Combined computed tomography-measured tumor density and RECIST for evaluating neoadjuvant therapy in locally advanced gastrointestinal stromal tumors

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Background: Deciding the most appropriate timing for surgical resection of locally advanced gastrointestinal stromal tumors (LAGISTs) has conventionally been challenging, because no well-established clinical guideline is available. In this study, we combined computed tomography (CT)-measured tumor density and Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) to evaluate the clinical responses in 12 patients with LAGISTs. We aimed to offer alternative approaches that can enhance the surgical resectability evaluation of LAGISTs after neoadjuvant therapy.

Methods: This study recruited 12 consecutive patients diagnosed with LAGISTs who had received neoadjuvant imatinib therapy primarily at the study institution from December 2010 to December 2017. They were followed up until December 2017. Tumor responses were simultaneously analyzed by measuring tumor density on CT images and applying RECIST. Clinicopathological features, clinical outcomes, and *KIT* and *PDGFR* gene mutation profiles were also evaluated.

Results: Analysis of tumor responses using the combined CT-measured tumor density and RECIST method revealed that 10 of 12 patients were considered as partial response (PR). One patient showed stable disease (SD) but was a borderline PR hence all 11 patients were resectable. Three of 7 GISTs patients who underwent resection were considered as stable disease according to RECIST but 2 of 3 were categorized as PR using our combined evaluation approach. The other one patient was a borderline PR with 28% of CT tumor density reduction. Of the 12 patients, five patients had *KIT* exon 11 deletion, two had *KIT* exon 11 insertion, three had point mutation and one was wild-type *KIT* and *PDGFRA*. However, *KIT* gene mutation status was not a useful indicator when evaluating surgical resectability in our study.

Conclusions: We suggest that our combined CT-measured tumor density and RECIST evaluation method may be beneficial for deciding an appropriate timing for surgical resection of LAGISTs.

Keywords: CT-measured tumor density; neoadjuvant therapy; locally advanced gastrointestinal stromal tumors

Introduction

Gastrointestinal stromal tumors (GISTs) account for only 1–3% of all malignant GI tumors (1). Curative resection is recommended in most cases, with exception for locally advanced gastrointestinal stromal tumors (LAGISTs) which are initially diagnosed as unsuitable for radical resection (2). Neoadjuvant imatinib therapy may be initially indicated if a tumor is borderline resectable or if resection may lead to prominent organ dysfunction. Imatinib can markedly repress GIST progression by inhibiting *KIT* and *PDGFRA* tyrosine kinases (2,3). Neoadjuvant imatinib therapy can facilitate surgical resection, reduce tumor spill or bleeding during surgery, or both; however, its role beyond these functions is unclear (4). One previous study observed *KIT* gene mutations in approximately 80% of GISTs (5). Another study found that primary imatinib resistance occurred more frequently in GISTs with *KIT* exon 9 mutations, *PDGFRA* D842V mutations, or wild-type *KIT* and *PDGFRA* (6).

GISTs are characterized by abundant hypervascularity (7), and their current gold standard evaluation method is fluorodeoxyglucose positron emission tomography (FDG PET) (8,9). Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) guidelines are also routinely used to evaluate the solid tumor response by using contrast-enhanced computed tomography (CT) (10,11). The most appropriate timing for resection is when shrinkage in tumor size or a decrease in angiogenesis is observed. This will subsequently enhance surgical success, reduce postoperative risks (bleeding/rupture) and complications, and improve the chance of function-sparing surgery. Currently, no well-established clinical tools are available to determine the most appropriate timing for surgical resection of LAGISTs. In this study, we combined CT-measured tumor density and RECIST criteria to evaluate the clinical responses of 12 patients with LAGISTs who received neoadjuvant imatinib therapy.

Methods

Patient demographics

This study recruited 12 consecutive patients diagnosed with LAGISTs who had received neoadjuvant imatinib therapy primarily at the study institution between December 2010 and December 2017. These patients were followed up after neoadjuvant therapy administration for a median of 27 months (range, 11–69 months). In the present study,

case series analysis was performed using a routinely updated and maintained electronic medical record database. Demographic data included age at diagnosis, sex, tumor size at presentation (pre- and post-treatment), and origin of the primary tumor. The primary tumor location was categorized into the following regions: the stomach (N=7), rectum (N=2), omentum (N=1), pelvic area (N=1) and pancreas (N=1). All aspects of this study were approved by the institutional review board of Kaohsiung Medical University Hospital (KMUHIRB-G (II)-20160019). This study is a retrospective review of 12 GIST patients and all patients had signed written informed consents.

Pathological and clinical data

All patients' medical records were reviewed, and their clinicopathological data were obtained through independent re-evaluation of original histopathological slides by two investigators with relevant experience. Both investigators were blinded to the routine diagnoses and patient outcomes. Discrepancies were resolved by simultaneous re-examination of the slides by both investigators. The maximum tumor diameter and mitotic count per 50 high-power fields (HPFs) were determined using the CT or pathological findings for the specimen of each LAGIST case; these examined data were then used to evaluate the risk of death and metastasis (12). The risk of tumor-related death or metastasis was determined by tumor location, tumor size, and mitotic count (per 50 HPFs) (12-18).

Treatment

Each enrolled patient was prescribed imatinib at a dosage of 400 mg/day over a treatment period of 5–30 months. For patients with grade 3 and 4 toxicities, the dosage of imatinib was reduced to 300 mg/day. Sunitinib at a dosage of 37.5 mg/day was applied as second-line therapy after first-line neoadjuvant imatinib therapy failed and disease progression was shown on computed tomography images. Regorafenib at a dosage of 120 mg/day was used as third-line treatment.

Evaluation of tumor response and toxicities

The tumor size and density of these enrolled patients were confirmed after their abdominal CT images were examined by two radiologists. Discrepancies were resolved by simultaneous re-examination of the images by both

radiologists. Tumor responses were evaluated using oncologic findings and CT images showing changes in tumor density in addition to applying RECIST 1.1 (8,10). The CT attenuation coefficient (density) was categorized as follows: grade 4, >30% decrease; grade 3, 11–30% decrease; grade 2, ≤10% decrease or increase; and grade 1, >10% increase (8).

In this study, we proposed that combining CT-measured tumor density and RECIST may be useful to determine the timing of surgical resection for patients with LAGISTs; this combined method suggests either a reduction of more than 30% for tumor density, or a tumor size reduction of more than 30% for a partial response (PR), as determined using RECIST 1.1. A complete response was defined as the disappearance of all lesions; PR was defined as a tumor size reduction of 30% or more or a tumor density reduction of 30% or more on CT images. In addition, stable disease (SD) was defined as having no symptomatic deterioration attributed to tumor progression, and progression disease (PD) was defined as an increase in tumor size of 20% or more and not meeting the criteria of PR based on tumor density on CT images. Adverse events (AE) were graded according to the Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/reporting/ctc.html).

KIT and PDGFRA gene mutation analysis

To obtain cancer tissue samples, CT-guided core biopsies were performed before neoadjuvant therapy administration. The biopsy specimens were embedded in paraffin, fixed in formalin, and then serially cut into 4-µm thick sections. DNA extraction was performed using the QIAGEN DNA extraction kit (QIAGEN Inc., Valencia, USA), according to the manufacturer's protocol. The concentration and quality of the extracted DNA were then determined using the NanoDrop 2000 spectrophotometer. The optical density at 260 or 280 nm of DNA derived from all patient specimens ranged from 1.8 to 2.0; thus, DNA samples were of high quality and suitable for subsequent experiments. The DNA samples were analyzed using polymerase chain reaction (PCR) performed on a PCR instrument from Applied Biosystems (Thermo Fisher Scientific Inc., MA, USA). Next, the KIT or PDGFRA primer (100 µM) and the 2X Tag polymerase reaction mix were added.

Statistical analyses

All statistical analyses were performed using SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA). Progression-free survival (PFS) was measured from the start date of treatment to the date of any type of progression or the final follow-up. Overall survival (OS) was defined as the period from the start of treatment to death from any cause or the final follow-up. The OS and PFS were plotted using the Kaplan-Meier method.

Results

Follow-up duration and survival evaluation

The median PFS was 27 months (range, 4–69 months) (*Figure 1A*) and the median OS was 27 months (range, 11–69 months) (*Figure 1B*). Among the 12 patients, 7 were still alive at the final follow-up conducted in December 2017.

Patient series, tumor characteristics, and mutation status

Twelve patients with pathologically confirmed GISTs were identified during the study period. *Table 1* provides a summary of their demographic and clinicopathological characteristics. The median age was 64.5 years (range, 35–83 years), and there were 8 (66.7%) male and 4 (33.3%) female patients. LAGISTs were located in the stomach of 7 patients (58.3%), the rectum of 2 patients (16.7%), the omentum of 1 patient (8.3%), the pelvic area of 1 patient (8.3%) and pancreas of 1 patient (8.3%).

KIT and PDGFRA gene mutation analysis revealed *KIT* exon 11 deletions in 5 patients (41.7%), *KIT* exon 11 insertion in 2 patients (16.7%), and *KIT* exon 11 point mutations in 3 patients (25.0%). Wild-type *KIT* and *PDGFRA* were noted in 1 patient (8.3%). The genotype of 1 patient (8.3%) was not sequenced due to insufficient specimen material.

Although RECIST 1.1 is the most well-established and widely used evaluation approach, its treatment efficacy for GIST is limited. Hence, we also applied CT-measured tumor density for better evaluation. The best clinical responses of 6 patients (50.0%) were PR evaluated with RECIST 1.1. Using our combined CT-measured tumor density and RECIST 1.1 for response evaluation, the best clinical responses of 10 patients (83.3%) were considered as PR. One other patient (8.3%) was a borderline PR with a tumor density reduction of 28% but was considered as SD using our combined evaluation approach (case 6).
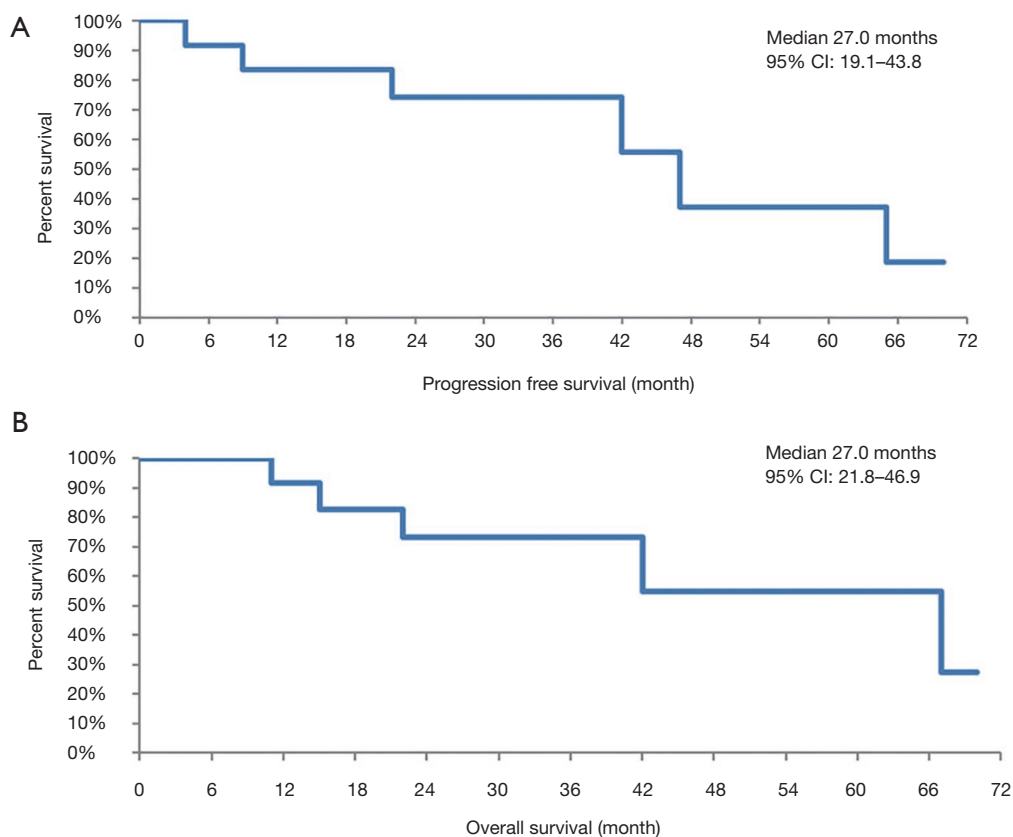
Notably, 9 patients (75%) who were simultaneously

Figure 1 Kaplan-Meier survival analysis. (A) Progression-free survival of all 12 cases (range, 4–69 months); (B) overall survival of all 12 cases (range, 11–69 months).

evaluated using RECIST 1.1 combined with CT-measured tumor density had more than 30% decrease in CT-measured tumor density (*Table 1*). No grade 3 or 4 AEs were observed during neoadjuvant imatinib therapy, and the two most common AEs (grade 1 or 2) were nausea/vomiting and edema (33.3% for both, *Table 1*).

The pathologic and treatment evaluation of each patient is presented in *Table 2*. *Table 3* shows the treatment outcome of all 12 patients. For all patients, their maximum tumor diameter before treatment ranged from 5.9 to 15.4 cm. We found that neoadjuvant imatinib therapy might decrease the tumor risk of GIST by reducing both tumor size and mitotic count (*Table 3*). Six patients (case 1, 2, 3, 4, 5, 7) with optimal tumor volume shrinkage showed PR evaluated using our combined CT tumor density and RECIST 1.1 approach had undergone radical resection (R0 resection) after 8–16 months of neoadjuvant imatinib therapy. One other patient (case 6) who was a borderline PR with a tumor density reduction of 28% but was considered as SD using

our combined evaluation approach also had radical resection (R0 resection) (*Table 3*).

Additionally, mutations in *KIT* exon 11 were observed in ten patients. Using our combined CT-measured tumor density and RECIST 1.1 method, all 5 patients (100%) with deletions of Trp-557, Lys-558, or both codons showed a PR and were categorized as grade 4 based on the CT attenuation coefficient (density). Using only RECIST 1.1 to evaluate the 5 patients with deletions in *KIT* exon 11, four patients (80%) showed a PR and one patient (20%) showed SD (*Table 4*).

When assessed using our combined evaluation approach, two patients with an insertion in *KIT* exon 11 were considered to have a PR (100%). Two (66.7%) of 3 patients with point mutations were considered to show a PR and 1 patient (33.3%) showed SD. By contrast, when patients with point mutations were assessed using only RECIST 1.1, 1 patient (33.3%) showed a PR and 2 patients (66.7%) showed SD. Each of these 3 patients with point mutations

Table 1 Demographic and clinicopathological characteristics of 12 LAGISTs patients

Characteristics	Number of cases (%)
Sex	
Male	8 (66.7)
Female	4 (33.3)
Median age (years, range)	64.5 [35–83]
Tumor location	
Stomach	7 (58.3)
Rectum	2 (16.7)
Omentum	1 (8.3)
Pelvic area	1 (8.3)
Pancreas	1 (8.3)
KIT gene mutation	
Exon 11 point mutation	3 (25.0)
Exon 11 deletion	5 (41.7)
Exon 11 insertion	2 (16.7)
Wild type	1 (8.3)
Not available	1 (8.3)
Best objective response (RECIST)	
Disease control	11 (91.7)
Partial response	6 (50.0)
Stable disease	5 (41.7)
Progressive disease	1 (8.3)
CT attenuation coefficient (density)	
Grade 4, decrease of more than 30%	9 (75.0)
Grade 3, 11–30% decrease	1 (8.3)
Grade 2, decrease ≤10% increase ≤10%	1 (8.3)
Grade 1, increase of >10%.	1 (8.3)
Combined computed tomography scans density and RECIST criteria	
Partial response	10 (83.3)
Stable disease	1 (8.3)
Progressive disease	1 (8.3)
Grade 1/2 adverse events	
Nausea/vomiting	4 (33.3)
Build-up of fluid (edema)	4 (33.3)
Skin itchy rash	2 (16.7)
Anemia	1 (8.3)
Liver toxicities	1 (8.3)
Oral mucositis	1 (8.3)

LAGISTS, locally advanced gastrointestinal stromal tumors.

was characterized as grade 4 (33.3%), grade 3 (33.3%), and grade 2 (33.3%) according to the CT attenuation coefficient (density) (*Table 4*).

Discussion

The standard treatment for primary GISTs is complete surgical resection. However, for some cases, complete resection is either unsuitable or impossible because of the anatomic site, tumor size, and high risk of rupture or metastasis (2). Given the hypervascularity of GISTs, the risk of rupture and eventual seeding or bleeding can be significant and lead to poor prognosis (9). Hence, determining the optimal treatment duration and the most appropriate timing for resection is critical in patients requiring potential resection. Currently, FDG PET is globally recognized as the gold standard evaluation method for GISTs. However, its high cost limits its use in routine imaging studies, and it is not feasible in patients whose baseline FDG PET results are negative for tumors (8).

Instead, contrast-enhanced CT is routinely used to evaluate the solid tumor response according to RECIST 1.1. Although RECIST 1.1 is a more favorable indicator of treatment response, the major drawback of RECIST 1.1 is that it relies solely on tumor size to monitor treatment response (8). By contrast, the criteria of Choi *et al.* exhibits high sensitivity and specificity in responders as it evaluates treatment response by assessing changes in the size (a tumor size reduction of more than 10%) or density of the target lesions (a tumor density reduction of more than 15% on CT images) (8,19). However, a minor alteration in tumor size or vascularity may have limited significance when evaluating the benefits of surgery in patients with LAGISTS.

Thus, our combined CT-measured tumor density and RECIST 1.1 method may be beneficial for deciding an appropriate timing of surgical resection in LAGISTS. This combined method suggests either a significant reduction of more than 30% for tumor density or a tumor size reduction of more than 30% defines a PR and thus suggest LAGIST patients could be resected. Case 4 was one of the examples that had both a significant reduction of more than 30% for tumor density and a tumor size reduction of more than 30% (*Figure 2*).

We discovered that 3 (42.9%) of the 7 patients who underwent resection had significant decrease in tumor density despite being determined as SD according to RECIST 1.1. Although neither patient exhibited a remarkable decrease in tumor size, surgical bleeding

Table 2 Pathologic and treatment evaluation of 12 LAGISTs patients

Case No.	Tumor location	Duration of neoadjuvant therapy	PFS (months)	OS (months)	Gene mutation	Survival (yes/no)
1	Rectum	Imatinib 16 months	65	67	*KIT* exon 11 point mutation	No (die of cancer)
2	Gastric	Imatinib 13 months	47	64	*KIT* exon 11 point mutation	Yes
3	Omentum	Imatinib 15 months	69	69	*KIT* exon 11 deletion	Yes
4	Gastric	Imatinib 8 months	27	27	*KIT* exon 11 deletion	Yes
5	Gastric	Imatinib 8 months	27	27	*KIT* exon 11 insertion	Yes
6	Gastric	Imatinib 9 months	26	26	*KIT* exon 11 point mutation	Yes
7	Pancreas	Imatinib 9 months	9	12	*KIT* exon 11 insertion	Yes
8	Gastric	Imatinib 9 months[a]	9	15	*KIT* exon 11 deletion	No (die of cancer)
9	Gastric	Imatinib 5 months	4	11	Wild type *KIT*	Lost follow up
10	Pelvic area	Imatinib 22 months	42	42	*KIT* exon 11 deletion	No (die of cancer)
11	Gastric	Imatinib 30 months	30	30	Pending data	Yes
12	Rectum	Imatinib 22 months[b]	22	22	*KIT* exon 11 deletion	Lost follow up

[a], partial response after 6 months of treatment, but progression after 9 months of treatment; [b], partial response after 13 months of treatment, but progression after 18 months of treatment. LAGISTs, locally advanced gastrointestinal stromal tumors.

was reduced and radical resection was also achieved. For instance, CT tumor density of case 6 had a significant reduction of nearly 30% and had subsequently undergone radical resection (*Figure 3*). This finding may be attributed to the decrease in tumor density, which corresponded to inhibited angiogenesis.

During the first 6 months of treatment, the treatment outcome was a PR in case 8, but disease progression was observed after the subsequent 3 months of treatment (*Table 3*). According to the gene mutation profile, only case 9 exhibited wild-type *KIT* and *PDGFRA*, and disease progressed after 4 months of treatment then lost follow-up; case 9 also showed disease progression identified by RECIST 1.1, which was consistent with the CT-measured tumor density finding. Moreover, although cases 10 and 11 showed SD as determined using RECIST 1.1, a notable decrease in CT-measured tumor density was observed; thus, these cases were considered PRs when evaluated using our combined CT tumor density and RECIST 1.1 method. Case 12 was considered to have a PR after 13 months of treatment, but disease progressed after 18 months of treatment.

Based on data from established clinical studies, imatinib is approved as a first-line neoadjuvant therapy for LAGISTs and as an adjuvant therapy without defining a specific treatment duration for patients with intermediate- to high-

risk primary GISTs after resection (20,21). Neoadjuvant imatinib therapy can enhance operative potential and reduce surgical complications and recurrence (22). Imatinib can markedly repress GIST activity by inhibiting the *KIT* and *PDGFRA* tyrosine kinases (3). One previous study reported that approximately 80% of GISTs exhibited *KIT* gene mutations (5), and our current study is consistent with this prior finding as *KIT* gene mutations were found in 10 of 11 patients (90.9%).

Various types of *KIT* exon 11 mutations have been discovered to be prognostically significant (23). A marked poorer disease-free survival and clinical outcome were observed in GIST patients with *KIT* exon 11 insertions or deletions (including Trp-557, Lys-558, or both codons) than in those with other types of exon 11 mutations or wild-type *KIT* (24,25). Despite that, *KIT* exon 11 mutation was not a useful predictor of tumor response and resectability in our study.

Among the 10 patients with *KIT* exon 11 mutations, two patients exhibited insertion mutations and were considered to have a PR when evaluated using our combined CT tumor density and RECIST 1.1 evaluation approach. The CT attenuation coefficient (density) for both patients was grade 4. Both patients in our study did not have a remarkably poorer disease-free survival and clinical outcome than those with other types of exon 11 mutations or wild-type *KIT*.

Table 3 Treatment outcomes for the 12 LAGIST patients

Case No.	Sex	Age (years)	Pre-treatment tumor maximum diameter (cm)	Post-treatment tumor diameter (cm)	Tumor size reduction (%)	CT tumor density reduction	Primary tumor mitotic count per 50 HPF	Post-resection tumor mitotic count per 50 HPF	Primary tumor risk	Post-resection tumor risk	Best overall response (RECIST/density)
1	M	50	5.9	2.1×1.85×1.8	−64.4	0	5	<5	High	Low	PR (PR/2)
2	F	60	9.6	7.0×5.1×2.8	−27.1	−44	<5	<5	Low	Low	PR (SD/4)
3	M	52	12.5	8.3×6.9×6.3	−33.6	−54	5	<5	High	High	PR (PR/4)
4	M	62	15.1	3.2×2.3×1.5	−78.8	−44	ND	<5	High	Very low	PR (PR/4)
5	F	83	11.1	7.0×5.2×5.2	−36.9	−35	ND	<5	High	Low	PR (PR/4)
6	M	70	7.7	6.3×4.0×3.8	−18.2	−28	ND	0	ND	Low	SD (SD/3)[c]
7	F	70	8.3	6.7×2.5×2.4	−19.3	−33	<5	<5	High	High	PR (SD/4)
8	M	72	14.5	9.5	−34.5	−40	ND	ND	High	No operation	PR (PR/4)[d]
9	F	35	7.7	8.2	+6.5	+23	ND	ND	ND	No operation	PD (PD/1)
10	M	67	14.9	10.8	−27.5	−69	ND	ND	High	No operation	PR (SD/4)
11	M	80	15.4	11.8	−23.4	−59	ND	ND	High	No operation	PR (SD/4)
12	M	53	9.3	6.2	−33.3	−86	ND	ND	High	No operation	PR (PR/4)[e]

Best overall response is evaluated using combined CT tumor density and RECIST 1.1. ND, unavailability of the original histological slides or paraffin-embedded wax blocks. [c], tumor density decreased by 28%; [d], after 6 months of treatment; [e], after 13 months of treatment. LAGIST, locally advanced gastrointestinal stromal tumor; PR, partial response; SD, stable disease; PD, progressive disease.

Table 4 Outcome evaluation according to the *KIT* and *PDGFRA* gene mutation statuses

Type of *KIT* exon 11 mutation	Deletion (presence of codon Trp-557 and/or Lys-558) (N=5)	Insertion (N=2)	Point mutation (N=3)	Wild type (N=1)
Combined computed tomography scans density and RECIST criteria, n [%]				
Complete response				
Partial response	5 [100]	2 [100]	2 [66.7]	
Stable disease			1 [33.3]	
Progressive disease				1 [100]
Best response under imatinib (RECIST criteria), n [%]				
Complete response				
Partial response	4 [80]	1 [50]	1 [33.3]	
Stable disease	1 [20]	1 [50]	2 [66.7]	
Progressive disease				1 [100]
CT attenuation coefficient (density), n [%]				
Grade 4, decrease of more than 30%	5 [100]	2 [100]	1 [33.3]	
Grade 3, 11–30% decrease			1 [33.3]	
Grade 2, decrease ≤10% increase ≤10%			1 [33.3]	
Grade 1, increase of >10%				1 [100]
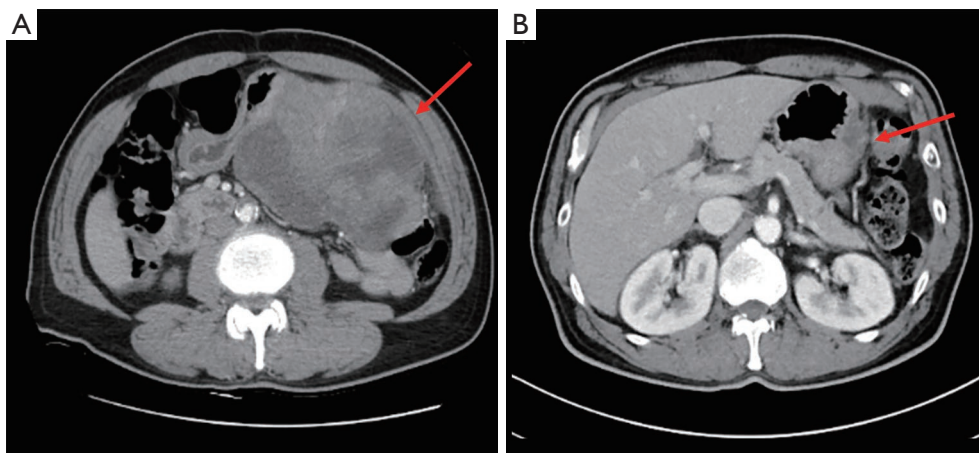
Figure 2 CT image of case 4 (A) before neoadjuvant imatinib treatment and (B) after neoadjuvant imatinib treatment (red arrow denotes location of tumor).

Five patients who exhibited deletions in Trp-557, Lys-558, or both codons were considered to have a PR when evaluated using our combined CT-measured density and RECIST 1.1 method. Moreover, all five showed a CT-measured tumor density reduction of more than 30%. When RECIST 1.1 guideline was used, four of the five patients (80%) showed a PR and one (20%) showed SD (*Table 4*).

Three patients with point mutations had contradictory results when evaluated using RECIST 1.1 and our combined evaluation approach. Determined using our
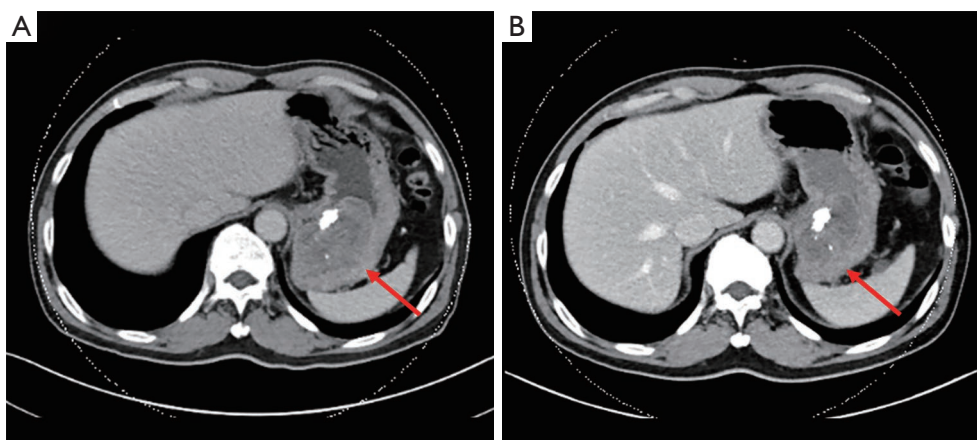
Figure 3 CT image of case 6 (A) before neoadjuvant imatinib treatment and (B) after neoadjuvant imatinib treatment (red arrow denotes location of tumor).

combined CT tumor density and RECIST 1.1 evaluation method, 2 of 3 patients with *KIT* point mutations were considered to have PR and 1 patient showed SD, whereas 1 patient showed a PR and 2 patients showed stable disease (SD) according to RECIST 1.1 (*Table 4*).

Additionally, primary imatinib resistance occurs more frequently in GISTs with wild-type *KIT* and *PDGFRA* (6). Consistent with the finding of Lee *et al.* (6), the only case with wild-type *KIT* and *PDGFRA* in our study eventually showed disease progression. For patients who do not respond to imatinib treatment, determining when to switch the regimen is equally crucial. Therefore, precise objective evaluation of the treatment response influences the regimen plan and is critical to patients with GISTs.

This study highlights the importance of utilizing both CT-measured tumor density and RECIST 1.1 for plausible surgical resection timing consideration. Comparing RECIST 1.1, CT-measured tumor density, and *KIT* and *PDGFRA* gene mutation profiles, our results suggest that our combined CT-measured tumor density and RECIST 1.1 method is more suitable for evaluating surgical resectability in patients with LAGISTs. However, a rather small sample size and a median follow-up duration of 27 months may be the limitations of this study. Future investigations could include a larger sample size and lengthening follow-up duration. We argue that long-term follow-up is crucial for LAGIST management, along with the aforementioned evaluation approach to determine tumor response and feasible surgical resection timing.

Conclusions

Our combined CT-measured tumor density and RECIST 1.1 method may potentially offer an alternative evaluation approach that may be beneficial for deciding the preferable timing for surgical resection of LAGISTs.

Acknowledgments

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2018.05.34). The authors have no conflicts

of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All aspects of this study were approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUHIRB-G (II)-20160019). This study is a retrospective review of 12 GIST patients and all patients had signed written informed consents.

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