

Effects of first-line therapies in patients with locally advanced gastrointestinal stromal tumors with *KIT* and *PDGFRα* gene mutations: A single-center study

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Abstract. Curative resection is typically recommended for treating gastrointestinal stromal tumors (GISTs). Exceptions are made for locally advanced GISTs (LAGISTs) where radical resection may be impossible. First-line imatinib therapy can be employed to treat GISTs harboring mutations in the tyrosine-protein kinase *KIT* (*KIT*) and platelet-derived growth factor receptor α (*PDGFRα*) genes to reduce the tumor size to resectable levels and minimize surgical risks. The present study investigated the treatment outcomes of patients with LAGISTs with different *KIT* and *PDGFRα* gene mutations who received first-line imatinib therapy. A total of 37 patients with LAGISTs who underwent first-line imatinib treatment were included, and the median follow-up period was 41 months. Treatment regimens included imatinib, with subsequent therapies, such as sunitinib and regorafenib, administered upon imatinib failure. The genetic profiles of *KIT* and *PDGFRα* were analyzed. Of the 37 patients, 24 (64.9%) successfully underwent curative resection. The

median progression-free survival (PFS) was 36 months and the median overall survival (OS) was 41 months. Patients presented with tumors with various genetic mutations, which differentially affected their PFS and OS and adverse events were typically manageable. However, the gene mutation status was not significantly associated with treatment response or surgical resectability (both $P > 0.05$). The present study elucidated the effects of first-line therapy on LAGISTs with genetic mutations, underscoring the effectiveness of imatinib treatment and the value of continual patient monitoring. Additional studies with long-term follow-up are required to evaluate treatment outcomes.

Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors occurring in the gastrointestinal tract (1), with an annual incidence is up to 10 to 15 cases per million individuals (2-6). The prognosis of GIST is associated with the tumor size and mitotic index, and median overall survival ranged from 47 to 57 months (2-6). Curative resection is advised for most patients with GISTs but not for those with locally advanced GISTs (LAGISTs), which are unsuitable for radical resection, those for whom resection presents risks of substantial organ dysfunction or those whose GISTs are borderline unresectable (2-6).

Mutations in the genes encoding the receptor tyrosine-protein kinase *KIT* (*KIT*) and platelet-derived growth factor receptor α (*PDGFRα*) may prompt considerations of treatment with first-line imatinib therapy (2-7). Imatinib inhibits GIST progression by targeting *KIT* and *PDGFRα*. This preoperative

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treatment modality can be employed in cases of LAGISTS that are unresectable or borderline unresectable. First-line imatinib therapy can enable surgical resection and minimize the risk of tumor spillage or bleeding during surgery. However, whether imatinib can be used to treat LAGIST with exon mutations of *KIT* and *PDGFR α* genes (4,8) remains to be elucidated. *KIT* gene mutations occur in ~80% of GISTs (8). Additionally, a higher occurrence of primary imatinib resistance was observed in GISTs with *KIT* exon 9 mutations, *PDGFR α* D842V mutations and wild-type *KIT* and *PDGFR α* compared with other types of gene mutation (9). Tyrosine kinase inhibitors (TKIs) such as imatinib have transformed therapeutic approaches for advanced GISTs. Currently, four TKIs, imatinib, sunitinib, regorafenib and ripretinib, are approved for use as first-line, second-line, third-line and fourth-line therapies, respectively (5,10). Ripretinib, a broad-spectrum *KIT* and *PDGFR α* inhibitor, is approved for the treatment of adult patients with LAGISTS who have received prior treatment with three or more kinase inhibitors, including imatinib. Furthermore, avapritinib, a type I kinase inhibitor, is approved for the treatment of adults with unresectable or metastatic GISTs harboring a *PDGFR α* exon 18 mutation, including *PDGFR α* D842V mutation (11). The present study specifically examined treatment outcomes for patients with LAGISTS with several gene mutations following first-line therapy with imatinib.

Materials and methods

Patient demographics. There are no clear criteria to define LAGIST at present. In the present study, LAGIST that was initially diagnosed was defined as being unsuitable for radical resection, risk of substantial organ dysfunction or borderline unresectable according to a previous study by our group (3). Fig. 1 depicts a flowchart of the patient recruitment process. A total of 41 patients who had received a diagnosis of a LAGIST and who underwent first-line treatment at a single institution (Kaohsiung Medical University Hospital, Kaohsiung, Taiwan) between December 2010 and July 2023 were included. A total of 3 of the 41 patients were excluded for having no gene data and 1 patient was excluded for being lost to follow-up after 1 month, leaving a total of 37 patients for final enrolment. Enrolled patients were closely monitored until January 2024. The inclusion criteria were as follows: i) Having an LAGIST that was initially diagnosed as unsuitable for radical resection; and ii) being at risk of substantial organ dysfunction or borderline unresectable (3,12-14). Following the administration of first-line therapy with imatinib, the included patients were followed for a median period of 41 months (range, 10 to 183 months). Tumor responses were assessed through concurrent analysis of computed tomography (CT) images and the genetic mutation profiles of *KIT* and *PDGFR α* genes. The present study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital [Kaohsiung, Taiwan; approval no. KMUHIRB-E(I)-20240084] and the requirement for patient consent was waived due to the respective nature of the study.

Treatment. Each patient received a prescription for imatinib at a daily dose of 400 mg, with a treatment duration ranging

from 3 to 56 months (median, 15 months). In cases where patients experienced grade 3 or 4 toxicities, the imatinib dose was reduced to 300 mg per day. Sunitinib was administered as a second-line therapy at a daily dose of 37.5 mg when the first-line imatinib treatment failed and disease progression was evident on CT scans performed every 3 months. Sunitinib was administered to improve the response after consultation with a multidisciplinary team (MDT), which comprised surgeons, radiologists, gastroenterologists and oncologists. Regorafenib was employed as a third-line treatment at a daily dose of 120 mg. After the radical resection, the adjuvant treatment was continued for a total of 36 months under close supervision by the MDT.

Evaluation of tumor response and toxicities. Tumor dimensions and density were verified through assessment of abdominal CT scans by two radiologists. Any discrepancies were resolved through a joint re-examination of the images by both radiologists. Tumor responses were assessed using CT images in accordance with the response evaluation criteria in solid tumors 1.1 (RECIST 1.1) (15). Adverse events (AEs) were categorized based on the Common Terminology Criteria for AEs, version 3.0 (16). In evaluating surgical resectability in patients with LAGISTS, the timing followed the method of combined CT-measured tumor density and RECIST 1.1 described in a previous study by our group (3). All enrolled patients were followed up by CT and laboratory data every 3 months for efficacy evaluation until surgical intervention. The decision to proceed with surgery was made using combined CT-measured tumor density and RECIST for evaluating surgical timing. With either a tumor size (tumor dimensions) reduction of >30% or a reduction of >30% of tumor density, surgery was considered (3). Surgical timing was confirmed by the MDT, which comprised surgeons, radiologists, gastroenterologists and oncologists. The clinical condition of the patients (such as age, Eastern Cooperative Oncology Group performance status and willingness of the patient to undergo surgery) was also considered.

***KIT* and *PDGFR α* gene mutations.** CT-guided core biopsies were performed prior to the initiation of the first-line imatinib therapy to collect tumor tissue specimens. Biopsy specimens were carefully embedded in paraffin, fixed using formalin and subsequently sectioned into slices measuring 4 μ m in thickness. DNA extraction was performed using the Qiagen DNA extraction kit (Qiagen, Inc.), following the manufacturer's instructions. The concentration and quality of the extracted DNA were assessed using a NanoDrop 2000 spectrophotometer. The optical density at either 260 or 280 nm for DNA extracted from all patient specimens fell within the range of 1.8 to 2.0, indicating that the DNA samples were of suitable quality for subsequent experiments. The DNA samples were subjected to analysis using polymerase chain reaction (PCR) in a PCR instrument from Applied Biosystems (Thermo Fisher Scientific, Inc.). Subsequently, the *KIT* or *PDGFR α* primers (at a concentration of 100 μ M) and the 2X PCR Master Mix (Thermo Fisher Scientific, Inc.) were introduced and mutations confirmed by Sanger sequencing. The thermocycling conditions were as follows: 95°C for 10 min, then 40 cycles of 95°C denaturation for 30 sec, 58°C annealing for 45 sec and 72°C extension for 45 sec, followed by a final

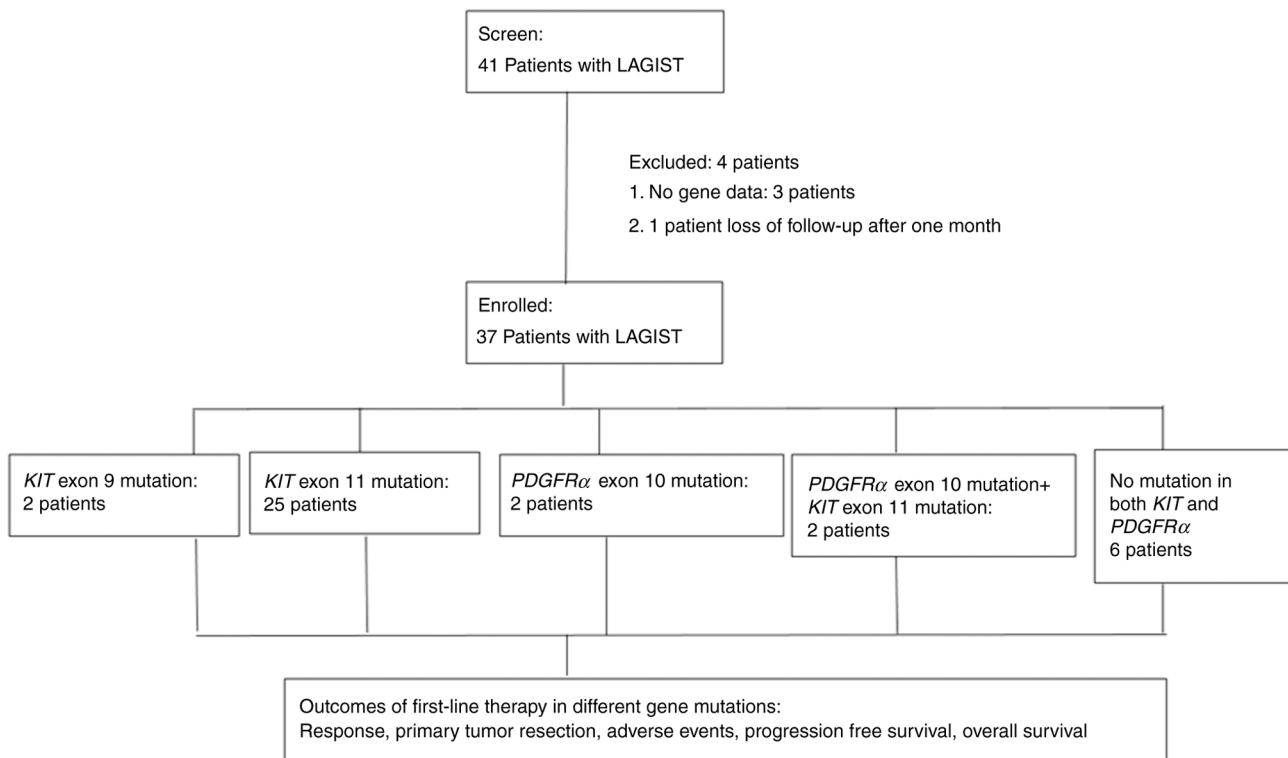


Figure 1. Flowchart of the patient recruitment process. LAGIST, locally advanced gastrointestinal stromal tumor; KIT, tyrosine-protein kinase KIT; PDGFR α , platelet-derived growth factor receptor α .

step of 72°C for 7 min. The primers for the *KIT* gene were as follows: Forward (exon 9), 5'-GATGCTCTGCTTCTGTAC T-3' and reverse (exon 9), 5'-GCCTAAACATCCCCTTAA ATTGG-3'; forward (exon 11), 5'-CTCTCCAGAGTGCTC TAATGAC-3 and reverse (exon 11), 5'-AGCCCCTGTTTCTAATGAC-3'; forward (exon 13), 5'-CGGCCATGACTG TCGCTGTAA-3' and reverse (exon 13), 5'-CTCCAATGG TGCAGGCTCCAA-3'; forward (exon 17), 5'-TCTCCTCCA ACCTAATAGTG-3' and reverse (exon 17), 5'-GGACTGTCA AGCAGAGAAT-3'; forward (exon 18), 5'-CATTTCAGC AACAGCAGCAT-3' and reverse (exon 18), 5'-CAAGGA AGCAGGACACCAAT-3'. The primers for *PDGFR α* gene were as follows: Forward (exon 10), 5'-GACTCTCAGGAA TTGGCC-3'; reverse (exon 10), 5'-CAGCTGATGAGTTGT CCTG-3'; forward (exon 12), 5'-GAACGTTGTTGGACT CTACTGTG-3' and reverse (exon 12), 5'-GCAAGGGAA AAGGGAGTCT-3'; forward (exon 14), 5'-GTAGCTCAG CTGGACTGATA-3' and reverse (exon 14): 5'-AATCCTCAC TCCAGGTCAGT-3'; forward (exon 18), 5'-CTTGCAGGG GTGATGCTAT-3' and reverse (exon 18), 5'-AGAAGCAAC ACCTGACTTTAGAGATTA-3'.

Statistical analysis. All statistical analyses were performed using SPSS version 21 (IBM Corp.). Progression-free survival (PFS) was calculated from the treatment initiation date to the date of any form of progression or the last recorded follow-up. Overall survival (OS) was defined as the duration from the commencement of treatment to either mortality from any cause or the last follow-up date. PFS and OS were evaluated using the Kaplan-Meier method and the log-rank test was employed to compare time-to-event distributions. Treatment

response rates, resection rates and AE rates were compared using Fisher's exact test. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient series, tumor characteristics and mutation status. The demographic and clinicopathological characteristics of the enrolled patients are presented in Table I. The median age of the cohort was 65 years, with total ages ranging from 33 to 87 years. Among the patients, 25 (67.6%) were men and 12 (32.4%) were women. The LAGISTs were located in various sites: Stomach (21 patients; 56.8%), omentum (1 patient; 2.7%), pancreas (1 patient; 2.7%), small intestine (5 patients; 13.5%), mesocolon (1 patient; 2.7%), pelvic area (1 patient; 2.7%) and rectum (7 patients; 18.9%).

Regarding genetic mutations, 29 patients (78.4%) had *KIT* mutations and 4 (10.5%) had *PDGFR α* mutations. A total of 2 patients (5.4%) had *KIT* exon 9 insertions, five (13.5%) had *KIT* exon 11 insertions, 14 patients (37.8%) had *KIT* exon 11 deletions, 5 (13.5%) had *KIT* exon 11 point mutations and 1 (2.7%) had *KIT* exon 11 duplications. A total of 2 patients (5.4%) had *PDGFR α* exon 10 point mutations and 2 patients (5.4%) had *PDGFR α* exon 10 point mutations with a *KIT* exon 11 deletion. A total of 6 patients (16.2%) had wild-type *KIT* and *PDGFR α* (Table I). Representative Sanger sequencing images depicting each respective mutation are shown in Figs. S1-7.

Treatment outcomes. Analysis of tumor responses using the RECIST 1.1 revealed that 20 of the 37 patients (54.1%)

Table I. Demographics of 37 patients with locally advanced gastrointestinal stromal tumor.

Characteristic	Patients, n (%)
Sex	
Male	25 (67.6)
Female	12 (32.4)
Median age (years, range)	65 (33-87)
Tumor location	
Stomach	21 (56.8)
Omentum	1 (2.7)
Pancreas	1 (2.7)
Small intestine (including duodenum)	5 (13.5)
Mesocolon	1 (2.7)
Pelvic area	1 (2.7)
Rectum	7 (18.9)
Type of gene mutation	
<i>KIT</i> exon 9 insertion	2 (5.4)
<i>KIT</i> exon 11 insertion	5 (13.5)
<i>KIT</i> exon 11 deletion	14 (37.8)
<i>KIT</i> exon 11-point mutation	5 (13.5)
<i>KIT</i> exon 11 duplication	1 (2.7)
<i>PDGFRα</i> exon 10-point mutation	2 (5.4)
<i>KIT</i> exon 11 deletion; <i>PDGFRα</i> exon 10-point mutation	2 (5.4)
No mutation in both <i>KIT</i> and <i>PDGFRα</i>	6 (16.2)
Mutation numbers	31 (83.8)
<i>KIT</i> exon 9	2 (5.4)
<i>KIT</i> exon 11	27 (73.0)
<i>PDGFRα</i> exon 10	4 (10.8)

KIT, tyrosine-protein kinase *KIT*; *PDGFRα*, platelet-derived growth factor receptor α .

achieved a partial response (PR) and 15 (40.5%) exhibited stable disease (SD). After therapy, 24 of the 37 patients (64.9%) with unresectable LAGISTs underwent primary tumor R0 resection (Table II). The median duration of first-line therapy was 16 months, with the total therapy duration ranging from 3 to 56 months. A total of 21 of the 24 patients eligible for resection were treated with imatinib; 3 patients subsequently switched to second-line sunitinib to achieve an improved response. However, the treatment response and surgical resectability rates of the 37 patients with LAGISTs following first-line therapy did not differ significantly in tumors with varying mutations of the *KIT* and *PDGFRα* genes (both $P > 0.05$; Table II). As of the final follow-up performed in January 2024, 21 of the patients were still alive. Sunitinib was administered for 4-52 months (median, 9 months) and regorafenib was administered for 5 months (case no. 5) and 24 months (case no. 21), up to the end of treatment or follow-up (Table III). Of the 21 patients with stomach LAGIST, 10 (47.6%) patients achieved PR, 9 (42.9%) patients SD and 2 (9.5%) patients progressive disease. Of the 5 patients with small intestine LAGIST, 3 (60%) patients achieved PR and 2 (40%) patients achieved SD. Of the 7 patients with rectal LAGIST, 6

(85.7%) patients achieved PR and 1 (14.3%) patient achieved SD (Table III). A total of 21 patients received adjuvant treatment with imatinib after the operation and 3 patients had adjuvant treatment with sunitinib (Table III). The adjuvant regimen was the same as that previously used in the first-line setting or the second-line setting. The median PFS of the 37 patients was 36 months, with the total PFS ranging from 4 to 141 months and a 5-year (60 months) PFS rate of 53.6% (Fig. 2). The median OS of the patients was 41 months, with total OS ranging from 10 to 183 months and a 5-year (60 months) OS rate of 55.7% (Fig. 3). AEs were reported by 78.4% of patients receiving first-line imatinib therapy, with the most commonly reported AEs being eyelid edema and nausea; these were experienced by 8 patients (21.6%). Anemia was experienced by 5 patients (13.5%). In addition, 3 patients (8.1%) had grade 3 anemia (Table IV).

Discussion

Curative resection is generally recommended for patients with GISTs, but such resection is not considered for patients with LAGISTs due to factors such as tumor location, size and increased risk of tumor rupture or metastasis (2-5). The present study reported on the experience of treating 37 patients with LAGIST at a single institution and the outcomes of first-line therapy in relation to various gene mutations. Although a higher proportion of men (67.6%) participated in the present study compared with other studies (55.0-66.7%), the median age (65 years) of the participants was consistent with that of those in other studies (57.4-63 years) (2,8,12).

The stomach was the most commonly affected region in the present study, consistent with findings reported in at least one other study (6). Most patients exhibited favorable clinical responses to first-line imatinib therapy; 20 (54.1%) experienced PR, 15 (40.5%) maintained SD and 2 (5.4%) exhibited disease progression. The data were consistent with the findings of other studies that demonstrated a 45-92% response rate (17-24), although studies have indicated a marked increase in primary resistance to imatinib, particularly in GISTs with *PDGFRα* mutations and those with mutations in exon 9 of the *KIT* gene (9,25). However, the mutation status of the *KIT* and *PDGFRα* genes was not helpful in predicting treatment response ($P = 0.602$) or surgical resectability ($P = 0.952$). Due to the relatively small patient number for each genetic mutation, it would not have been suitable from the perspective of statistics to create Kaplan-Meier plots or waterfall plots by grouping the patients by gene. The most common AEs of all grades were nausea, vomiting, gastritis, edema, eye lid edema, general malaise, skin rash, diarrhea, fatigue, renal function impairment, liver function impairment, hand-foot skin reaction, anemia and leukopenia and that of grade ≥ 3 was anemia (Table IV). No significant differences were observed in the AEs experienced during first-line therapy by patients whose tumors exhibited any mutations; comparisons were made among *KIT* exon 9 insertion, *KIT* exon 11 insertion, *KIT* exon 11 deletion, *KIT* exon 11 point mutation, *KIT* exon 11 duplication, *PDGFRα* exon 10 point mutation, *KIT* exon 11 deletion, *PDGFRα* exon 10 point mutation and no mutation in both *KIT* and *PDGFRα* (Table IV). The AEs noted in the present study were generally mild, well-tolerated and manageable with no marked hematologic toxicity at standard

Table II. Treatment outcome of first-line therapy in different gene mutations of 37 patients with locally advanced gastrointestinal stromal tumor.

Mutation	Patients, n (%)	Partial response, n (%)	Stable disease, n (%)	Progressive disease, n (%)	Primary tumor resection, n (%)	No primary tumor resection, n (%)
<i>KIT</i> exon 9 insertion	2 (100.0)	1 (50.0)	1 (50.0)	0	1 (50.0)	2 (100.0)
<i>KIT</i> exon 11 Insertion	25 (100.0)	14 (56.0)	10 (40.0)	1 (4.0)	17 (68.0)	25 (100.0)
Deletion	5 (20.0)	2 (40.0)	3 (60.0)	0	4 (80.0)	5 (20.0)
Point mutation	14 (56.0)	9 (64.2)	4 (28.6)	1 (7.1)	8 (57.1)	14 (56.0)
Duplication	5 (20.0)	3 (60.0)	2 (40.0)	0	4 (80.0)	5 (20.0)
<i>PDGFRα</i> exon 10 point mutation	1 (4.0)	0	1 (100.0)	0	1 (100.0)	1 (4.0)
<i>KIT</i> exon 11 deletion; <i>PDGFRα</i> exon 10 point mutation	2 (100.0)	0	2 (100.0)	0	1 (50.0)	2 (100.0)
No mutation in both <i>KIT</i> and <i>PDGFRα</i>	2 (100.0)	2 (100.0)	0	0	1 (50.0)	2 (100.0)
Total	6 (100.0)	3 (50.0)	2 (33.3)	1 (16.7)	4 (66.7)	6 (100.0)
P-value	37 (100.0)	20 (54.1)	15 (40.5)	2 (5.4)	24 (64.9)	37 (100.0)
			P=0.732		P=0.977	

A total of 5 patients without operation are currently still undergoing therapy. KIT, tyrosine-protein kinase KIT; PDGFR α , platelet-derived growth factor receptor α .

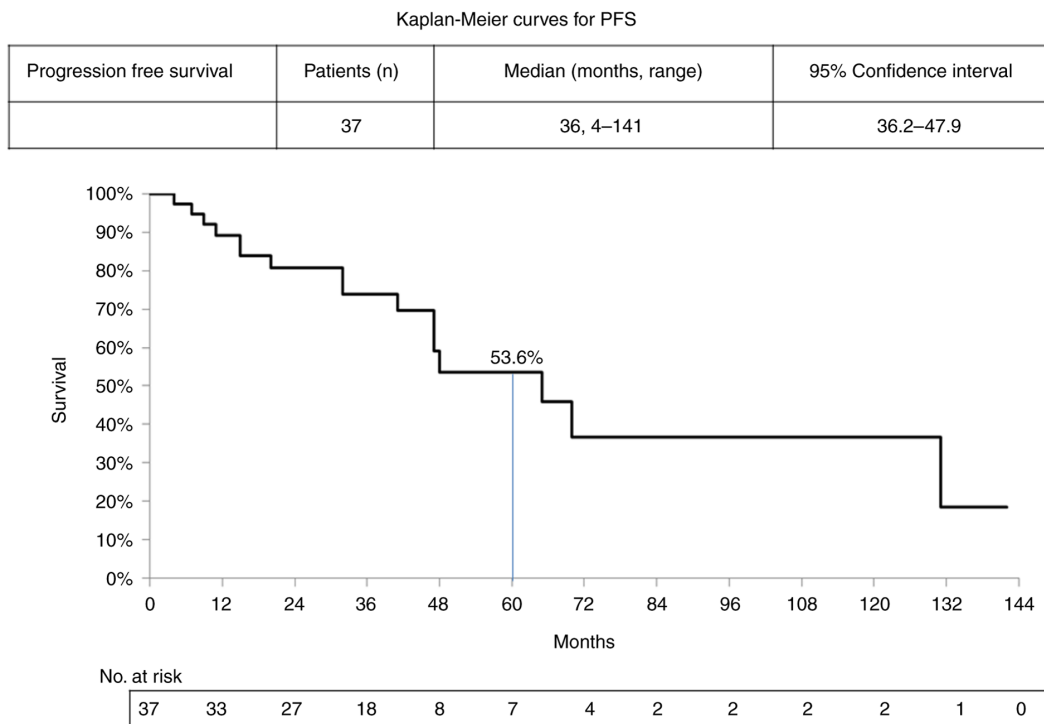


Figure 2. Kaplan-Meier curves for PFS of first-line therapy. The median PFS of the 37 patients was 36 months and the total PFS ranged from 4 to 141 months. PFS, progression-free survival.

dosages in patients treated with first-line imatinib therapy in another multicenter cohort study (26). In the present study, 24 (64.9%) patients with initially unresectable LAGISTs

underwent primary tumor resection. In addition, 21 patients who received treatment with first-line imatinib and 3 who achieved PR following treatment with first-line imatinib but

A, Resvponders

Case no.	Sex	Age, years	Tumor location	Duration of first-line imatinib therapy, months	PFS of first-line imatinib therapy, months	Duration of second-line therapy, months	PFS of second-line therapy, months	Duration of third-line therapy, months	PFS of third-line therapy, months	OS, months	Gene analysis result	Best overall response/resection	Survival
1	M	62	Stomach	8	32	-	-	-	-	32	Deletion in <i>KIT</i> exon 11 (c.1648_1671del 24; p.K550_W557del)	PR/Yes	No
2	F	83	Stomach	8	15	-	-	-	-	33	Insertion in <i>KIT</i> exon 11 (p.Y578_D579insPY)	PR/Yes	No
3	F	74	Stomach	17	48	-	-	-	-	58	Deletion in <i>KIT</i> exon11 (c.1674_1676delGGT; p.K558_V559>N); point mutation in exon 10 of <i>PDGFRα</i> (c.1432T>C) (p.S478P)	PR/No	Lost follow up
4	M	74	Stomach	16	66	-	-	-	-	66	Deletion in <i>KIT</i> exon 11 (c.1669_1674del; p.Trp557_Lys558del)	PR/Yes	Yes
5	M	48	Stomach	41	41	14	14	5	5	70	Deletion in <i>KIT</i> exon 11 (c.1669_1674del6; p.W557_K558del); point mutation in <i>PDGFRα</i> exon 10	PR/Yes	Yes
6	M	67	Stomach	14	48	-	-	-	-	48	Mutation was not found in <i>KIT</i> exon 9,11,13,17,18; mutation was not found in <i>PDGFRα</i> exon 10,12,14,18	PR/Yes	Yes

Table III. Continued.

A, Responders

Case no.	Sex	Age, years	Tumor location	Duration of first-line imatinib therapy, months	PFS of first-line imatinib therapy, months	Duration of second-line therapy, months	PFS of second-line therapy, months	Duration of third-line therapy, months	PFS of third-line therapy, months	OS, months	Gene analysis result	Best overall response/resection	Survival
7	M	54	Stomach	14	45	-	-	-	-	45	Insertion in <i>KIT</i> exon 11 (p.H580_581insYDH)	PR/Yes	Yes
8	M	46	Stomach	11	25	-	-	-	-	25	Mutation was not found in <i>KIT</i> exon 9,11,13,17,18; mutation was not found in <i>PDGFRα</i> exon 10,12,14,18	PR/Yes	Yes
9	F	66	Stomach	21	22	-	-	-	-	22	Point mutation in <i>KIT</i> exon 11 (c.1676 T>A; p.V559D)	PR/Yes	Yes
10	M	78	Stomach	15	15	-	-	-	-	15	Deletion in <i>KIT</i> exon 11 (c.1661_1675 del; p.E554_558del)	PR/No	Yes
11	M	52	Omentum	15	141	4	126	-	-	141	Deletion in <i>KIT</i> exon 11 (c.1671_1676del GAAGGT; p.W557_V559>C)	PR/Yes	Yes
12	M	51	Small intestine	16	59	-	-	-	-	73	Deletion in <i>KIT</i> exon 11	PR/Yes	Yes
13	F	57	Duodenum	11	41	-	-	-	-	41	Deletion across <i>KIT</i> intron 10 of exon 11 boundary	PR/Yes	Yes
14	M	76	Small intestine	29	31	-	-	-	-	31	Insertion in <i>KIT</i> gene exon 9 (p.S501_A502insAY)	PR/No	Yes

Table III. Continued.

A, Responders

Case no.	Sex	Age, years	Tumor location	Duration of first-line imatinib therapy, months	PFS of first-line imatinib therapy, months	Duration of second-line therapy, months	PFS of second-line therapy, months	Duration of third-line therapy, months	PFS of third-line therapy, months	OS, months	Gene analysis result	Best overall response/resection	Survival
15	M	50	Rectum	15	65	-	-	-	-	67	Point mutation in <i>KIT</i> exon 11 (c.1727T>C; p.L576P)	PR/Yes	No
16	M	53	Rectum	20	20	-	-	-	-	22	Deletion in <i>KIT</i> exon 11 (c.1669_1674del TGGGAG; p.W557_K558del)	PR/No	Lost follow up
17	M	64	Rectum	15	15	22	22	-	-	60	Mutation was not found in <i>KIT</i> exon 9,11,13,17,18; mutation was not found in <i>PDGFRα</i> exon 10,12,14,18	PR/Yes	Lost follow up
18	M	81	Rectum	6	7	-	-	-	-	17	Deletion in <i>KIT</i> exon 11 (c.1674_1676delGGT; p.K558_V559>N)	PR/No	No
19	M	41	Rectum	18	27	9	9	-	-	27	Point mutation in <i>KIT</i> exon 11 (c.1674 G>T; p.K558N) and (c.1676T>C; V. 559)	PR/No	Yes
20	F	73	Rectum	8	18	-	-	-	-	18	Deletion in <i>KIT</i> exon 11 (c.1669_1674del; p.W557_K558del)	PR/Yes	Yes

Table III. Continued.

B, Non-responders													
Case no.	Sex	Age, years	Tumor location	Duration of first-line imatinib therapy, months	PFS of first-line imatinib therapy, months	Duration of second-line therapy, months	PFS of second-line therapy, months	Duration of third-line therapy, months	PFS of third-line therapy, months	OS, months	Gene analysis result	Best overall response/resection	Survival
21	F	60	Stomach	13	47	5	6	24	26	118	Point mutation in <i>KIT</i> exon 11 (c.1669T>A; p.W557R)	SD/Yes	No
22	M	70	Stomach	9	32	-	-	-	-	32	Point mutation in <i>KIT</i> exon 11 (c.1679_1680TT>AG; p.V560E)	SD/Yes	Lost follow up
23	M	80	Stomach	36	47	-	-	-	-	47	Duplication mutation at 12bp in <i>KIT</i> exon11	SD/Yes	Lost follow up
24	F	38	Stomach	41	70	8	10	-	-	82	Deletion in exon 11 of <i>KIT</i> gene (delK550_Q556insM)	SD/No	No
25	F	72	Stomach	11	48	-	-	-	-	48	Insertion in <i>KIT</i> exon 11 (p.K558dup); mutation was not found in <i>PDGFRα</i> exon 10,12,14,18	SD/Yes	Yes
26	M	65	Stomach	19	36	-	-	-	-	36	Mutation was not found in <i>KIT</i> exon 9,11,13,17,18; mutation was not found in <i>PDGFRα</i> exon 10,12,14,18	SD/Yes	Yes

Table III. Continued.

B, Non-responders													
Case no.	Sex	Age, years	Tumor location	Duration of first-line imatinib therapy, months	PFS of first-line imatinib therapy, months	Duration of second-line therapy, months	PFS of second-line therapy, months	Duration of third-line therapy, months	PFS of third-line therapy, months	OS, months	Gene analysis result	Best overall response/resection	Survival
27	F	33	Stomach	16	43	-	-	-	-	43	Deletion in <i>KIT</i> exon 11 (c.1674_1676 del; p.K558_V559 delinsN)	SD/Yes	Yes
28	M	44	Stomach	10	19	-	-	-	-	19	Point mutation in <i>PDGFRα</i> exon 10 (c.1436G>A; p.R479Q)	SD/Yes	Yes
29	M	87	Stomach	3	11	-	-	-	-	11	Deletion in <i>KIT</i> exon 11 (c.1735_1737 del; p.D579del)	SD/Yes	Lost follow up
30	M	72	Stomach	9	9	4	4	-	-	14	Deletion in <i>KIT</i> exon 11 (c.1671_1676del GAAGGT; p.W557_V559>C)	PD/No	Lost follow up
31	F	35	Stomach	4	4	5	5	-	-	10	Mutation was not found in <i>KIT</i> exon 9,11,13,17,18; mutation was not found in <i>PDGFRα</i> exon 10,12,14,18	PD/No	Lost follow up
32	F	70	Pancreas	11	83	-	-	-	-	83	Insertion in <i>KIT</i> exon 11 of <i>KIT</i> gene (p.K558>NP)	SD/Yes	Yes
33	F	41	Duodenum	29	29	-	-	-	-	29	Mutation was not found in <i>KIT</i> exon 9,11,13,17,18; mutation was not found in <i>PDGFRα</i> exon 10,12,14,18	SD/No	Yes

Table III. Continued.

B, Non-responders										
Case no.	Sex	Age, years	Tumor location	Duration of first-line imatinib therapy, months	PFS of first-line imatinib therapy, months	Duration of second-line therapy, months	PFS of second-line therapy, months	Duration of third-line therapy, months	PFS of third-line therapy, months	OS, months
34	M	67	Duodenum	36	36	-	-	-	-	36
										Gene analysis result
										Insertion in <i>KIT</i> exon 11 (p.P573_T574insDP)
35	M	74	Mesocolon	56	131	52	52	-	-	183
										Point mutation in exon 10 of <i>PDGFRα</i> gene (c.1432T>C; p.S478P)
36	M	67	Pelvic area	21	41	12	12	-	-	42
										Deletion in <i>KIT</i> exon 11 (delK558_V559insN)
37	M	58	Rectum	29	77	17	48	-	-	77
										Insertion in <i>KIT</i> exon 9 (p.S501_A502insAT)
										Best overall response/resection
										SD/No
										SD/No
										SD/No
										SD/Yes
										Survival
										Yes
										No
										Lost follow up
										Yes

PR, partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival; KIT, tyrosine-protein kinase KIT; PDGFRα, platelet-derived growth factor receptor α.

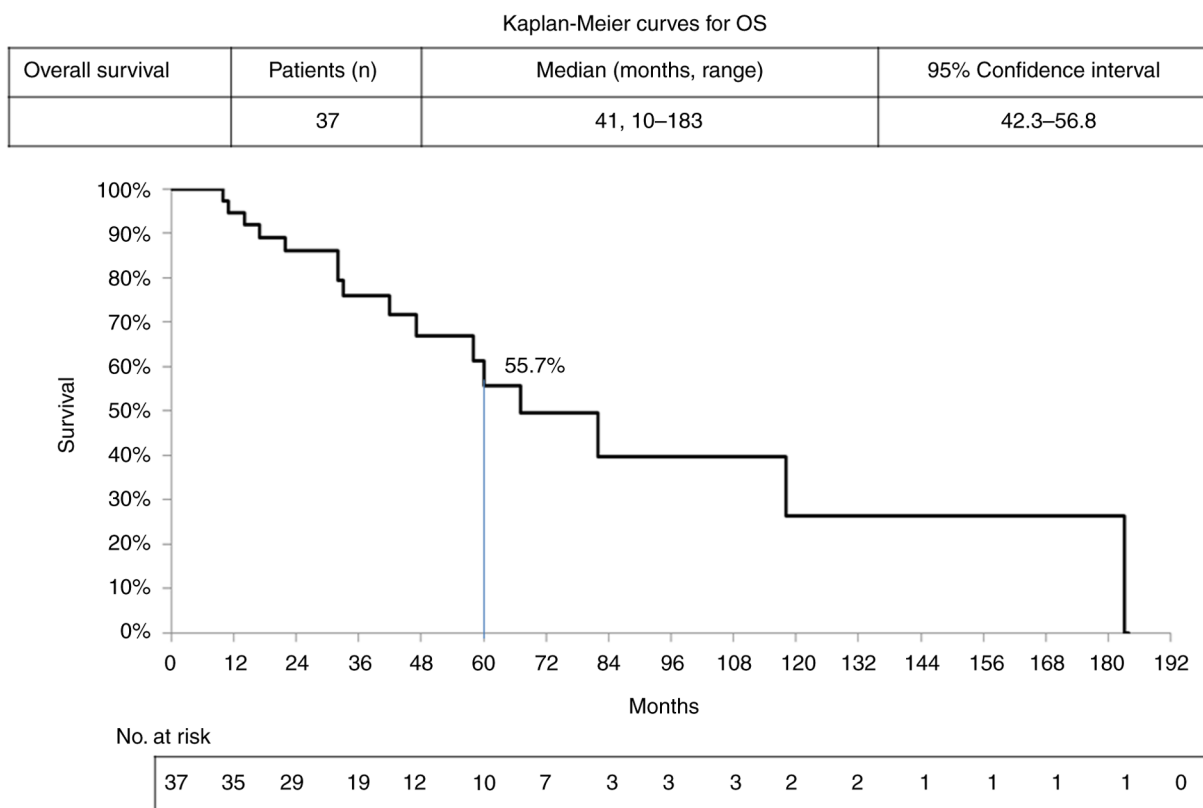


Figure 3. Kaplan-Meier curves for OS. The median OS of the 37 patients was 41 months and the total OS ranged from 10 to 183 months. OS, overall survival.

then SD switched to second-line sunitinib, which achieved a superior response. Second-line sunitinib treatment was effective for these patients with LAGISTs, increasing the likelihood of achieving complete resection and minimizing the risk of tumor spillage. The present study demonstrated that omental LAGIST had the best response rate (100%) when compared with rectal LAGIST (85.7%), small intestinal LAGIST (60%) and gastric LAGIST (47.6%), indicating omental and rectal LAGIST show a better response to imatinib compared with other organs. In addition, the responders group had a higher resection rate (70%) compared with the non-responders group (58.8%).

Overall, the median PFS was 36 months, longer than the 18-20 months reported in a previous study (20). Additionally, at the conclusion of follow-up, 21 patients (56.8%) were still alive. The different response rate and survival outcomes may arise from the different definitions of LAGIST, different gene mutation patterns, different tumor sites, different ethnicity and different treatment doses. For instance, a previous study enrolled 746 patients with a median PFS of 18 months in the standard-dose arm and 20 months for those receiving high-dose imatinib (20).

Although the ideal length of imatinib therapy remains debatable, imatinib should be administered in clinical settings until a maximal response is achieved. According to the National Comprehensive Cancer Network guidelines, achieving a maximal response may require treatment for >6 months (27). A previous study that evaluated treatment responses discovered that a maximal response is typically achieved after ~12 months of treatment (26). In the 24 patients in the present study who subsequently underwent resection, the median time to primary

tumor resection was 16 months. Determining the ideal duration of first-line treatment should involve regular response assessments to determine the optimal timing for surgical intervention (22,26-28). Combined CT-measured tumor density and RECIST evaluations may aid in determining an appropriate timing for LAGIST surgical resection (3).

Clinical research suggests the benefits of imatinib therapy in patients with GISTs. If it is technically resectable, neoadjuvant therapy can preserve organ function, avoid tumor rupture, reduce postoperative complications and increase the R0 resection rate to up to 91% compared with 85% (29). For unresectable GISTs, the response rate of first-line imatinib therapy is 45-69% (30). A previous study revealed that 15.7% of patients with initially unresectable GIST became resectable under first-line imatinib therapy (31). In the present study, the patients were all initially unresectable and imatinib was used as the first-line therapy instead of neoadjuvant therapy.

A higher occurrence of primary imatinib resistance was observed in GISTs with *KIT* exon 9 mutations, GISTs with *PDGFRα* D842V mutations and GISTs with wild-type *KIT* and *PDGFRα*. Hence, evaluation is needed of the potential differences in treatment responses based on different mutation types in a prospective, multicenter clinical trial. The present study has certain limitations. First, a retrospective design was employed with a non-randomized controlled trial and a relatively small sample size from a single institution for the mutation association analysis. Therefore, the findings require verification in a prospective, multicenter clinical trial required to associate gene mutations with other TKIs. Second, the present study lacked comprehensive information on the GIST-associated gene mutation status of the patients, which may influence the risk of

Table IV. Adverse events of first-line therapy in different gene mutations in 37 patients with locally advanced gastrointestinal stromal tumor.

Adverse events	<i>KIT</i> exon 9 insertion (n=2), n (%)	<i>KIT</i> exon 11 insertion (n=5), n (%)	<i>KIT</i> exon 11 deletion (n=14), n (%)	<i>KIT</i> exon 11 point mutation (n=5), n (%)	<i>KIT</i> exon 11 duplication (n=1), n (%)	<i>PDGFRα</i> exon 10 point mutation (n=2), n (%)	<i>KIT</i> exon 11 deletion; <i>PDGFRα</i> exon 10 point mutation (n=2), n (%)	No mutation in both <i>KIT</i> and <i>PDGFRα</i> (n=6), n (%)
All grade								
Nausea	-	2 (40.0)	4 (28.6)	1 (20.0)	-	-	-	1 (16.7)
Vomiting	-	-	2 (14.3)	1 (20.0)	-	-	-	1 (16.7)
Gastritis	-	-	1 (7.1)	1 (20.0)	-	-	-	-
Edema	1 (50.0)	1 (20.0)	2 (14.3)	2 (40.0)	-	-	-	-
Eyelid edema	1 (50.0)	2 (40.0)	1 (7.1)	1 (20.0)	-	1 (50.0)	-	2 (33.3)
General malaise	-	1 (20.0)	-	-	-	-	-	-
Skin rash	-	2 (40.0)	1 (7.1)	1 (20.0)	-	-	-	-
Diarrhea	-	-	-	1 (20.0)	-	1 (50.0)	-	-
Fatigue	-	-	1 (7.1)	1 (20.0)	-	-	-	-
Renal function impairment	-	-	-	-	-	-	-	1 (16.7)
Liver function impairment	-	-	1 (7.1)	-	-	-	-	-
Hand-foot skin reaction	1 (50.0)	-	1 (7.1)	-	-	-	-	-
Anemia	-	-	3 (21.4)	-	-	1 (50.0)	-	1 (16.7)
Leukopenia	-	-	1 (7.1)	-	-	-	-	1 (16.7)
P-value	P=0.967							
Grade ≥3								
Anemia	-	-	2 (14.3)	-	-	-	-	1 (16.7)

KIT, tyrosine-protein kinase *KIT*; *PDGFRα*, platelet-derived growth factor receptor α .

recurrence and survival outcomes for GISTs. Third, the relatively brief follow-up duration may have resulted in an underestimation of the effects of first-line imatinib therapy on PFS and OS. A total of 1 patient progressed fast (first-line failure, 4 months; second-line, 5 months) and was lost to follow-up after 10 months (case no. 31), and at the time of the study's conclusion, 5 patients are still under treatment, 21 patients are still alive and 9 patients have a short follow-up time of <24 months. In spite of the limitations of the present study, it is evident that first-line imatinib therapy is effective and safe in reducing tumor size in patients with LAGISTs, yielding comparable rates of complete resection.

In conclusion, the gene mutation status was demonstrated to have limited value as an indicator for assessing treatment response and surgical resectability. Additionally, no significant variations were observed in complication rates. Although most patients clinically benefited from first-line imatinib therapy with manageable side effects, future studies with long-term follow-ups are required to verify the results.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

WCS and JYW were involved in the conception and design of this study. WCS wrote the manuscript. WCS, CWH, HLT, YCC and TKC performed data acquisition. WCS, PJC, YSY and TCY contributed to the analysis and interpretation of data. JYW reviewed and edited the manuscript and supervised the study. WCS and JYW confirmed the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study fully complied with the Declaration of Helsinki and was approved by the Institutional Review Board

of Kaohsiung Medical University Hospital [approval no. K MUHIRB-E(1)-20240084]. According to regulations at our institution, patient consent was waived for the present study due to its retrospective nature.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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