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Effect of c-*kit* Mutation on Prognosis of Gastrointestinal Stromal Tumors[1]

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ABSTRACT

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. Gain-of-function mutations in the juxtamembrane domain of the c-*kit* gene have been found in several GISTs. In this study, we examined the correlation between the presence of c-*kit* mutation and prognosis in 124 cases of GIST. DNA samples were extracted from paraffin sections. Exon 11 of the c-*kit* gene encoding the juxtamembrane domain and exon 17 encoding the kinase domain were amplified by PCR and sequenced. Most GISTs (89%) express the KIT protein, and missense mutations of exon 11 were found in 71 of 124 GISTs (57%). No mutations were detectable in exon 17. These 71 mutation-positive GISTs were larger in size and had more frequently invaded adjacent tissues than did the 53 mutation-negative GISTs. Histologically, the mutation-positive GISTs showed higher mitotic figures and more necrosis and hemorrhage. The patients with mutation-positive GISTs showed more frequent recurrences ($P = 0.0005$) and higher mortality ($P = 0.0001$) than did those with mutation-negative GISTs. The c-*kit* mutation was an independent prognostic factor for overall and cause-specific survival of the patients with GISTs. These results suggest that GISTs may be divided into mutation-positive and -negative subtypes. The prognosis was worse in patients with mutation-positive GISTs than in those with mutation-negative GISTs. Thus, mutation of the c-*kit* gene may be a good prognostic marker of GISTs.

INTRODUCTION

GIST[3] is the most common mesenchymal tumor of the human gastrointestinal tract (1). Recently, we found that c-*kit* receptor tyrosine kinase (KIT) is expressed by most GISTs (2). GISTs also express CD34 antigen (3), and their phenotype resembles that of ICCs, which express both KIT and CD34 (2, 4). Moreover, because loss-of-function mutations of the c-*kit* gene result in depletion of ICCs (5–8) and because its gain-of-function mutations are associated with GISTs (2), the GISTs are likely to have originated from ICCs.

The c-*kit* is the cellular homologue of the oncogene v-*kit* of the HZ4 feline sarcoma virus, and KIT is structurally similar to receptors of macrophage colony-stimulating factor and platelet-derived growth factor (9–11). Although the gain-of-function mutations of the c-*kit* gene are observed in both mast cell neoplasms (12–14) and GISTs (2), the location of c-*kit* mutations differs between human mast cell neoplasms and human GISTs. The particular aspartic acid in the tyrosine kinase domain changes to valine in mast cell neoplasms (13, 14), whereas deletion, point mutation, or both in the juxtamembrane domain are observed in GISTs (2).

Most GISTs are sporadic, and the juxtamembrane mutations of the c-*kit* gene have been observed only within the tumors (2). Recently, we found a family with multiple GISTs (15). Family members with multiple GISTs showed a juxtamembrane mutation of the c-*kit* gene not only in tumors but also in peripheral leukocytes. This clearly indicated that the juxtamembrane domain mutation of c-*kit* plays an important role in the induction of human GISTs.

Some GISTs are typical benign tumors, and most of these are found incidentally at the time of endoscopical examination as submucosal tumors (16, 17). In contrast, other GISTs metastasize to the liver and disseminate in the peritoneal cavity (16, 17). Most of the latter type GISTs do not respond to radiotherapy and/or chemotherapy and ultimately kill the hosts (17, 18). Large tumor size, the presence of intratumoral necrosis, and frequent mitotic figures are considered to indicate poor prognosis (17–20). The clinical behavior of GISTs, however, is difficult to predict using conventional prognostic factors. Discrimination of malignant GISTs based on an objectively defined factor would be of practical importance. In this study, we examined whether the presence of mutation in the juxtamembrane domain of the c-*kit* gene is important as a prognostic factor and found it to indicate a significantly poorer prognosis.

MATERIALS AND METHODS

Patients. During the period 1987–1997, 154 patients with primary mesenchymal tumors of the gastrointestinal tract underwent surgery at the First Department of Surgery, Osaka University Graduate School of Medicine, and its affiliated hospitals. Of 154 tumors resected, 13 were diagnosed as neurogenic, 12 were diagnosed as myogenic, and 1 could not be characterized by H&E staining and immunohistochemistry. The remaining 129 tumors were diagnosed as GISTs. One GIST patient dropped out of the study after surgery, and no good samples for DNA sequencing were obtained from four GIST patients. Therefore, a total of 124 patients (73 men and 51 women) were enrolled in this study.

The mean age of the GIST patients at the time of diagnosis was 60 years [median, 60 years; 95% CI, 58–62 years]. The locations of the tumors were as follows: 1 in the esophagus, 95 in the stomach, 20 in the small intestine, and 8 in the large intestine. At the time of diagnosis and during the follow-up period, distant metastasis was examined by routine chest X-ray, ultrasonography, and computed tomography. Distant metastasis was found in three patients (2%) at the time of diagnosis, two to the liver and one to both liver and bone; the remaining 121 patients (98%) were free of distant metastasis. Peritoneal dissemination was found in eight patients at the time of surgery. Thus, curative surgery was performed for 113 patients, and the patients with distant metastasis or peritoneal dissemination underwent only local resection. Thirty-two patients suffered from recurrences, and 13 patients received reoperation for recurrences. Ninety patients were alive on June 30, 1998, and 34 patients died during the follow-up period. The mean follow-up period was 4.1 years (median, 3.3 years). The study was performed under the authors' institutional guidelines, and informed consent for this analysis was obtained from living patients.

Tissue Specimens. Paraffin sections (3 μm thick) of formalin-fixed tissues were used for conventional H&E staining and for immunohistochemistry (2). Rabbit polyclonal antibody against human KIT (K963; IBL, Fujioka, Japan) or against bovine S-100 protein (DAKO, Glostrup, Denmark), and mouse monoclonal antibody against human CD34 (QBend10; Novocastra Laboratories, Newcastle, United Kingdom) or against human desmin (DAKO) were used as the primary antibodies. Biotinylated goat antirabbit IgG (DAKO) or biotinylated rabbit antimouse IgG (DAKO) was used as the secondary antibody. Mesenchymal tumors were identified as myogenic when they were positive for desmin (1), as neurogenic when they were positive for S-100 protein (1), or as GISTs when they were histologically compatible with GIST and positive for KIT and/or CD34 (1, 21).

In each tumor, the following items were determined using H&E sections:

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[3] The abbreviations used are: GIST, gastrointestinal stromal tumor; ICCs, interstitial cells of Cajal; CI, confidence interval; RR, relative risk.

cell shape, mitosis (mean mitotic number per 10 high-power field), cellularity (sparse, moderate, or dense), pleomorphism, tissue necrosis, and hemorrhage (22). All histological specimens were reviewed by one of us (S. H.) without any information about the clinical outcome and DNA sequencing.

DNA Sequencing. DNA was extracted from formalin-fixed, paraffin-embedded tissues using DEXPAT (Takara Shuzo Co., Shiga, Japan). Exons 11 and 17 of the c-*kit* gene were amplified by PCR using the following oligonucleotide primer pairs (23): for exon 11, 5′-GATCTATTTTTCCCTTTCTC-3′/5′-AGCCCCTGTTTCATACTGAC-3′; and for exon 17, 5′-CCTCCAACCTAATAGTGTAT-3′/5′-TCTGGCTAGACCAAAATCAC-3′ and 5′-CATGGTCGGATCACAAAGAT-3′/5′-ATTATGAAAGTCACGGAAAC-3′. The PCR products were dissolved in a loading buffer to denature double-stranded DNA and then electrophoresed (23). Direct sequencing was performed at least two times using different PCR products obtained from the same samples. Mutations were confirmed by at least a second PCR and sequencing. The c-*kit* gene was considered positive for a mutation when repeated sequencing of different PCR products of a sample showed the same sequence. A model 373A DNA sequencer (Applied Biosystems, Foster City, CA) was used. These procedures were performed by one of us (M. T.) without any information about the clinical outcome and pathological examination.

Statistical Methods. Fisher's exact test, χ^2 test, Student's *t* test, and Kaplan-Meier method for postoperative survival with log rank test were used for statistical comparisons. The relative importance of various prognostic factors for the postoperative survival (alive = 0 and death = 1) and recurrence (no recurrence = 0 and recurrence = 1) was analyzed with Cox's proportional hazard model. The end points included any relapse of GISTs for the analysis of disease-free survival and cumulative probability of postoperative recurrence, death from GISTs for the analysis of cause-specific survival, and any death for the analysis of overall survival and cumulative probability of mortality. Logistic regression analysis with the forward stepwise method was used to examine the relationship between the c-*kit* mutation (mutation negative = 0 and positive = 1) and other possible prognostic factors. The possible prognostic factors included age, sex, location of tumors, tumor size, macroscopic invasion to neighboring structures, distant metastasis at the time of diagnosis, peritoneal dissemination at the time of surgery, curability, tumor rupture, cell type, mitotic cell number, cellularity, pleomorphism, presence of necrosis, presence of hemorrhage, and presence of c-*kit* mutation. Assumptions of proportional hazards were tested. Two-sided *P*s of <0.05 were considered to represent statistical significance.

RESULTS

The juxtamembrane domain of KIT is encoded by exon 11, and the tyrosine kinase domain, including the particular aspartic acid at codon 816, is encoded by exon 17 (24). We amplified exons 11 and 17 by PCR and sequenced them. Missense mutations of exon 11 were observed in 71 of 124 GISTs, but no mutations were detectable in exon 17. Of these 71 juxtamembrane domain mutations, 44 cases showed deletion of amino acid(s), 8 cases showed deletion and conversion of amino acids, 14 cases had conversion of amino acid(s), and 5 cases showed miscellaneous types of mutations (Table 1). Both original and recurrent tumors could be examined for five patients. The same c-*kit* abnormalities were observed in both the original and recurrent tumors of three patients; no mutations were observed in both tumors of the remaining two. Abnormalities were most frequently observed at codons 557 and 558, and considerable numbers of mutations were observed in codons 550–556 and 559–562. Although

Table 1 *Mutated codons observed in sporadic GISTs*[a]

Type of Mutation	No. of cases	Codon 550								560										570																		580
Wild type		K	P	M	Y	E	V	Q	W	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
Simple deletion	12	K	P	M	Y	E	V	Q	—	—	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	10	K	P	M	Y	E	V	Q	W	K	—	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	2	—	—	—	—	—	—	—	—	—	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	2	K	P	M	Y	E	V	Q	—	—	—	—	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	2	K	P	M	Y	E	V	Q	—	—	—	—	—	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	2	K	P	M	Y	E	V	Q	W	—	—	—	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	2	K	P	M	Y	E	V	Q	W	K	—	—	—	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	—	—	—	—	—	—	—	—	—	—	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	—	—	M	—	—	—	—	W	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	—	M	Y	E	V	Q	W	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	—	—	—	—	V	Q	W	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	—	—	—	—	—	Q	W	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	P	M	—	—	—	—	W	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	P	M	Y	—	—	—	—	—	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	P	M	Y	E	—	—	—	—	—	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	P	M	Y	E	V	—	—	—	—	—	—	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	P	M	Y	E	V	Q	—	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	P	M	Y	E	V	Q	W	K	V	V	—	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	P	M	Y	E	V	Q	W	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	—	H	K
Deletion and point mutation	1	I	—	—	—	—	—	Q	W	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	—	L	Y	E	V	Q	W	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
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	1	K	P	M	Y	E	V	Q	W	M	—	—	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
Point mutation alone	5	K	P	M	Y	E	V	Q	W	K	V	D	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	2	K	P	M	Y	E	V	Q	G	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	2	K	P	M	Y	E	V	Q	W	K	D	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
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	1	K	P	M	Y	E	V	Q	R	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	P	M	Y	E	V	Q	W	K	A	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	P	M	Y	E	V	Q	W	K	V	V	K	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	P	M	Y	E	V	Q	W	K	V	V	E	E	I	N	G	N	N	D	V	Y	I	Y	P	T	Q	L	P	Y	D	H	K
Miscellaneous	2	K	P	M	Y	E	V	Q	W	NP	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	—	—	—	—	—	I	I	W	K	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	P	M	Y	E	V	—	—	—	—	H	H	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K
	1	K	P	M	Y	E	V	Q	F	P	V	V	E	E	I	N	G	N	N	Y	V	Y	I	D	P	T	Q	L	P	Y	D	H	K

[a] All mutations were located in exon 11 (codons 550–592). The numbers of patients who had the same mutations in exon 11 are shown. —, deleted nucleotides; point mutations are underlined. The miscellaneous types of mutations are boxed.

Table 2 *Clinicopathological features of* c-kit *mutation-negative and -positive GISTs*

c-*kit* mutation	Negative (−)	Positive (+)	*P*
No.	53	71	
KIT expression[a]	47/53 (89%)	63/71 (89%)	1.0000[b]
CD34 expression[a]	45/53 (85%)	63/71 (89%)	0.7203[b]
Age (yr)	58 (54–61)[c]	62 (60–65)[c]	0.0251[d]
Tumor size (cm)	5.2 (4.2–6.2)[c]	8.1 (6.7–9.5)[c]	0.0014[d]
Macroscopic invasion	0	11	0.0024[e]
Cellularity			0.0635[e]
Sparse	2	3	
Moderate	41	41	
Dense	10	27	
Mitosis per high-power field	2.1 (1.2–3.0)[a]	4.8 (2.8–6.8)[a]	0.0452[d]
Necrosis[f]	1	15	0.0020[e]
Hemorrhage[f]	2	12	0.0239[e]

[a] Expression of KIT and CD34 was determined by immunohistochemistry.
[b] χ^2 test.
[c] Numbers in parentheses are 95% CIs.
[d] Student's *t* test.
[e] Fisher's exact test.
[f] The presence of necrosis and hemorrhage was determined histologically.

Table 3 *Correlation between* c-kit *mutation and clinical outcome of GISTs*

c-*kit* mutation	Negative (−)	Positive (+)	*P*
No.	53	71	
Follow-up periods (yr)	4.7 (3.9–5.4)[a]	3.7 (3.0–4.4)[a]	0.0543[b]
Recurrences	6	26	0.0010[c]
Local	3	8	
Liver	3	16	
Peritoneal cavity	1	9	
Distant loci[d]	0	3	
Prognosis			0.0008[c]
Alive	48	42	
Dead	5	29	
By GIST	3	25	
By other causes	2	4	
5-year survival (%)	86 (74–98)[a]	49 (35–63)[a]	0.0001[e]

[a] Numbers in parentheses are 95% CIs.
[b] Student's *t* test.
[c] χ^2 test.
[d] Distant metastatic recurrences include each one of lung alone, bone alone, and lung plus bone.
[e] Kaplan-Meier method with log-rank test.

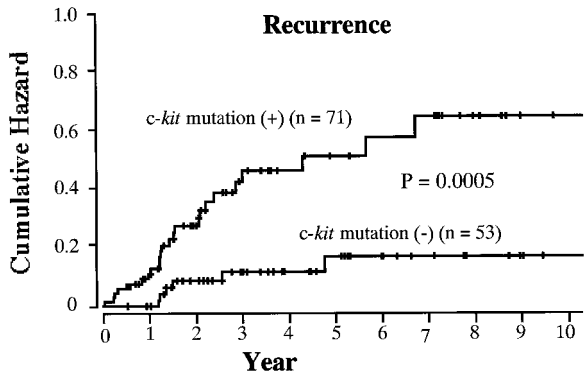

Fig. 1. Kaplan-Meier estimate of cumulative probability of postoperative recurrence. Cumulative probability of postoperative recurrence is shown. The end point includes any relapse of GISTs for the analysis of cumulative probability of postoperative recurrence. The *P* between the patients with the mutation-positive GISTs and the patients with the mutation-negative GISTs was computed by log-rank test.

mutations are rare in other codons, we detected a mutation at codons 568, 572, and 579 (Table 1).

Although 89% of the GISTs expressed KIT, only 57% of the GISTs had the mutation. In other words, a considerable proportion of GISTs expressed KIT but had no mutation. Also, the c-*kit* mutation did not affect the proportion of GISTs with CD34 expression (Table 2).

Next, we examined whether the presence of c-*kit* mutation could be associated with other clinicopathological features of GISTs. More mutation-positive GISTs than mutation-negative GISTs were found in the older patients (Table 2). The mutation-positive GISTs were larger in size and showed more frequent invasion of adjacent tissues. Histologically, the mutation-positive GISTs showed higher mitotic counts and more necrosis and hemorrhage within the tumors. The other factors were not significant. Taken together, the mutation-positive GISTs had more malignant histological features than the mutation-negative GISTs. Multivariable analysis with the forward stepwise logistic regression analysis indicated that the age ($P = 0.0332$, RR = 1.04, 95% CI = 1.02–1.07), tumor size ($P = 0.0171$, RR = 1.11, 95% CI = 1.06–1.21), and tissue necrosis ($P = 0.0232$, RR = 11, 95% CI = 4–92) were independently related to the presence of c-*kit* mutation.

We also examined whether the presence of c-*kit* mutation was associated with the clinical outcome. The mutation-positive GISTs showed more frequent recurrences and resulted in higher mortality than the mutation-negative GISTs during the comparable follow-up periods (Table 3). The patients with mutation-positive GISTs showed worse 5-year survival than did those with the mutation-negative GISTs.

Cumulative hazards of recurrence and mortality were compared between the patients with mutation-positive GISTs and mutation-negative GISTs. Significant differences were detected with a higher recurrence rate observed in the patients with mutation-positive GISTs (Fig. 1). The mortality rate of these patients was higher than that of those with mutation-negative GISTs (Fig. 2). Multivariable analysis with Cox's proportional hazard model and forward stepwise method indicated that distant

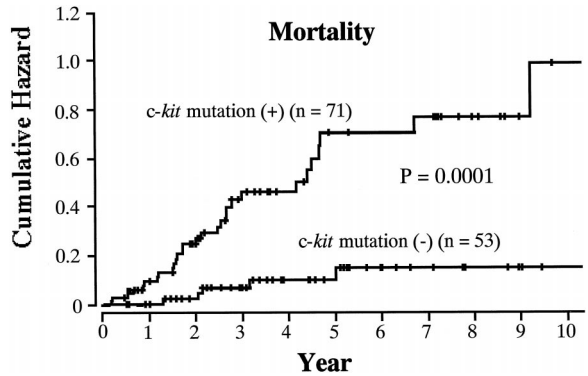

Fig. 2. Kaplan-Meier estimate of cumulative probability of postoperative mortality. Cumulative probability of postoperative death is shown. The end point includes any death for the analysis of cumulative probability of the mortality. The *P* between the patients with the mutation-positive GISTs and the patients with the mutation-negative GISTs was computed by log-rank test.

Table 4 *Independent prognostic factors in GIST patients*[a]

Factors	*P*	RR	95% CI
Overall survival			
Macroscopic invasion	0.0004	4.8	2.0–12
Distant metastasis	0.0012	11	2.6–45
Curability	0.0186	2.7	1.2–6.0
Mitosis per high-power field	0.0001	1.1	1.05–1.14
c-*kit* mutation	0.0266	3.1	1.1–8.6
Cause-specific survival			
Tumor size	0.0161	1.1	1.01–1.20
Distant metastasis	0.0001	72	11–470
Curability	0.0041	3.7	1.5–9.1
Mitosis per high-power field	0.0017	1.1	1.08–1.20
c-*kit* mutation	0.0188	4.6	1.3–16

[a] The relative importance of various prognostic factors for postoperative overall survival was analyzed with Cox's proportional hazard model and stepwise method. Results of the final step are shown. The end points included any death for the analysis of overall survival. Macroscopic invasion (absence = 0 and presence = 1), distant metastasis (absence = 0 and presence = 1), curability (curative surgery = 0 and noncurative surgery = 1), mitosis number per high-power field, and c-*kit* mutation (absence = 0 and presence = 1) were suggested as independent factors for the overall prognosis. Similar to overall survival, the relative importance of various prognostic factors for cause-specific survival was analyzed using the end point of death from GISTs. Tumor size (cm), distant metastasis, curability, mitosis per high-power field, and c-*kit* mutation were suggested as independent factors for the cause-specific survival.

metastasis, surgical curability, mitotic counts, and c-*kit* mutation were independent prognostic factors for overall and cause-specific survival (Table 4). The patients with mutation-positive GISTs showed worse overall and cause-specific prognoses than those with mutation-negative GISTs.

DISCUSSION

Most of the GISTs examined here expressed both KIT and CD34, confirming our previous findings (2). Kindblom *et al.* (4) reported that practically all GISTs could be stained with an anti-KIT antibody. Although 89% of GISTs expressed KIT, only 57% of GISTs showed mutation in the juxtamembrane domain of the c-*kit* gene. The proportion of KIT expression was comparable between mutation-positive and mutation-negative GISTs. This indicates that some KIT-positive GISTs can develop without mutation in the juxtamembrane domain of the c-*kit* gene. GISTs have been associated with neurofibromatosis type 1 (25, 26). There is a possibility that some mutations of the *NF-1* gene may result in development of KIT-positive GISTs from ICCs, which are also KIT-positive (2, 4).

We compared histopathological features between mutation-positive and mutation-negative GISTs and found that the mutation-positive GISTs showed more malignant features. There are at least possible two explanations for this: (*a*) GISTs may be classified into two subtypes, c-*kit* mutation-positive and mutation-negative GISTs, with the former being more malignant; and (*b*) mutation-negative GISTs may acquire more malignant phenotype due to the addition of c-*kit* mutation. However, we have not observed any cases, in which mutation-negative GIST had changed to mutation-positive GIST.

In GISTs, mutations of the c-*kit* gene were observed only in the juxtamembrane domain. This is consistent with our previous results (2). Mutations were observed in 57% of GISTs in our study, and other groups have reported 21 and 42% (27, 28). The difference in mutation rates appears to be due to the proportion of malignant GISTs, as suggested by our data and the previous report (28). Moreover, most mutations were located between codons 550 and 560, as described previously (2, 27, 28). However, some mutations were found at codons 561, 562, 568, 572, and 579. The mutation at codon 579 was confirmed to be a gain-of-function mutation as reported for the mutation of codons 550–560 (2, 29). All of these mutations are likely to be gain-of-function mutations.

Finally, we compared clinical outcome between the mutation-positive and mutation-negative GISTs and found more frequent recurrences and poorer prognosis with mutation-positive GISTs. In fact, 25 of 71 patients with mutation-positive GISTs died from the GISTs, whereas only 3 of 53 patients with mutation-negative GISTs died from the GISTs during comparable follow-up periods. The c-*kit* mutation was an independent prognostic factor for overall and cause-specific survival. Considering these findings, we concluded that the c-*kit* gene should be examined for mutation in exon 11 to predict the prognosis of patients with GISTs.

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