The most useful prognostic factors are tumour size, mitotic counts per 50 high-power fields (5 mm^2) and anatomical location. For GISTs in the oesophagus and extra-visceral locations (including the omentum, mesentery, pelvis and retroperitoneum), risk stratification criteria for the jejunum/ileum are currently applied.[10,11]

Reporting of oesophageal GISTs has been limited to individual case reports and case series comprising small numbers, and patient demographics and their molecular characteristics are largely unknown.[2–6,12–14] The present study aims to analyse the clinicopathological features, *KIT*/*PDGFRA* mutation status and long-term follow-up results for 27 patients with a primary oesophageal GIST and to examine parameters that may predict prognosis.

Materials and methods

Mesenchymal tumours involving the oesophagus, coded as 'leiomyoma', 'leiomyosarcoma', 'smooth muscle tumour' and 'stromal tumour', were retrieved from the pathology files of Samsung Medical Center in Seoul, Korea and Oregon Health and Science University Hospital in Portland, OR, USA. For the period from October 1996 to December 2015, we identified 16 GISTs based on their overall likeness to previously characterized stromal tumours of the stomach/small intestine and on their KIT expression.[15] An additional six tumours were collected retrospectively from three hospitals in Korea, and five cases were identified from the consultation files of one of the authors (C.L.C.). This study was approved by the institutional review boards of the participating institutions.

The location of the epicentre or predominant mass of the tumour was used to determine whether the neoplasm was oesophageal or gastric in origin.[11] For tumours growing into the mediastinum, a connection to the oesophageal wall was confirmed based on reported radiological and intra-operative findings. Pathological reports and tumour slides for each case were re-examined by a pathologist (G.K.), and the following parameters were recorded: tumour size in greatest dimension, cell type (spindle, epithelioid or mixed), mitoses per 5 mm^2, presence of coagulative necrosis (i.e. ghosts of tumour cells identified in the necrosis) and immunohistochemical profile.[16] Cellularity was not included because considerable variation was noted, even within the same tumour, and therefore could not be quantified accurately using conventional histological examination.[17,18] Clinical data (including date of the last follow-up visit, time to recurrence and survival information) were obtained from medical records. Recurrence and metastasis were defined as a biopsy-proven tumour or a lesion deemed suspicious on cross-sectional imaging.[19]

Unstained slides or paraffin blocks were available for mutation analysis for 21 of the 27 cases. Specimens were examined microscopically to identify areas of tumour suitable for testing. Tumours were then macrodissected, and DNA was extracted and purified as described previously.[20,21] Exons 9, 11, 13 and 17 of *KIT*, exons 12, 14 and 18 of *PDGFRA* and exon 15 of *BRAF* were amplified by polymerase chain reaction (PCR), and products were screened for mutations by one of two methods: bidirectional Sanger sequencing or real-time PCR with high-resolution melting curve analysis.[20–22] DNA sequencing was used to confirm any suspected mutations based on the melting curve analysis. Four tumours that were wild-type for *KIT* and *PDGFRA* were screened further for mutations in 21 other genes using next-generation sequencing of a custom AmpliSeq library on an Ion Torrent PGM (Thermo Fisher Scientific, Waltham, MA, USA), as described previously,[23] and were evaluated by immunohistochemistry for succinate dehydrogenase (SDH)B (1:800 dilution, HPA002868, Sigma-Aldrich, St Louis, MO, USA), as described previously.[24]

Results

CLINICAL FINDINGS

The patient demographics are listed in Table 1. These comprised 14 men (52%) and 13 women (48%), whose age at diagnosis ranged from 22 to 80 years (mean: 56 years). Six oesophageal GISTs larger than 7 cm (cases 4, 13, 14, 17, 23 and 27) showed growth into the mediastinum. Sixteen (59%) GISTs were located in the lower third of the oesophagus. In all patients, we failed to find any relationship with syndromic GIST such as Carney triad, Carney–Stratakis syndrome, familial GIST syndrome or neurofibromatosis type 1.

Table 1. Demographics of 27 patients with esophageal gastrointestinal stromal tumour

Case no.	Age (years)	Gender	Level of location	Initial treatment
1	60	M	NA	Enucleation
2	59	M	Lower	Partial oesophagectomy
3	59	F	Lower	Enucleation
4	63	F	Mid	Partial oesophagectomy
5	61	F	Lower	Enucleation
6	29	F	Lower	Enucleation
7	47	M	Mid	Enucleation
8	59	F	Lower	Enucleation
9	51	F	Lower	Enucleation
10	62	M	Lower	Partial oesophagectomy
11	59	M	NA	Enucleation
12	47	M	Mid	Enucleation
13	77	M	Lower	Partial oesophagectomy
14	70	M	Lower	None (diagnostic biopsy only)
15	47	M	Lower	Partial oesophagectomy
16	65	M	Lower	Partial oesophagectomy
17	51	M	Lower	Enucleation
18	62	F	Lower	Partial oesophagectomy
19	45	F	NA	Enucleation
20	80	F	NA	Imatinib (after biopsy diagnosis)
21	62	F	NA	Partial oesophagectomy
22	52	M	Lower	Oesophagectomy (for adenocarcinoma)
23	58	F	NA	Enucleation
24	66	M	Lower	Enucleation
25	61	M	Lower	Enucleation
26	38	F	NA	Enucleation
27	22	F	NA	Partial oesophagectomy

M, male; F, female; NA, data not available.

PATHOLOGICAL FINDINGS

The pathological characteristics of the 27 primary oesophageal GISTs are shown in Table 2. Tumour size ranged from 0.4 to 15 cm (mean: 5.6 cm), and mitotic activity varied widely from 0 to more than 30/5 mm^2. Of the GISTs with $\leq$ 5 mitoses/5 mm^2, two were $\leq$ 2 cm, eight were > 2 and $\leq$ 5 cm and three were > 5 cm. Of the tumours with > 5 mitoses/5 mm^2, five were > 2 and $\leq$ 5 cm, four were > 5 and $\leq$ 10 cm and one was > 10 cm. All cases had a spindle-cell morphology (Figure 1A). Tumour necrosis was observed in eight cases; these tumours were either 8 cm or larger (cases 4 and 14) or had > 5 mitoses/5 mm^2 (cases 8, 10, 11, 13, 15 and 19). All tumours were positive for KIT expression (Figure 1B). DOG1, CD34, SMA and SDHB expression was observed in 100% (six of six), 92% (12 of 13), 47% (nine of 19) and 100% (five of five) of cases, respectively (Figure 1C,D). Desmin was negative in two cases (cases 3 and 9). Because of the small sample size, an association among geographic region and ethnicity and other clinicopathological factors could not be evaluated.

MOLECULAR FINDINGS

Fifteen (71%) of the 21 GISTs tested harboured a deletion or substitution mutation in *KIT* exon 11, one (5%) had a primary mutation in *KIT* exon 13 (K642E) and five (24%) were wild-type for both *KIT* and *PDGFRA* (Table 3). Ten of the exon 11 deletions involved codons 557 and/or 558. A *BRAF* exon 15 V600E was identified in an incidentally detected *KIT*/*PDGFRA* wild-type GIST (case 22). Among the recurrent patients, case 8 revealed a homozygous deletion mutation in *KIT* exon 11 (reported previously by our group[25]), and case 19 developed a secondary mutation in *KIT* exon 13 (V654A) during imatinib treatment. Among the wild-type GISTs, cases 7 and 21 had no detectable mutation in *SDHA*/*B*/*C*/*D* in a custom next-generation sequencing assay, and all five cases (cases 7, 9, 12, 21 and 22) were SDHB-positive by immunohistochemistry. However, there was no clear correlation between mutation type and histological or immunohistochemical data.

CLINICAL OUTCOME

Two patients had metastases at presentation (cases 14 and 15), and 25 underwent successful surgical resection (either oesophagectomy or enucleation). Follow-up data were available for 20 of the 27 patients (Table 2). None of the patients had received any adjuvant therapy before suffering recurrence or metastasis. One patient (case 20) declined surgery and was instead treated daily with 200 mg imatinib. A total of seven patients, including one (case 24)

Table 2. Pathological features and clinical outcome of 27 patients

Case No.	Size (cm)	Mitoses (/5mm^2)	Tumour necrosis	Resection margin status	Immunohistochemistry					Recurrence/metastasis (months)	Patient outcome (months)
					KIT	DOG1	CD34	SMA	SDHB		
1	1.8	1			Pos	ND	Pos	Neg	ND		ANED (45)
2	5	0		Neg	Pos	ND	Pos	Pos	ND		ANED (131)
3	4	3			Pos	ND	Pos	Pos	ND		ANED (67)
4	9	2	Present	Neg	Pos	ND	ND	Neg	ND		ANED (148)
5	4.5	0			Pos	ND	ND	Neg	ND		ANED (20)
6	4.5	1			Pos	Pos	ND	Pos	ND	NA	NA
7	6.5	1			Pos	ND	ND	ND	Neg		ANED (16)
8	3.5	> 10	Present	Pos (microscopic)	Pos	Pos	Pos	Neg	ND	Local recurrence (27) and pleural mets (110)	AWD (167)
9	4	1			Pos	ND	Pos	Neg	Neg	NA	NA
10	4	> 30	Present	Neg	Pos	Pos	ND	Pos	ND		ANED (143)
11	3.5	6	Present		Pos	ND	ND	Neg	ND		ANED (147)
12	5.5	0			Pos	ND	Neg	Pos	Neg		ANED (25)
13	15	> 20	Present	Neg	Pos	ND	Pos	ND	ND		DOC (1)
14	8	NI	Present		Pos	ND	Pos	Pos	ND	Liver mets (at pesentation)	NA
15	5.2	> 20	Present	Neg	Pos	ND	ND	ND	ND	LN mets (at presentation)	NA
16	3.2	0		Neg	Pos	ND	Pos	Pos	ND	NA	NA
17	7.5	20		Pos (microscopic)	Pos	ND	Pos	ND	ND	Local recurrence (10)	AWD (73)
18	4	5		Neg	Pos	ND	Pos	Neg	ND	NA	NA
19	5.8	> 10	Present		Pos	ND	Pos	Neg	ND	Local recurrence and liver mets (39)	AWD (140)
20	4.5	NI			Pos	ND	Pos	Neg	ND		DOC (76)
21	5	> 10		Neg	Pos	Pos	ND	Pos	Neg		ANED (57)
22	0.4	0		Neg	Pos	ND	ND	ND	Neg	NA	NA
23	12	NA			Pos	Pos	ND	Neg	ND	Abdominal cavity (94)	DOC (228)
24	NA	NA			Pos	Pos	ND	Pos	ND	Local recurrence (85)	AWD (201)
25	5	6			Pos	ND	ND	ND	ND	Local recurrence (20)	ANED (140)
26	4	2			Pos	ND	ND	ND	ND		ANED (117)
27	10	> 30		Neg	Pos	ND	ND	ND	ND	Liver and spine mets (23)	DOD (41)

NA, data not available; NI, not identified; ND, not done; ANED, alive with no evidence of disease; AWD, alive with disease; DOC, died of other cause; DOD, died of disease; SMA, smooth muscle actin; SDHB, succinate dehydrogenase B; Pos, positive; Neg, negative; mets, metastasis.

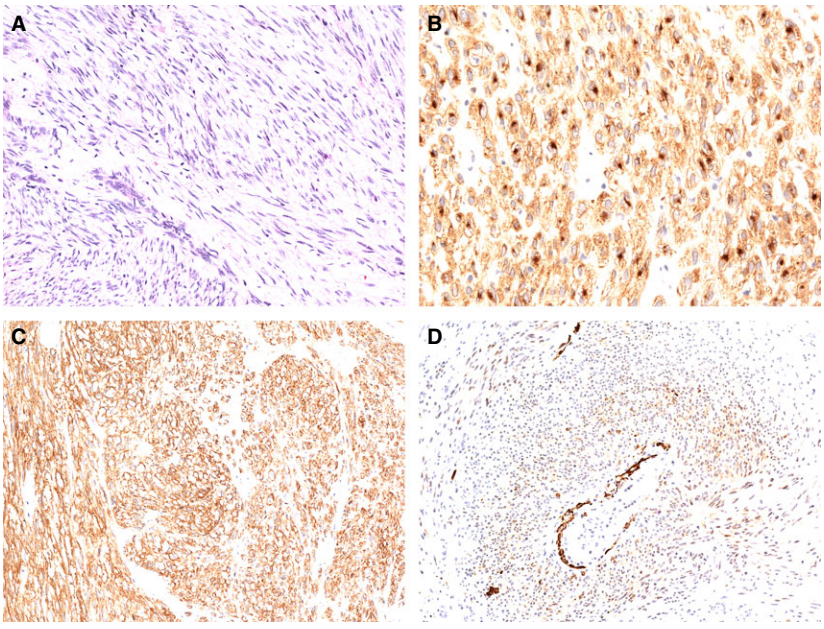

Figure 1. A primary oesophageal gastrointestinal stromal tumour (GIST) mimicking typical gastric GIST with perinuclear vacuoles. The spindle cell GIST contains abundant perinuclear vacuoles and shows nuclear palisading (**A**, haematoxylin and eosin). The tumour showed strong positivity for KIT (**B**), DOG1 (**C**) and smooth muscle actin (**D**).

with unknown tumour size, developed local recurrence and/or metastasis during a median follow-up after 96.5 months (range: 1–228). Six (86%) patients were treated with enucleation, and in two cases (cases 8 and 17) the tumour cells had extended into the inked or cauterized resection margin (Table 2). Two tumours were 10 cm or larger (cases 23 and 27), and the other four (cases 8, 17, 19 and 25) showed high mitotic counts (> 5/5 mm^2). Four cases (cases 8, 17, 19 and 24), as well as one (case 15) with lymph node metastasis at initial diagnosis, had KIT exon 11 deletions affecting codons 557 and/or 558. The mean interval between initial diagnosis and recurrence/metastasis was 42.6 months, with one patient (case 23) having a delay of 94 months. Overall, 12 patients (60%) were alive with no evidence of disease, four (20%) were alive with disease, three (15%) died of other causes (e.g. intracerebral haemorrhage) and one (5%) died of disease progression.

Discussion

To our knowledge, this is the largest series of oesophageal GISTs for which long-term follow-up and mutation analyses are available. Most *KIT* mutations were detected in the juxtamembrane domain of exon 11, and the mutation spectrum of oesophageal GISTs resembled that of gastric GISTs. The most frequent events were deletions in exon 11 and usually involved codons 557 and/or 558. Although the number of cases was too small to evaluate the significance of specific mutations in determining prognosis, five of nine cases with metastatic/recurrent GISTs were available for mutation analysis, and all these tumours demonstrated *KIT* exon 11 deletions affecting codons 557 and/or 558 (Table 3). This is similar to gastric GISTs, in that deletions involving these codons are associated with malignant behaviour.[21,26] Rare mutations in GIST, such as *KIT* K642E and *BRAF* V600E, were also identified in this series.[27–29] Interestingly, we did not identify any *KIT*/*PDGFRA* wild-type GISTs with a SDH deficiency. It has been shown that SDH-deficient GISTs are the most common subtype of *KIT*/*PDGFRA* wild-type GISTs in the stomach, but do not appear to be a factor in the oesophagus.[30]

There are potential pitfalls in the diagnosis of oesophageal mesenchymal tumours. Due to their rarity, diagnosis of a GIST in the oesophagus requires a high degree of scepticism. GIST histology ranges from paucicellular, benign-looking spindle-cell tumours to large sarcomatous tumours with high mitotic activity.[10] Six of our cases were misinterpreted initially as smooth muscle or neurogenic tumours, but were revised to GIST following review by expert pathologists and additional immunostaining for KIT and/or DOG1 during this study or at the time of tumour recurrence. Contributing factors to the misdiagnosis of these cases include failure to perform further immunohistochemistry or molecular testing after a positive finding for a myogenic marker (such as SMA or desmin). In a previous multi-institutional study, smooth muscle differentiation was found to be more

Table 3. Mutation results of 27 oesophageal gastrointestinal stromal tumours

	Mutations		
Case no.	*KIT*	*PDGFRA*	*BRAF*
1	Exon11: p.V559G	Not detected	Not detected
2	Exon 11: p.V559_Y570del	Not detected	Not detected
3	**Exon 11: p.E554_E562del**	Not detected	Not detected
4	**Exon 11: c.1648-5_1672del**	Not detected	Not detected
5	**Exon 11: p.W557_V559del**	Not detected	Not detected
6	Exon 11: p.V555I	Not detected	Not detected
7	Not detected	Not detected	Not detected
8	**Exon 11: p.W557_V559del** (homozygous)	Not detected	Not detected
9	Not detected	Not detected	Not detected
10	Not done	Not done	Not done
11	**Exon 11: p.W557_K558del**	Not detected	Not detected
12	Not detected	Not detected	Not detected
13	**Exon 11: p.W557_K558del**	Not detected	Not detected
14	Not done	Not done	Not done
15	**Exon 11: p.Q556_V559delinsH**	Not detected	Not detected
16	Exon 11: p.V559D	Not detected	Not detected
17	**Exon 11: p.W557_K558del**	Not detected	Not detected
18	*KIT* Exon 13: p.K642E	Not detected	Not detected
19	**Exon 11: p.W557_K558del** (primary), Exon 13: p.V654A (secondary)	Not detected	Not detected
20	Exon 11: positive for deletion/insertion (detected by D-HPLC)	Not detected	Not detected
21	Not detected	Not detected	Not detected
22	Not detected	Not detected	Exon 15: p.V600E
23	Not done	Not done	Not done
24	**Exon 11: p.W557_K558del**	Not detected	Not detected
25	Not done	Not done	Not done
26	Not done	Not done	Not done
27	Not done	Not done	Not done

D-HPLC, denaturing high-pressure liquid chromatography (bold type indicates the mutations involving codons 557 and/or 558).

common in oesophageal GISTs than in GISTs from other sites.[31] We also detected SMA expression in approximately half the tested cases, but were careful not to misconstrue this as evidence for a smooth-muscle tumour. Additional immunostaining for CD34 and DOG1 is important for the differential diagnosis of KIT-weak or SMA-positive tumours.[7] The high frequency of *KIT* exon 11 mutations suggests that molecular testing could be used to confirm diagnosis of a GIST with unusual locations or atypical

morphology and to predict responses for the treatment with targeted drugs such as imatinib.

Recently, pooled analyses from two case series demonstrated that the prognosis of oesophageal GISTs is worse than that of gastric GISTs.[13,14] Although tumour size and mitotic activity provide some indication of the malignant potential of GIST, it is often not possible to predict the clinical course of a given tumour prior to surgery. Local recurrence occurred in two (cases 8 and 25) of our patients with tumour size ≤ 5 cm with high mitotic counts. The optimal surgical approach (oesophagectomy versus enucleation) also remains controversial with regard to tumour size.[3–5] From a technical viewpoint, treating GIST with enucleation may reduce peri-operative morbidity and mortality compared to oesophagectomy, but it also increases the risk of microscopic residual disease and tumour rupture.[32,33] Some authors maintain that negative microscopic margins serve as a reliable prognostic indicator of tumour recurrence, while others suggest that recurrence is due more probably to the biological behaviour of the tumour itself.[32] Although our series contained small numbers of cases, our results suggest that neoadjuvant imatinib treatment can be considered in patients with high mitotic rates and/or larger tumour sizes to obtain negative microscopic margins (R0 resection) and to reduce the risk of intraoperative complications, including tumour rupture.

In summary, oesophageal GISTs occur typically in older adults, with no differences between men and women, and display similar *KIT* mutations to those found in gastric GISTs. GISTs in the oesophagus demonstrate a clinical behaviour spectrum from indolent to aggressive, which might be related to tumour size, mitotic activity and resection margin status. Importantly, these should be distinguished from other mesenchymal tumours to ensure optimal patient management.

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Conflicts of interest

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