

ORIGINAL ARTICLE

The location of KIT and PDGFRA gene mutations in gastrointestinal stromal tumours is site and phenotype associated

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Aims: To assess the relation between KIT and PDGFRA mutations and the site of origin, histological phenotype, and pathomorphologically determined risk assessment in gastrointestinal stromal tumours (GISTs).

Methods: A series of 83 clinicopathologically characterised GISTs from 79 patients was analysed for KIT and PDGFRA mutations by polymerase chain reaction amplification, single strand conformation polymorphism analysis, and direct DNA sequencing.

Results: KIT or PDGFRA mutations were found in 57 and 11 GISTs, respectively. Most KIT mutations involved exon 11 (46 cases), followed by exon 9 (10 cases). The PDGFRA mutations mostly affected exon 18 (eight cases), followed by exon 12 (three cases). There was a significant association between KIT exon 9 mutations and an intestinal origin of GISTs, and between PDGFRA mutations and gastric origin of the tumours. In addition, the presence of PDGFRA mutations was significantly associated with epithelioid/mixed histology, as was the absence of identified receptor tyrosine kinase mutations. Vice versa, KIT exon 11 mutations were almost exclusively found in spindle cell GISTs. Furthermore, the presence of any KIT and PDGFRA mutations and the presence of KIT mutations alone were significantly associated with high risk/malignant GISTs.

Conclusions: The location of KIT and PDGFRA mutations in GISTs is associated with the site of origin and histological phenotype. Genotyping of GISTs may be a helpful additional parameter in determining the biological profile of these tumours.

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal tumours of the gastrointestinal tract, and are thought to be derived from interstitial cells of Cajal or from stem cells with the capacity to differentiate towards interstitial cells of Cajal.^{1,2}

Most GISTs contain activating mutations of KIT (exons 9, 11, 13, and 17)^{3,4} or, less frequently, the PDGFRA gene (exons 12 and 18).^{5–9} KIT and PDGFRA have approximately 35% homology,^{10,11} and belong to the PDGFR subfamily of receptor tyrosine kinases, which are involved in the regulation of cell growth, proliferation, adhesion, migration, differentiation, and apoptosis.^{12,13} The downstream signalling consequences of various KIT and PDGFRA mutations in GISTs are similar, as are the additional cytogenetic changes associated with tumour progression.^{5,14}

“Most gastrointestinal stromal tumours contain activating mutations of KIT or, less frequently, the PDGFRA gene”

The crucial role of KIT or PDGFRA mutations in the development of GISTs is underlined by the finding of germline mutations in families with multiple GISTs,^{15,16} and by a mouse model with constitutive KIT activation, in which multiple tumours and hyperplasia of the interstitial cells of Cajal are found.¹⁷

In our study, we analysed the relation between the location and type of KIT (exon 9, 11, 13, and 17) and PDGFRA (exons 10, 12, 14, 18) mutation in 83 GISTs from 79 patients and the pathomorphological characteristics of the tumours, including the site of origin, histological subtype, and pathomorphological risk assessment based on tumour size and mitotic count.

METHODS

Clinicopathological features

Consecutive tumour samples obtained between 1996 and 2003 were retrieved from the archives of the institute of

pathology, Heidelberg University, Germany. Tables 1 and 2 summarise the clinicopathological data. The diagnosis of GIST was based on previously published criteria.¹⁸ The histological slides from all cases were reviewed (by GM and SA), to confirm the diagnosis and to assess the histological subtype (spindle cell versus epithelioid versus mixed histology GIST) and the mitotic count in 50 high power fields. In each case, CD117 (c-KIT) immunostaining was performed using a polyclonal antiserum (1/500 dilution; A-4052; Dako, Hamburg, Germany) after heat induced epitope retrieval (citrate buffer, pH 6.0) on an automated staining system (Techmate 500+; Dako). CD117 immunostaining was evaluated semiquantitatively as follows: +, all tumour cells strongly positive; (+), all tumour cells weakly positive; –, all tumour cells negative; +>–, positive clearly outnumber negative tumour cells; +/-, positive and negative tumour cells in about equal proportions; –>+, negative clearly outnumber positive tumour cells. Pathomorphological risk assessment of the GISTs was performed according to both Miettinen and colleagues¹⁹ and Fletcher *et al.*¹⁸

Analysis of KIT and PDGFRA mutations

Tumour tissue was microdissected from 8–10 µm serial sections. Extraction of genomic DNA was performed by proteinase K digestion, followed by ethanol precipitation using standard procedures. KIT exons 9, 11, 13, and 17 and PDGFRA exons 10, 12, 14, and 18 were screened for mutations using polymerase chain reaction (PCR) amplification of genomic DNA and subsequent single strand conformation polymorphism analysis, followed by direct sequencing of PCR products displaying aberrant bands. Table 3 provides details of the primers used. PCR

Abbreviations: GIST, gastrointestinal stromal tumour; PCR, polymerase chain reaction

Table 1 Summary of the clinicopathological and genetic data of GISTs with gastric origin

No.	Sex/ Age	Tumour type	Phenotype	CD117	Size (cm)	Mitoses/HPF	Risk assessment		Gene	KIT/PDGFRA mutation
							Mieftinen*	Fletcher*		
1	F/33	P	SP	+	6.5	>10	PM	HR	KIT	Y502_503FinsAY (exon 9)
2	M/64	P	SP	+	16	>10	PM	HR	KIT	K5501_P551_555Vdel (exon 11)
3	F/53	P	SP	+	4	≤5	PB	LR	KIT	Y553_556Qdel (exon 11)
4	M/65	P	SP	+	10.5	≤5	PM	HR	KIT	E554_556Qdel (exon 11)
5	M/65	P	SP	+	3.2	≤5	PB	LR	KIT	Y553_558Kdel (exon 11)
6	F/16	P	EP	+	2.2	>10	PM	HR	KIT	K550_558Kdel (exon 11)
7	F/37	P	SP	+	16	≤5	PM	HR	KIT	Y553_559Vdel (exon 11)
8	M/59	M	SP	+	5	>10	M	M	KIT	E554_559Vdel (exon 11)
9	F/55	P	SP	+	3.5	≤5	PB	LR	KIT	Q556_560Vdel (exon 11)
10	F/53	P	EP	(+)/-	8	≤5	UC	IR	KIT	W557_558Kdel (exon 11)
11	M/53	R	SP	+	4.5	>10	R	R	KIT	W557_558Kdel (exon 11)
12	M/42	P	MIX	+	11	>10	PM	HR	KIT	W557_V559delinsP (exon 11)
12a	M/42	M	MIX	+	1.8	>10	M	M	KIT	W557_V559delinsP (exon 11)
13	M/54	P	SP	+	5	>10	PM	HR	KIT	V559_561Edel (exon 11)
14	F/78	P	SP	+	5	≤5	PB	IR	KIT	W557R (exon 11)
15	F/58	P	MIX	+	5	6-10	PM	HR	KIT	W557R (exon 11)
16	F/71	P	SP	+	5.5	≤5	UC	IR	KIT	W557R (exon 11)
17	F/80	P	SP	+	6.2	6-10	PM	HR	KIT	W557R (exon 11)
18	F/84	P	SP	+	2.3	≤5	PB	LR	KIT	W560D (exon 11)
19	M/50	P	SP	+	6	6-10	PM	HR	KIT	W560D (exon 11)
20	F/63	P	EP	+	5.5	≤5	UC	IR	KIT	L576P (exon 11)
21	F/69	P	SP	+	18	>10	PM	HR	KIT	W557insNP (exon 11)
22	M/64	P	SP	+	7	6-10	PM	HR	KIT	D579_580HinsQTPYD (exon 11)
23	M/74	M	SP	+	8	≤5	M	M	KIT	H580_K581insDPTQPYDH (exon 11)
24	F/60	P	SP	+>-	9	>10	PM	HR	KIT	W582_583EinsEPPNRLSF (exon 11)
25	M/29	P	SP	+>-	4.5	≤5	PB	LR	KIT	W582_583EinsEPPNRLSF (exon 11)
26	M/48	P	SP	+>-	6.5	≤5	UC	IR	KIT	572_573ins PTQLPYDHKWEFPR (exon 11)
27	M/72	P	SP	+	7.7	≤5	UC	IR	KIT	R586_587NinsPYDHKWEFPR (exon 11)
28	M/80	P	EP	+>-	12.5	6-10	PM	HR	KIT	N822K (exon 17)
29	F/76	P	EP	->(+)	2.3	≤5	PB	LR	PDGFRA	V561D (exon 12)
30	M/71	R	EP	+>-	13.5	≤5	R	R	PDGFRA	V561D (exon 12)
31	F/68	P	MIX	+>-	5.5	≤5	UC	IR	PDGFRA	V561D (exon 12)
32	F/59	P	EP	->(+)	5.5	≤5	UC	IR	PDGFRA	D842V (exon 18)
33	M/52	P	EP	->(+)	3.5	≤5	UC	IR	PDGFRA	D842V (exon 18)
34	F/69	P	EP	(+)/-	6	≤5	UC	IR	PDGFRA	D842V (exon 18)
35	F/32	P	EP	+	3.3	>10	PM	HR	PDGFRA	D842V (exon 18)
36	F/72	P	EP	->(+)	3	6-10	PM	IR	PDGFRA	D842V (exon 18)
37	M/62	P	EP	+>-	12.5	≤5	PM	HR	PDGFRA	D842_845Hdel (exon 18)
38	F/52	P	SP	+>-	12	>10	PM	HR	PDGFRA	D842_846Ddel (exon 18)
38a	F/55	R	SP	+>-	11	>10	PM	HR	PDGFRA	R841_843delinsKV (exon 18)
39	M/50	P	EP	+>-	5	≤5	PB	R	PDGFRA	R841_843delinsKV (exon 18)
40	M/58	P	EP	+>-	5	≤5	PB	IR	WT	WT
41	M/57	P	EP	(+)>-	1.7	≤5	PB	VLR	WT	WT
42	F/60	P	EP	+>-	1.2	≤5	PB	WT	WT	WT
43	F/59	P	EP	+	4	≤5	PB	LR	WT	WT
44	M/58	P	EP	->(+)	7.3	≤5	UC	IR	WT	WT
45	F/33	P	EP	+	2.4	≤5	PB	LR	WT	WT

CD117 immunostaining was evaluated semiquantitatively as follows: +, all tumour cells strongly positive; (+), all tumour cells weakly positive; -, all tumour cells negative; +>- , positive clearly outnumber negative tumour cells; +/ -, positive and negative tumour cells in about equal proportions; ->+ , negative clearly outnumber positive tumour cells.

*Mieftinen et al.¹⁹ Fletcher et al.¹⁸
 EP, epithelioid; GIST, gastrointestinal stromal tumour; HPF, high power field; HR, high risk; IR, intermediate risk; LR, low risk; M, metastasis (liver); MIX, mixed; P, primary tumour; PB, probably benign; PM, probably malignant; R, recurrence (locoregional); SP, spindle; UC, uncertain malignant potential; VLR, very low risk; WT, wild type.

reactions were carried out under standard conditions with an annealing temperature of 60°C. Denatured PCR products were electrophoretically analysed on 10% polyacrylamide gels containing 10% glycerol and visualised by silver staining.

PCR fragments with a suspicious migratory pattern were directly sequenced on an ABIPrism 377–18 DNA sequencer (Applied Biosystems, Foster City, California, USA) using the BigDye Termination kit (Applied Biosystems), according to the manufacturer's instructions.

Statistical analysis

Associations between status, location, and type of KIT or PDGFRA mutation and tumour site, histological phenotype, and pathomorphological risk assessment were evaluated using Fisher's exact test for count data. Continuous data were analysed using the Wilcoxon rank test. All tests were two tailed.

RESULTS

Molecular results

Overall, KIT or PDGFRA mutations were detected in 68 of the 79 patients with GIST whereas 11 patients had no detectable mutations (tables 1, 2).

The detected mutations within KIT exon 11 were heterogeneous and consisted of 22 simple deletions, 13 point

mutations, five deletions with amino acid substitutions, five internal tandem duplications, and one insertion with an amino acid change. Most KIT exon 11 mutations (39 of 46) were located at the 5' end, whereas all internal tandem duplications (5–14 amino acids) were clustered in the 3' part. The most common genetic alteration in KIT exon 11 resulted in a W557R substitution (five cases), followed by a deletion of W557_558K and a V560D substitution (four cases each). Codons 557 or 558 were involved in 23 of the 46 KIT exon 11 mutation positive cases.

The 10 cases with KIT exon 9 mutations showed an identical 6 bp insertion, resulting in the tandem duplication of the amino acids Ala502 and Tyr503.

The only KIT exon 17 mutation identified was a N822K substitution based on a c.2466T > A point mutation.

PDGFRA mutations affecting exon 18 consisted of a D842V substitution (five cases), two different simple deletions (delD842_846D and delD842_845H), and a deletion with amino acid substitution (delR841_843InsKV). Furthermore, three tumours harboured a V561D substitution in PDGFRA exon 12.

Association between KIT or PDGFRA mutations and pathomorphological characteristics

Tables 1 and 2 provide the site of origin, the histological phenotype, the pathomorphological risk assessment, and the mutational status of the individual GISTs.

Table 2 Summary of the clinicopathological and genetic data of GISTs with intestinal origin

No.	Sex/Age	Site (origin)	Tumour type	Phenotype	CD117	Size (cm)	Mitoses/HPF	Risk assessment		Gene	KIT/PDGFRA mutation
								Miettinen*	Fletcher*		
46	F/64	DUO	P	SP	+	6	≤5	PM	IR	KIT	Y502_503insAY (exon 9)
47	F/40	DUO	P	MIX	+	14	≤5	PM	HR	KIT	P551_558KdelinsLM (exon 11)
48	M/55	DUO	P	SP	+	5	≤5	PB	IR	KIT	K550_558Kdel (exon 11)
49	M/57	DUO	P	SP	+	4	≤5	PB	LR	KIT	W557_558Kdel (exon 11)
50	M/78	DUO	P	SP	+	5	≤5	PB	IR	KIT	V559_565Gdel (exon 11)
51	M/51	DUO	P	MIX	+	1.5	≤5	PB	VRL	WT	WT
52	M/41	SI	P	MIX	+	6.5	>10	PM	HR	KIT	Y502_503FinsAY (exon 9)
53	F/69	SI	P	MIX	+	10	>10	PM	HR	KIT	Y502_503FinsAY (exon 9)
53a	F/69	L (SI)	M	MIX	+	2.2	>10	M	M	KIT	Y502_503FinsAY (exon 9)
54	M/71	SI	P	SP	+	4	≤5	UCM	LR	KIT	Y502_503FinsAY (exon 9)
55	M/39	SI	P	MIX	+	12	>10	PM	HR	KIT	Y502_503FinsAY (exon 9)
56	M/36	L (SI)	M	SP	+	3	≤5	M	M	KIT	Y502_503FinsAY (exon 9)
57	M/56	L (SI)	M	SP	+>-	21	6–10	M	M	KIT	Y502_503FinsAY (exon 9)
58	F/55	L (SI)	M	SP	+	5.5	>10	M	M	KIT	Y502_503FinsAY (exon 9)
59	F/60	PER (SI)	R	SP	+	11	>10	R	R	KIT	Y570_578Ydel (exon 11)
60	F/78	SI	P	SP	+	6	6–10	PM	HR	KIT	IVS10-2A_1673Adel (exon 11)
61	F/66	SI	P	SP	+	6	>10	PM	HR	KIT	K550_558Kdel (exon 11)
62	F/26	PER (SI)	R	SP	+	19	>10	R	R	KIT	K558_563Idel (exon 11)
63	M/54	SI	P	SP	+	16	>10	PM	HR	KIT	M552I_554Edel (exon 11)
64	M/57	SI	P	MIX	->(+)	7	6–10	PM	HR	KIT	Q556_572Ddel (exon 11)
65	M/65	SI	P	SP	+	8	>10	PM	HR	KIT	I563_576Ldel (exon 11)
66	F/80	SI	P	SP	+	8.5	>10	PM	HR	KIT	D579del (exon 11)
67	M/65	SI	P	SP	-	4	>10	PM	HR	KIT	P551_555Vdel (exon 11)
68	F/63	SI	P	EP	+	10	>10	PM	HR	KIT	P551_555Vdel (exon 11)
69	F/46	SI	P	SP	+	4	>10	PM	HR	KIT	W557R (exon 11)
70	F/53	SI	P	SP	+	5	≤5	UCM	IR	KIT	V560G (exon 11)
71	F/62	SI	P	SP	+>-	10	>10	PM	HR	KIT	V560D (exon 11)
72	M/70	SI	P	SP	+	13	>10	PM	HR	KIT	V560D (exon 11)
73	F/70	SI	P	MIX	+	26	6–10	PM	HR	WT	WT
74	M/58	SI	P	SP	+	1.3	≤5	PB	VLR	WT	WT
75	F/68	PER (SI)	R	SP	-	5.3	>10	R	R	WT	WT
76	F/65	CO	P	SP	+>-	28	>10	PM	HR	KIT	W557F_560Vdel (exon 11)
77	M/60	REC	P	SP	->+	12	>10	PM	HR	KIT	Y502_503insAY (exon 9)
77a	M/60	L (REC)	M	SP	+	2	>10	M	M	KIT	Y502_503FinsAY (exon 9)
78	M/73	REC	P	SP	+	6.5	>10	PM	HR	KIT	W557_558Kdel (exon 11)
79	M/59	PER (REC)	R	SP	+>-	2	>10	R	R	KIT	W557_V559delinsC (exon 11)

CD117 immunostaining was evaluated semiquantitatively as follows: +, all tumour cells strongly positive; (+), all tumour cells weakly positive; -, all tumour cells negative; +>-, positive clearly outnumber negative tumour cells; +/-, positive and negative tumour cells in about equal proportions; ->+, negative clearly outnumber positive tumour cells.

*Miettinen *et al.*,¹⁹ Fletcher *et al.*¹⁸

CO, colon; DUO, duodenum; EP, epithelioid; GIST, gastrointestinal stromal tumour; HPF, high power field; HR, high risk; IR, intermediate risk; L, liver; LR, low risk; M, metastasis; MIX, mixed; P, primary tumour; PB, probably benign; PER, peritoneum; PM, probably malignant; R, locoregional recurrence; REC, rectum; SI, small intestine; SP, spindle; UC, uncertain malignant potential; VLR, very low risk; WT, wild type.

Table 3 Primers used in our study

Primer	Sequence	Length (bp)
KIT 9F	5'-GCC ACA TCC CAA GTG TTT TAT G-3'	310
KIT 9R	5'-GAG CCT AAA CAT CCC CTT AAA TTG-3'	
KIT 11F	5'-CCA GAG TGC TCT AAT GAC TG-3'	223
KIT 11R	5'-AGC CCC TGT TTC ATA CTG AC-3'	
KIT 13F	5'-CTT GAC ATC AGT TTG CCA GTT GT-3'	203
KIT 13R	5'-GAC AGA CAA TAA AAG GCA GCT TG-3'	
KIT 17F	5'-TGG TTT TCT TTT CTC CTC CAA-3'	184
KIT 17R	5'-GCA GGA CTG TCA AGC AGA GA-3'	
PDGFRA 10F	5'-GGC CCT ATA CIT AGG CCC TTT T-3'	251
PDGFRA 10R	5'-TGT CCT GAC TGT TGA GGA ACT-3'	
PDGFRA 12F	5'-CTC TGG TGC ACT GGG ACT TT-3'	233
PDGFRA 12R	5'-GCA AGG GAA AAG GGA GTC TT-3'	
PDGFRA 14F	5'-TCT GAG AAC AGG AAG TTG GTA GC-3'	208
PDGFRA 14R	5'-CCA GTG AAA ATC CTC ACT CCA-3'	
PDGFRA 18F	5'-CTT GCA GGG GTG ATG CTA TT-3'	230
PDGFRA 18R	5'-AGA AGC AAC ACC TGA CTT TAG AGA TTA-3'	

With respect to the primary site, KIT exon 9 mutations were associated with GISTs of intestinal origin ($p = 0.002$; fig 1B, C), whereas PDGFRA mutations were largely confined to tumours of gastric origin ($p = 0.002$; fig 1E, F). Immunohistochemically, tumours with KIT mutations

showed stronger CD117 staining than those with PDGFRA mutations (tables 1, 2; fig 1B, E).

With regard to the histological phenotype, KIT exon 11 mutations were almost exclusively seen in spindle cell GISTs ($p < 0.0001$), and PDGFRA mutations were associated

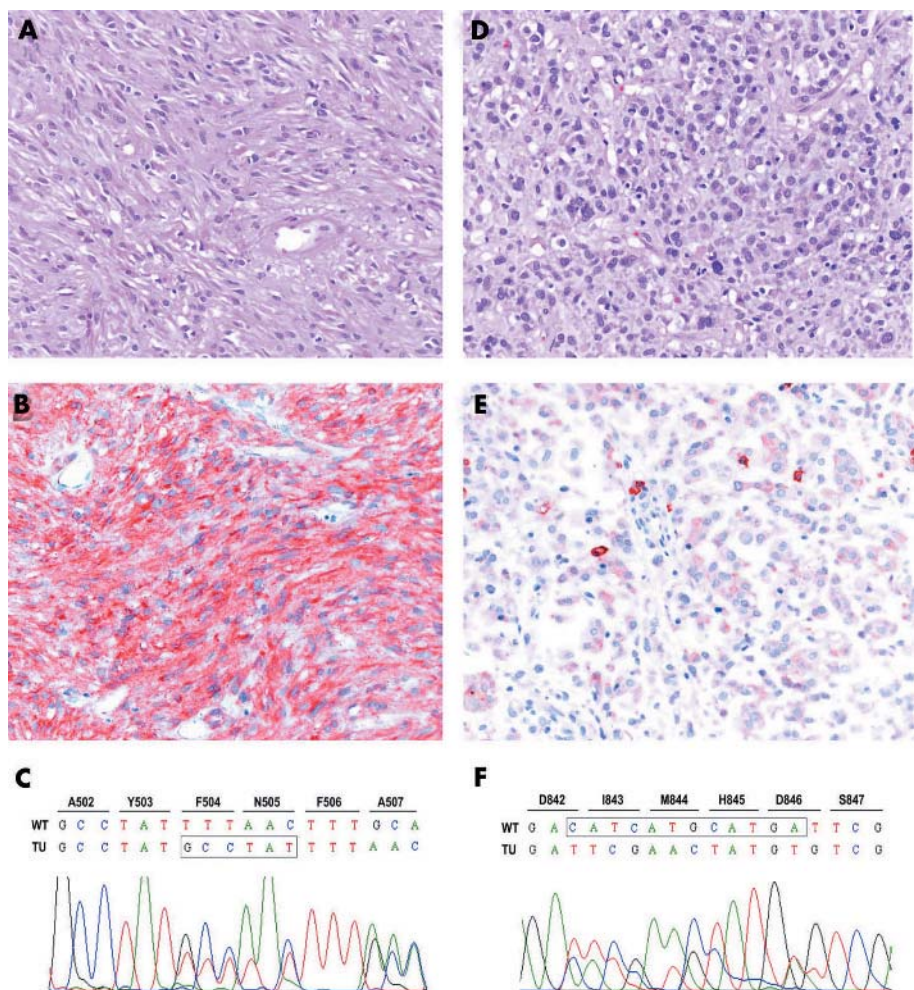


Figure 1 (A–C) Spindle cell gastrointestinal stromal tumour (GIST) of the duodenum (case 46) harbouring internal tandem repeat Y502_503FinsAY (KIT exon 9). (A) Haematoxylin and eosin (H&E) staining; (B) CD117 (KIT) immunostaining; and (C) DNA sequencing. (D–F) Epithelioid GIST of the stomach (case 37) harbouring a D842_846Ddel PDGFRA exon 18 mutation. (D) H&E staining, (E) CD117 (KIT) immunostaining; and (F) DNA sequencing.

with epithelioid/mixed histology GISTs ($p < 0.0002$), as was the absence of detectable KIT or PDGFRA mutations ($p = 0.002$).

Applying the risk categories of the primary tumours according to Miettinen *et al*,¹⁹ the presence of any KIT and PDGFRA mutations and of any KIT mutation was associated with “probably malignant” GISTs ($p = 0.003$ and $p = 0.041$, respectively). Applying the risk assessment of primary tumours according to Fletcher *et al*,¹⁸ “high risk” GISTs were associated with any KIT and PDGFRA mutations ($p < 0.0002$), any KIT mutations ($p = 0.002$), and KIT exon 11 mutations ($p = 0.02$). There was no association between different KIT or PDGFRA mutations and tumour size, patient age, or sex. However, tumours lacking detectable mutations were smaller than those harbouring KIT or PDGFRA mutations (median diameter, 4.0 v 6.1 cm; $p = 0.033$, Wilcoxon rank test).

DISCUSSION

Since the identification of KIT mutations in GISTs by Hirota *et al* in 1998,¹ considerable progress has been made in our understanding of the biological mechanisms of these tumours and in their therapeutic management. Activating mutations of the KIT receptor tyrosine kinase are considered to be a crucial event in the pathogenesis of GISTs and have been identified in up to 92% of these tumours.^{3 4 20} In some of the remaining cases, mutations in the PDGFRA gene leading to constitutive activation of the receptor have been found.⁵⁻⁹

Recently, an association between mutations in KIT exon 9, the second most common mutational site in GISTs, and primary intestinal origin of the tumours has been reported.^{20 21} This finding is confirmed by our data. In addition, we found a significant association between PDGFRA exon 12 and 18 mutations and gastric origin of the tumours, in line with previously published PDGFRA mutated cases.⁸ Furthermore, we detected a significant association between PDGFRA mutations and epithelioid/mixed phenotype. These data fit well with the previously reported absence of KIT mutations in most gastric GISTs with an epithelioid phenotype.^{20 22 23}

Internal tandem duplications of the 3' end of KIT exon 11 have recently been reported to be associated with gastric GISTs of spindle cell phenotype, predominantly arising in elderly women.^{20 24} Our series supports this hypothesis because all five tumours with internal tandem duplications affecting the 3' end of KIT exon 11 originated in the stomach and were of spindle cell phenotype. However, four of these five patients were men.

Initial studies have suggested an association between the occurrence of KIT exon 11 mutations in GISTs and malignancy,²⁵⁻²⁷ whereas others have failed to find such an association.^{3 28} Our data show a significant association between KIT exon 11 mutations and “high risk” GISTs according to Fletcher *et al*.¹⁸

“We found an association between KIT exon 9 mutations and intestinal gastrointestinal stromal tumours, which have previously been shown to have a more aggressive clinical behaviour than gastric tumours”

Recently, deletions/insertions in KIT exon 11,²⁹ KIT exon 11 mutations affecting codons 557 and/or 558,³⁰ and KIT exon 9 mutations^{20 21} have been associated with a worse disease outcome, but these data are controversial because other studies could not corroborate these findings.^{3 28 31} In our series, neither KIT exon 11 mutations specifically affecting codon 557 and/or 558 nor KIT exon 9 mutations showed an association with a pathomorphologically determined high

Take home messages

- KIT and PDGFRA mutations were identified in 68 of 79 patients with gastrointestinal stromal tumours (GISTs) and the location was associated with both the site of origin, the histological phenotype of the tumours, and response to imatinib treatment
- KIT or PDGFRA mutations were associated with pathomorphologically high risk/malignant GISTs
- The type and location of receptor tyrosine kinase mutations in GISTs may be a helpful additional parameter in determining the biological profile of these tumours

risk/malignant phenotype. However, we found an association between KIT exon 9 mutations and intestinal GISTs, which have previously been shown to have a more aggressive clinical behaviour than gastric tumours.³²

Imatinib mesylate—a selective inhibitor of ABL, BCR-ABL, KIT, and PDGFR tyrosine kinases—has a high response rate in patients with advanced GISTs, which are largely radiotherapy and chemotherapy resistant.^{4 7 33 34} Several recent studies have provided evidence that the type and location of KIT or PDGFRA mutations in GISTs predicts the response to imatinib treatment. In two clinical phase II studies comprising a total of 164 patients with GISTs, tumours harbouring a KIT exon 11 mutation had a significantly higher response rate and a longer event free and overall survival compared with those containing a KIT exon 9 mutation or no mutation.^{4 7} Tumours with the PDGFRA exon 18 mutation D842V showed no response to imatinib treatment, whereas patients with GISTs harbouring other PDGFRA mutations achieved partial remission.^{4 7}

In summary, our data show that the location of KIT and PDGFRA mutations, which were identified in more than 68 of the 79 patients examined, is associated with both the site of origin and the histological phenotype of the tumours. Moreover, alterations in the KIT or the PDGFRA gene are associated with pathomorphologically high risk/malignant GISTs. In addition to the previously reported relation between KIT or PDGFRA mutational status and both clinical behaviour and response to imatinib treatment, our data suggest that the type and location of receptor tyrosine kinase mutations in GISTs may be a helpful additional parameter in determining the biological profile of these tumours.

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