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Impact of the KIT/PDGFRA genotype on prognosis in imatinib-naïve Japanese patients with gastrointestinal stromal tumor

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Abstract

Background: Most gastrointestinal stromal tumors (GIST) harbor a mutation in *KIT* or platelet-derived growth factor receptor alfa (*PDGFRA*). Although genotyping is a useful predictive marker of tyrosine kinase inhibitors, whether it can predict prognosis remains controversial.

Methods: Data on 402 patients with GIST who underwent macroscopically complete surgery and received no neoadjuvant/adjuvant therapy were selected from a prospective GIST database at the three, participating hospitals. The types and locations of *KIT* and *PDGFRA* mutations were analyzed by direct sequencing of the amplified genes. The association between the genotypic characteristics and prognosis was then examined.

Results: Tumor genotypes were analyzed in 398 of 402 (99%) patients, and 120 mutation patterns were identified. *KIT* mutations had broad malignancy potential which differed according to the type of mutation. Deletion and deletion-insertion type mutations were associated with worse RFS while duplication and substitution type mutations were associated with favorable RFS *KIT* deletion/deletion-insertion, including codons 557 and 558, were especially associated with worse RFS on multivariate analysis both of all the patients and those with *KIT* mutations.

Conclusions: Specific GIST genotypes were significantly associated with a risk of recurrence. Genotype analysis may be useful for predicting the prognosis and determining the indications for adjuvant imatinib in patients with GIST.

KEYWORDS

gastrointestinal stromal tumor, genotype, imatinib-naïve, KIT, PDGFRA

1 | INTRODUCTION

The gastrointestinal stromal tumor (GIST) is the commonest form of gastrointestinal tract sarcoma, and *KIT* and platelet-derived growth factor receptor alfa (*PDGFRA)* are its key drivers.[1–3] Although primary surgery and complete resection are indicated for most cases of localized GIST, a relapse occurs in 40%-50% of cases treated with surgery alone.[4–5]

A recent clinical trial demonstrated that 3 years of postoperative adjuvant imatinib therapy improves both the recurrence-free survival (RFS) and overall survival rates in patients with high-risk GIST.[6] The

risk stratification used in the clinical trial was based on the National Institutes of Health (NIH) consensus criteria and tumor rupture. Modified NIH consensus criteria, including primary tumor site, rupture, tumor size, and mitotic count, have been recommended for GIST risk assessment based on the results of a clinical trial of adjuvant imatinib. The advantage of using these modified NIH consensus criteria was validated in a previous, large cohort study,[4] which demonstrated their superiority to the conventional NIH criteria (Fletcher criteria) or the Armed Forces Institute of Pathology (AFIP) criteria for assessing risk.

In most cases of operable GIST, the tumor genotype is not routinely analyzed despite its being a reliable and reproducible marker. Several studies have suggested the prognostic significance of genotype.[7-12] Specifically, a *KIT* exon 11 deletion mutation affecting codons 557 and 558 was first reported in 2003 as a possible cause of malignancy.[7] Subsequently, other studies reported similar results. On the other hand, the *PDGFRA* and wild-type mutations are generally recognized as giving rise to more indolent tumors.[13] Both the favorable and unfavorable genotypes are reportedly associated with recurrence-free survival, but their predictive value for prognosis is not so great as to enable them to replace the conventional risk factors.

The present study examined cases of GIST in Japanese patients treated with surgery alone and investigated the frequency, characteristics, and prognostic significance of the genotypes.

2 | PATIENTS AND METHODS

2.1 | Patients

In total, 428 patients with GIST who underwent macroscopically complete surgery (R0-1) between January 1978 and December 2014 were extracted from the prospective GIST database of Osaka University Hospital, Osaka Police Hospital, and Kanagawa Cancer Center. Patients with a concurrent metastasis or history of neoadjuvant or adjuvant therapy were excluded. If a tumor was judged to have ruptured by the attending surgeon either preoperatively or intraoperatively, the observation was recorded in the operative report irrespective of the degree of rupture. All the tumors were diagnosed as GIST based on morphological features and immunostaining for *KIT*/CD34 and additionally DOG-1 if needed. Our study included 112 patients who underwent surgery before 2000 when the diagnostic criteria for GIST were not fully established. Therefore, the pathological diagnoses of all the tumors resected before 2000 were reviewed again by pathologists, including Dr Seiichi Hirota, a co-author of the present study, who comprehensively evaluated the morphological features, immunostaining, and tumor genotypes to confirm that all the tumors were GISTs. Finally, 402 patients were enrolled (Figure S1).

2.2 | Genotyping

Tumor genotyping was performed on fresh or formalin-fixed, paraffin- embedded tissue samples. Whenever fresh-frozen samples

or fresh samples kept in RNAlater storage reagent were available, mRNA was extracted using the previously described method. Reverse transcriptase-polymerase chain reaction (RT-PCR) identified amplifications of nearly entire regions of the *KIT* and *PDGFRA* gene, confirming the expression of *KIT* and *PDGFRA* mRNA in cells in the samples analyzed. If fresh samples were unavailable, DNA was extracted from paraffin-embedded specimens. Mutations of *KIT* exons 9, 11, 13, and 17 and *PDGFRA* exons 12 and 18 were examined at all the participating centers, and other examinations were added in accordance with the protocol of each center. *KIT* exon 8 and *PDGFRA* exon 14 were added to the analysis at Osaka University Hospital and Osaka Police Hospital. Direct sequencing of the amplified products was then carried out. Tumors harboring neither *KIT* nor *PDGFRA* mutations were defined as wild-type mutation-derived regardless of the presence or absence of NF-1/SDH/RAS pathway mutations.

2.3 | Statistical analysis

Recurrence-free survival (RFS) was defined as the period from the date of surgery to the date of the last follow-up or an event, recurrence or death. The χ^2 test was used to evaluate the association between clinicopathological categories. The Kaplan-Meier method and the log-rank test were used to estimate RFS. The association between clinicopathological and molecular factors and RFS was assessed using the hazard ratio (HR) and 95% confidence interval (CI) in univariate and multivariate Cox proportional hazard analysis. IBM SPSS Statistics, version 26 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses. $P < 0.05$ was considered to indicate statistical significance.

3 | RESULTS

3.1 | Patient characteristics

Clinicopathological and molecular data were obtained from 401 patients (99.3%) for the tumor site, from 400 patients (99%) for the tumor diameter, from 365 patients (90.3%) for the mitotic count, and from 399 patients (98.8%) for tumor rupture. The median age of the total cohort was 63 years. Most of the tumors originated in the stomach (304/402, 75.6%) followed by the small intestine (76/402, 18.9%) and colorectum (14/402, 3.5%). The median tumor diameter was 4.5 cm, and the median mitotic count per 50 high power fields (50HPF) was five. Ten patients (2.5%) had a tumor rupture, and 163 patients (40.5%) were categorized as high-risk according to the modified NIH classification (Table 1).

3.2 | Tumor genotypes

Tumor genotyping was performed in all 402 patients, and mutations were detected in samples from 398 patients (99%), except in four

TABLE 1 Patient characteristics

	n (%)
Age	
Median (range)	63 (16-89)
Sex	
Male	220 (54.7)
Female	182 (45.3)
Tumor location	
Esophagus	2 (0.5)
Stomach	304 (75.6)
Small intestine	76 (18.9)
Colon or rectum	14 (3.5)
Others	3 (0.7)
Not available	4 (1.0)
Tumor size (cm)	
Median (range)	5 (0-500)
Not available	4 (1.0)
Mitotic count (/50HPFs)	
Median (range)	5 (0-500)
Not available	39 (9.7)
Tumor rupture	
Yes	10 (2.5)
No	387 (96.3)
Not available	5 (1.2)
Risk classification (Modified NIH)	
Very low	32 (8.0)
Low	127 (31.6)
Intermediate	47 (11.7)
High	163 (40.5)
Not available	33 (8.2)

Abbreviations: HPF, high-power field; NIH, the National Institutes of Health.

samples of insufficient quality and/or quantity. *KIT* or *PDGFRA* mutations were identified in 93.5% (376/402) of the cohort. The mutational sites in *KIT* (352/402, 87.5%) and *PDGFRA* (24/402, 5.7%) were identified, and 22 (5.4%) tumors were found to be of the *KIT/PDGFRA* wild type.

Table S1 shows the patient and tumor characteristics by genotype. Age was significantly associated with genotype. Only three patients (3/402, 0.7%) were younger than age 20 years, and two of them had a wild-type tumor. Wild-type GISTs occurred in female patients with relatively greater frequency (14/22, 63.6%) than the other genotype groups. The primary tumor site was significantly associated with genotype (Pearson's chi-square test, $P = 0.001$). The proportion of tumors of gastric origin was highest for *PDGFRA* mutations (22/24, 91.6%) followed by *KIT* mutations (268/352, 76.1%) and wild-type tumors (14/22, 63.6%). Both *PDGFRA* mutations and wild-type tumors had a lower mitotic count than *KIT* mutations. A high mitotic count (>10/50 HPFs) was found in 38.2% (121/316) of

KIT mutation tumors and in only 9.3% (4/43) of *PDGFRA* mutation tumors and wild-type tumors.

3.3 | KIT

Table 2 shows the tumor characteristics associated with a risk of recurrence by exon and *KIT* mutation type. The most frequent mutation site was exon 11 (320/352, 90.9%) followed by exons 9 (20/352, 5.6%), 17 (8/352, 2.2%), and 13 (4/352, 1.1%). The median mitotic count did not differ significantly among the exons; however, the mean mitotic count per 50 HPFs was higher in exons 9 and 11 (14.0 and 20.3, respectively) and lower in exons 13 and 17 (5.6 and 2.8, respectively) because both exons 9 and 11 involved tumors with a mitotic count >50 per 50 HPFs.

Among the 352 *KIT* mutations, the most common type was deletion (n = 159, 45.1%) followed by substitution (n = 104, 29.5%), deletion-insertion (n = 39, 11%), duplication (n = 27, 7.6%), and insertion (n = 15, 4.2%). Thirteen tumors with deletion type mutations had a missense mutation and apparently had concurrent insertion of other amino acids but were categorized as having deletion type mutations rather than true deletion-insertion type mutations.

The median mitotic count per 50 HPFs was >5 in deletion and deletion-insertion type mutations and <5 in duplication, substitution, and insertion type mutations. Mutations involving codons 557-558 had a particularly higher mitotic count in the deletion type mutations (15/50 HPFs) and deletion-insertion type mutations (22.5/50HPFs).

Figure 1 shows a bar graph of cumulative mutations by codon. The most frequently mutated codon was 557 (n = 126) followed by 558 and 559 (n = 118 each). The duplication type mutation occurred only in codons 502_503 in *KIT* exon 9 or downstream from codon 570 in *KIT* exon 11.

In the *KIT* gene, 114 variations in mutation pattern and location were identified. The most common mutation pattern was the W557_K558 deletion (n = 34). This genotype had an average mitotic count but generated large tumors, 75% of which were classified as high-risk according to the modified NIH criteria. A502_Y503 duplication in exon 9 was also associated with high-risk tumors (Table 3).

3.4 | PDGFRA

Among 23 patients with a *PDGFRA* mutation, five different genotypes (one for exon 12 and four for exon 18) were identified. The most common type was D842V (n = 17) followed by V561D and D842del (n = 2 each). Four of 17 (23.5%) tumors with a D842V mutation were classified as high risk according to the modified NIH criteria.

3.5 | Survival

The median follow-up period in all 402 patients was 54.4 months (range: 1.4-121.6 months). The survival of the patients was

TABLE 2 Tumor characteristics associated with risk of recurrence by exon and type of *KIT* mutation

	n	Tumor size (cm) Median (range)	Mitotic count (/50HPF) Median, mean (range)	Non-gastric n (%)	High risk n (%)
KIT exon 9	20	8.8 (2.0-30.0)	5.0, 14.0 (0-85)	16 (80.0)	13 (65.0)
KIT exon 11	320	4.5 (0.8-30.0)	5.0, 20.3 (0-500)	66 (20.6)	134 (41.8)
KIT exon 13	4	3.6 (1.0-7.5)	2.0, 5.6 (0-15)	2 (50.0)	2 (50.0)
KIT exon 17	8	5.1 (0.7-22.0)	3.0, 2.8 (0-5)	2 (25.0)	2 (25.0)
Duplication	27	4.2 (2.0-30.0)	2.0, 12.4 (0-100)	13 (48.1)	9 (33.3)
Substitution	104	4.0 (0.7-25.0)	4.0, 6.2 (0-50)	19 (18.2)	24 (23.0)
Deletion	159	5.0 (0.8-27.0)	9.0, 28.9 (0-500)	28 (17.6)	83 (52.2)
Involving codons 557-558	81	6.0 (0.8-27.0)	15.0, 40.7 (0-500)	10 (12.3)	53 (65.4)
Others	78	4.5 (1.0-23.0)	5.0, 17.0 (0-250)	18 (23.0)	30 (38.4)
Insertion	15	7.0 (2.5-21.0)	5.0, 11.4 (0-50)	8 (53.3)	11 (73.3)
Deletion-insertion	39	4.7 (1.5-30.0)	7.0, 27.2 (0-200)	15 (38.4)	23 (58.9)
Involving codons 557-558	22	5.6 (1.8-30.0)	22.5, 40.3 (1-200)	6 (27.2)	14 (63.6)
Others	17	3.8 (1.5-12.0)	4.0, 13.2 (0-50)	9 (52.9)	9 (52.9)

Abbreviation: HPF, high-power field.
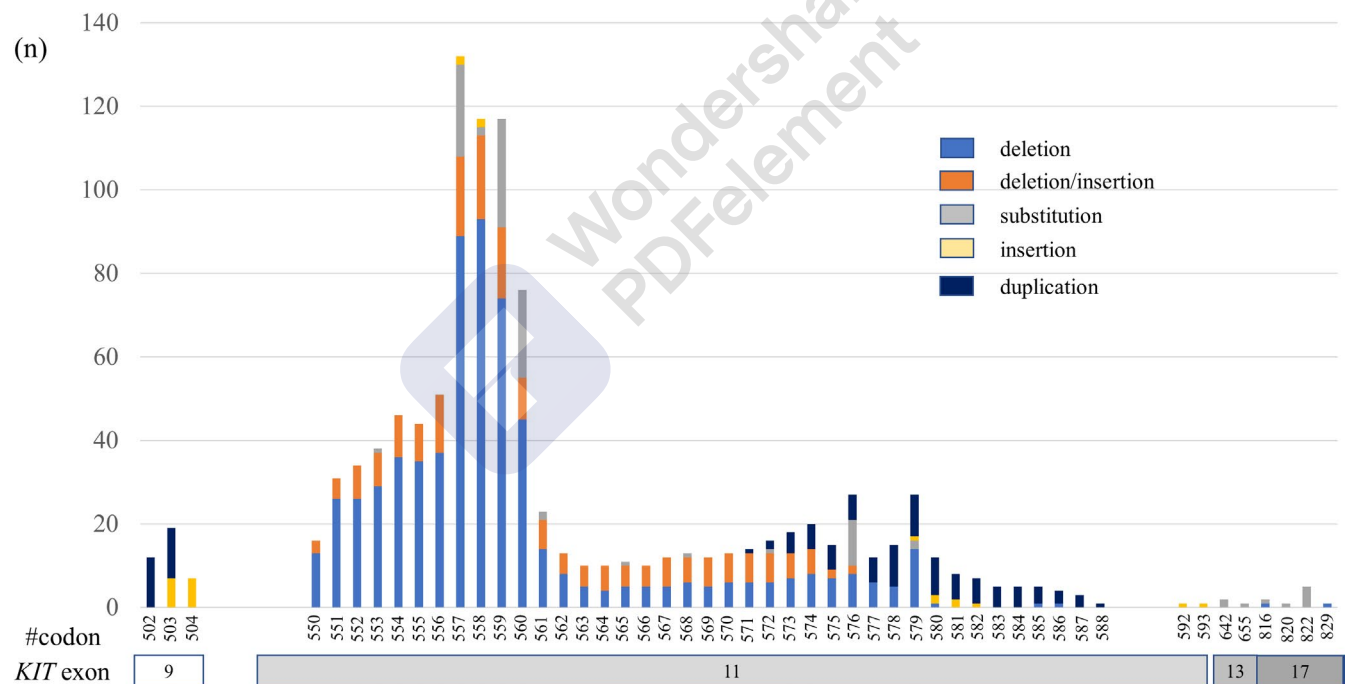
FIGURE 1 Frequency of mutated codons in *KIT* exons 9, 11, 13, and 17

assessed in terms of the association between RFS and mutated genes, *KIT* exons, *KIT* mutation types, and mutated *KIT* codons (Figure 2).

First, the ten-year RFS rate in patients with a *PDGFRA* mutation-derived tumor or a wild-type tumor was relatively favorable (65.9% and 69.7%, respectively) compared with tumors derived from a *KIT* mutation (51.2%) although the difference was not significant (Figure 2A). The hazard ratio for recurrence was 0.47 for *PDGFRA*

to *KIT* (95% CI 0.17-1.28, *P* = 0.141) and 0.52 (95% CI 0.19-1.42, *P* = 0.207) for wild-type to *KIT*.

Although the tumors with an exon 9 or 11 mutation had a higher mean mitotic count than tumors with an exon 13 or 17 mutation, our analysis found no significant difference in RFS among the tumors deriving from mutated *KIT* exons (Figure 2B). The hazard ratio for recurrence was 1.79 for exon 9 to exon 11 (95% CI: 0.93-3.43; *P* = 0.079), and the number of patients with exon 9

TABLE 3 Characteristics of common *KIT* mutations

Exon	Mutated codons	Type	Total n	Gastric site n (%)	High-risk n (%)	Size, cm Median (range)	Mitosis/50HPF Median (range)
11	W557_K558	Deletion	34	30 (88.2%)	25 (73.5%)	7.0 (1.3-27.0)	5 (0-500)
11	W557R	Substitution	18	16 (88.8%)	3 (16.6%)	3.4 (2.0-7.0)	2 (0-34)
11	V559_V560	Deletion	15	12 (80%)	6 (40%)	5.0 (1.0-20.0)	5 (0-60)
11	V559D	Substitution	15	15 (100%)	2 (13.3%)	4.0 (1.9-24.0)	3 (0-25)
11	V560D	Substitution	13	13 (100%)	2 (15.3%)	4.5 (1.5-7.0)	5 (0-10)
11	D579	Deletion	12	11 (91.6%)	1 (8.3%)	4.0 (2.5-15.0)	3 (0-50)
9	A502_Y503	Duplication	12	3 (25%)	6 (50%)	4.7 (2.0-30.0)	3 (0-83)
11	V559A	Substitution	10	8 (80%)	3 (30%)	4.5 (3.2-25.0)	5 (2-20)
11	K558_V559	Deletion	9	9 (100%)	3 (33.3%)	3.8 (2.0-8.0)	10 (0-90)
11	L576P	Substitution	9	6 (66.6%)	4 (44.4%)	4.0 (2.0-12.0)	5 (0-50)

mutations was insufficient to prove that exon 9 mutations were significantly associated with worse RFS than exon 11 mutations. The number of patients with a *KIT* exon 13 or exon 17 mutation was too small (four and eight, respectively) to have sufficient statistical power.

Meanwhile, the RFS rate significantly varied by mutation type (Figure 2C). Deletion and deletion-insertion mutations were associated with poor RFS while duplication and substitution mutations were associated with a more favorable RFS. The hazard ratio for recurrence in the deletion-insertion type mutations to duplication type mutations was 2.66 (95% CI: 1.11-6.37; $P = 0.027$).

To investigate deletion and deletion-insertion type mutations further, the loci of the mutations were examined, focusing on codons 557-558 where the deletion and deletion-insertion type mutations were most frequently found in this study. As a result, the deletion type mutations, including those at codons 557-558, were found to be associated with even poorer RFS (Figure 2D). The hazard ratio for the recurrence of deletions involving 557/558 (n = 80) to those not involving 557/558 (n = 79) was 2.08 (95% CI: 1.23-3.53; $P = 0.006$). The deletion-insertion type mutation was associated with a poor RFS irrespective of the codon locus, and RFS did not differ significantly between the presence and absence of deletion-insertion at 557/558. The hazard ratio for the presence (n = 80) to the absence (n = 79) of deletion-insertion at 557/558 was 2.30 (95% CI: 0.79-6.66; $P = 0.123$).

On univariate analysis, tumor size (continuous variable), mitotic count (continuous variable), primary tumor site (gastric vs non-gastric), rupture, and genotype (*KIT* exon 11 duplication vs wild-type vs *PDGFRA* vs *KIT* del/del-ins [deletion/deletion-insertion] including codons 557 to 558 vs *KIT* exon 9 vs other *KIT* mutations) were associated with RFS. When the factors were analyzed using Cox multivariate analysis, independent factors of RFS were found to be genotype ($P = 0.007$), mitotic count ($P < 0.001$), tumor size ($P < 0.001$), and tumor site ($P < 0.001$) (Table 4). When the analysis was limited only to *KIT* mutations, genotype (*KIT* exon 11 duplication

vs *KIT* not including codons 557-558 vs *KIT* del/del-ins including codons 557-558 vs *KIT* exon 9) remained an independent prognostic factor ($P = 0.016$) (Table S4).

4 | DISCUSSION

The present study examined both the clinical characteristics and prognostic impact of genotype in GIST and demonstrated that each genotype had different clinical features, with some genotypes having a significant impact on RFS. When assessed by genotype, *PDGFRA* mutation-derived tumors were strongly associated (22/24:91.7%) with a gastric origin (Table S1). Wild-type tumors frequently occurred young, female patients. Both the tumors with *PDGFRA* mutations and wild-type tumors were relatively small and had a lower mitotic count. *KIT* exon 9 mutations were associated with tumors of a non-gastric origin. These findings are likely to hold true irrespective of region or race because they are consistent with the results of previously reported studies from other countries.[11,12,14] Further, if the genotype regulates the biological behavior of GIST, it may also have implications for the prognosis.

Thus far, several studies have reported that genotype was an independent factor of RFS,[11,12] but no optimal genotype subgroup has yet been identified. Joensuu et al[11] reported that the presence of *KIT* mutations had an independent, adverse influence on RFS when the mutated gene (*KIT* vs *PDGFRA* or wild-type) was analyzed using Cox multivariate analysis. Another study demonstrated that *KIT* exon 11 deletion/deletion-insertion involving codons 557 to 558 was associated with inferior RFS.[8] Furthermore, a recent study demonstrated that *KIT* exon 9 duplication and *KIT* exon 11 deletions involving codons 557-558 were related to inferior disease-free survival.[11] In the present study, genotype was an independent factor of RFS on Cox multivariate analysis in both the entire cohort and in cases of *KIT* mutation only, together with tumor size, mitotic count, and the primary site. Among these factors, mitotic count was most strongly related to RFS, and genotype had a weaker impact than the conventional
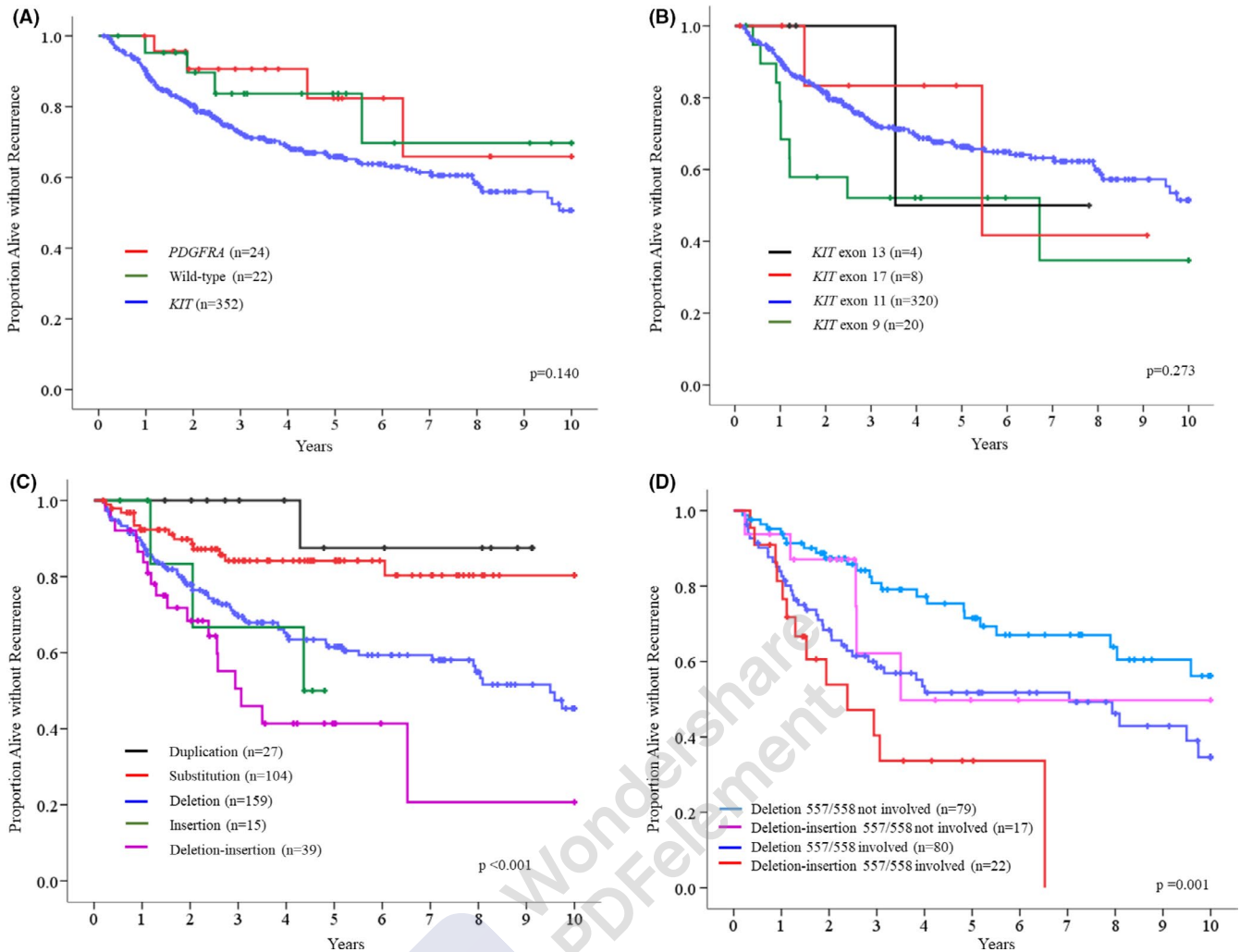
FIGURE 2 Recurrence-free survival (RFS) by mutation status (A), mutated *KIT* exons (B), mutation type (C) with or without involvement of codons 557 and 558 (D)

factors. Tumor rupture was not independently associated with RFS probably because patients with ruptured GIST most often received adjuvant imatinib and were excluded from the analysis and tumor rupture was a rare event.

Internal tandem duplications in *KIT* exon 11 have been recognized as a favorable subset of *KIT* mutations.[15] Among 35 patients with a *KIT* exon 11 duplication mutation in a case series by Joensuu et al,[12] only one patient (2.9%) experienced a recurrence. In the present study, four of 12 patients (33.3%) with a duplication in *KIT* exon 11 fell into the intermediate or high-risk category, and only one of them experienced a recurrence. Although it may be untenable to say that *KIT* duplication mutations are essentially indolent based only on an analysis of a small number of patients, it may be said that *KIT* mutations comprise a heterogeneous category consisting of several subgroups, with the prognosis depending on the genotype. Differences in prognosis by mutation subtype can be explained by the locations of the mutations in *KIT*. Tryptophan-557 is known to have an inhibitory effect on the activation of tyrosine kinase through its hydrophobicity. Substitution of proline for lysine-558 produces

high spontaneous receptor phosphorylation in vitro.[16] The combination of codons 557 and 558 thus constitute an important region for suppressing spontaneous phosphorylation; therefore, alterations affecting these codons may cause strong spontaneous phosphorylation in *KIT*, worsening the prognosis through a high mitotic index and high tumor proliferation activity. The duplication type mutations clearly develop in codons downstream from 558 and never reach 557-558, suggesting that they are associated with a relatively favorable prognosis.

In terms of the frequency and type of *PDGFRA* mutation, the present study found five different types of *PDGFRA* mutation in 23 patients (5.7%). The most common type was the D842V substitution (17/23, 73.9%), which had the same risk of recurrence as other mutations (data not shown). Although the number of patients and the mutation types were limited, *PDGFRA* mutations were likely to have more homogeneous characteristics than *KIT* mutations regardless of the *PDGFRA* subtype.

The present study has several limitations. First, as a retrospective cohort study, it included patients from prospective GIST

TABLE 4 Univariate and multivariate analyses of recurrence-free survival in the entire cohort (n = 402)

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Tumor size (cm, continuous)	1.124 (1.096-1.152)	<0.001	1.104 (1.068-1.141)	<0.001
Mitotic count (/50HPFs, continuous)	1.005 (1.004-1.007)	<0.001	1.004 (1.002-1.006)	<0.001
Primary tumor site				
Gastric	1.0 (reference)		1.0 (reference)	
Non-gastric	2.273 (1.578-3.276)	<0.001	2.385 (1.498-3.795)	<0.001
Tumor rupture				
Negative	1.0 (reference)		1.0 (reference)	
Positive	3.852 (1.872-7.927)	<0.001	0.847 (0.342-2.100)	0.720
Tumor genotype		<0.001		0.007
KIT exon11 duplication	1.0 (reference)		1.0 (reference)	
Wild type	2.390 (0.249-22.988)	0.451	2.531 (0.263-24.370)	0.422
PDGFRA	2.693 (0.301-24.102)	0.376	1.564 (0.140-17.440)	0.716
KIT del/delins including codons 557 to 558	10.313 (1.426-74.592)	0.021	7.552 (1.027-55.522)	0.047
KIT exon 9	10.565 (1.351-82.609)	0.025	3.791 (0.472-30.450)	0.210
Other KIT mutations	3.904 (0.539-28.286)	0.178	3.743 (0.512-27.345)	0.193

Abbreviations: CI, confidence interval; PDGFRA, platelet-derived growth factor receptor alfa.

databases at three Japanese centers. To avoid selection bias, mutation analysis was performed for all patients with GIST irrespective of recurrence risk, but data on three patients were not available. Second, the study period was long and included patients who underwent surgery before 2000. Therefore, the pathological and molecular findings were reassessed and the diagnosis of patients who underwent surgery before 2000 were confirmed to exclude patients with non-GIST tumors. No difference in RFS by the period was found (data not shown).

In summary, the genotypic characteristics of GIST were found to be consistent worldwide, and genotype was found to have a significant impact on RFS. Certain, clinical features correlated with tumors arising from *PDGFRA* mutations or wild-type tumors, which are usually less sensitive to imatinib. The expression of *KIT* exon 9 mutations or *KIT* exon 11 deletion mutations involving codons 557-558 had an additional, worsening impact on RFS if the patient was already judged to be high-risk according to the conventional factors. *KIT* exon 11 duplication mutations might have a favorable prognosis and warrant further investigation.

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DISCLOSURES

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